Ebtesam A. Al-Suhaimi *Editor*

Emerging Concepts in Endocrine Structure and Functions

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Foreword

LAGEPP

LABORATOIRE D'AUTOMATIQUE DE GÉNIE DES PROCÉDÉS ET DE GÉNIE PHARMACEUTIQUE

Villeurbanne, 19 octobre 2021

Foreword By Professor H. Fessi
Claude Bernard University Lyon1.
Villeurbanne, France

This book titled **Emerging concepts in endocrine structure and functions** is interesting, original and well thought as evidenced by his structure of chapters and content as depicted by the author Professor Ebtesam Al-Suhaimi. The main aim of this e-book is to update the readers about advances in the development of Endocrine Physiology the science is the base of functions of the Endocrine system with its domination in the body. Consequently, the scope of this Book covers a scale of topics including the list stated in its index.

This book starts with a very complete introduction on the endocrinology by giving comprehensive and classical definition of hormones and Chemical signals and messengers, General characteristics of the endocrine glands.

Emerging concepts in endocrine structure and functions is a valuable resource for biology scientists, clinicians and postgraduate students searching updated and crucially important information for developing Endocrine physiology & pathophysiology and plans for Endocrine research. The book assigns a chapter for a new additions; the adipose tissue as an endocrine tissue. Details about stem cell in each endocrine gland highlighted throughout or concluded each chapter, the feature, which is not found in the most of existing books of physiology. This book includes ten chapters covering many topics includes such as description of the functions and the histological properties of the glands along with coloured cross sections and figures to reinforce understanding of the general and detailed functions, regulation, and interrelationships. The author finishes this book by a consistent chapter on Adipose tissue and local hormones in which adipose tissue as an endocrine tissue**,** adipokines, local hormones and stem cells in adipose tissue are discussed.

Finally, its interesting to notice that, the inclusive texts are written in updating manner using up to date references that mostly published in well-known indexed sources. Consequently, without any hesitation, I am recommending this book for biology scientists, clinicians and postgraduate students searching and researches in the field of Endocrinology.

Signature

Department of Pharmacy, cosmetic and bio-pharmacy

Preface

In this book, our approach has been not only to describe what hormones do, but to emphasize the mechanisms by which they act at the cellular and molecular level. Endocrine, autocrine, and paracrine and many more delivery signals are discussed. This book focuses on basic and advanced fundamental endocrinology with new concepts on the role of endocrine stem cells, adipose tissue hormones, and new ovarian oogenesis theory. Particular attention is paid to structure-action relationship of some hormones to enhance the appreciation of how these hormones act. Additionally, adipose tissue as an emerging endocrine gland is discussed in a separate chapter. The book covers these endocrinology topics:

- Delivery signaling
- Biological synthesis of hormones
- Mechanism of hormone action
- Pituitary and associated hypothalamus
- Thyroids and parathyroids
- Adrenals, pineal, and circadian rhythm
- Endocrine pancreas
- Reproductive endocrinology
- Stem cell endocrinology
- Hormones of adipose tissue

In addition, we have emphasized the significant progress in the understanding of the biology of hormone signal transduction, immune and inflammatory responses, and some pathophysiological process and their interaction with the endocrine system.

The book is supported with original illustrations and histological sections with a total of approximately 100 figures. Each chapter is enriched with current citations and references. We have included extensive sections on References and further reading at the end of each chapter. We hope that the information in this book will be of value to the reader and any comments on the book will be welcome.

Dammam, Saudi Arabia — Ebtesam A. Al-Suhaimi

Acknowledgments

This work was prepared to enrich the knowledge of the endocrine field and for the interested reader in Endocrinology, the core science that we have to utilize to create a promising strategy for basic and medical Endocrinology and metabolism. Dear parents, thank you for always supporting me. You are my role models. My father advised me to author this book on endocrine. He is the first one who had given me a reputed book in the Endocrinology field. I would like to thank the individuals who had spent their unlimited support: my children: Hind, Abdulrahman, Fatima, and Abdullah. My big sister Mrs Naimah is the loyal sister who stood by me during this work and since I started my university career. To my husband, my sisters, and brothers, who offered their assistance. I would also like to thank Dr. Amal Akbar for her help in completing some of the figures. I would also express my gratitude to the laboratories in the Biology Department at College of Science at Imam Abdulrahman bin Faisal University where I prepared the histology images, to Professor Issam Abdul Majid who expended a great deal of effort giving his advice, and to Imam Abdul Rahman bin Faisal University.

Ebtesam A. Al-Suhaimi

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About the Editor

Ebtesam A. Al-Suhaimi is a Professor in Biology Department, College of Science, at Imam Abdulrahman bin Faisal University (IAU), and the Dean of the IAU's Institute for Research and Medical Consultations (IRMC). Dr. Al-Suhaimi has more than two decades of research excellence in endocrinology, physiology, immunology, animal biology, and behavior sciences. With an advanced degree in physiology and a doctorate in endocrinology, Professor Al-Suhaimi authored more than 50 peer-reviewed articles dedicated to the human and animal endocrine systems. In addition, Dr. Al-Suhaimi coauthored several endocrinology books and chapters. Her book titled *Endocrine Physiology* in Arabic is taught in many educational organizations throughout Saudi Arabia. Professor Ebtesam is an active mentor and engaged supervisor of all graduate students at the IAU and IRMC. She is also a highly respected life scientist who served IAU as a Vice Dean for Scientific Research from 2009 till 2018, promoting organizational research cooperation between fundamental and applied research groups and teams. Professor Ebtesam is a member of the Endocrine Society, Saudi Biological Society, and the Saudi Society of Endocrinology and Metabolism and serves the greater scientific community as an Editorial Member and Reviewer of several peer-reviewed journals.

Introduction to Endocrinology

1

Ebtesam A. Al-Suhaimi

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Abstract

Endocrine (hormones) system and central nerve system are two types of communication system between different parts of the body through chemical and electrical signals, to keep the body homeostasis against internal and external stresses. Endocrine system controls important functions such as metabolism, reproduction and homeostasis by regulating secretion of molecular messengers known as hormones from glands located throughout the body. This chapter defines the location and function of endocrine glands and explains how coordination between endocrine and nerve cells regulates secretion of hormones, neurotransmitters, cytokines and electrical signals. Hormone has been defined primarily as a stimulant, inhibitor, or chemical messenger that after releasing in the systemic circulation imparts specific change in cellular activity of targeted cells. Present classification of hormones delivery describes autocrine signal where the sender cell is the origin/identical to the receptor cell. Matching to this state, paracrine signalling defines signalling from a hormone-producing cell to a near target cell. Juxtacrine signalling explains the delivery of signals from adjacent cells by direct contacting cell contact, whereas endocrine signalling (classic model) defines the signalling between endocrine cell and the receptor cells (distant cells/organs) via the blood circulation. The classic model of endocrine functions is greatly improved with the field of intracrinology which is becoming extensively recognized. Intracrine principal concepts have been accepted as intracrinology to study physiological functions and to develop strategy for advanced drug treatments. Signalling protrusions is an emerging function of contact-mediated cell message that can deliver signals in both ways, from sender (endocrine cell) to target cell and vice versa in directly contact through extended distances. These mechanisms are effective in normal functions, tissue development and diseases. This emerging concept of the various signaling could be applied on the sites that synthesize hormones and target cells responding to hormones. Generally, hormone is an organic molecule synthesized biochemically and secreted by cells of endocrine glands in intracrine, juxtacrine, paracrine, or autocrine signals. Hormones can be classified into peptides and proteins, steroid hormones and amino acid derivatives according to their chemical nature, secretion pattern and mechanism of action. Terpenes are also type of hormones that varied greatly and contain retinoids, carotenoids, dolichols, steroid hormones, aromatic metabolites. Aberrant or mis-regulation of hormone signalling pathways has been related with inflammatory disorders including cancer, diabetes, neurological and cardiovascular diseases. Recent data evidenced the role of long non-coding RNAs (lncRNAs) in tumour initiated in organs that play endocrine functions.

Keywords

Steroids · Peptides · Glycoprotein · Amino acid derivatives · Ectopic hormones · Terpenes

Abbreviations

ACTH	Adrenocorticotropic hormone
FSH	Follicle-stimulating hormone
FSHRH	Follicle-stimulating hormone-releasing hormone
hCG	Human chorionic gonadotropin
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid-stimulating hormone

1.1 Comprehensive and Classical Definition of Hormones

The word hormone is derived from the Greek *hormao* meaning 'to spur on', which indicates that hormone is a stimulant or an inhibitor chemical messenger that is responsible for a specific change in the cellular activity of its target cell. Hormones are secreted in the bloodstream to bring about the molecular effects. Hormones can be excitatory such as growth hormone as well as can be inhibitory such as somatostatin. Simply, hormone can be defined as a secreatory biochemical organic molecule from the cells of the endocrine glands within the body (in vivo) (Fig. 1.1) or outside the body (in vitro) in small quantities. Hormone is carried by the blood or intracellular fluids to the target site where it binds to the specific receptors on the target cells, tissues, or organ, consequently produced conformational changes in the vital and dynamic functions of the body. In contrast, several studies have shown that it is not necessary that all hormones follow the same route for the delivery to the target site because few hormones are not reaching the system circulation and produce their effects through autocrine or paracrine actions. Therefore, understanding of cellular pathways, receptor binding and route of delievery can make more comprehensive approach to uncover the term of hormone (Ironsid 1991).

1.2 Hormonal Delivery Signalling

Hormones utilize different mechanisms of cell signalling to produce their biological effects (Fig. 1.2). As the endocrine system regulates the entire body functions, classic model of endocrine functions and discrete research areas of hormones signals were integrated to provide high capacity and effective responses between secreted and receptor cells. Many delivery signals have been evidenced and showed ability of particular hormone to exert its classic endocrine signal and novel actions using other

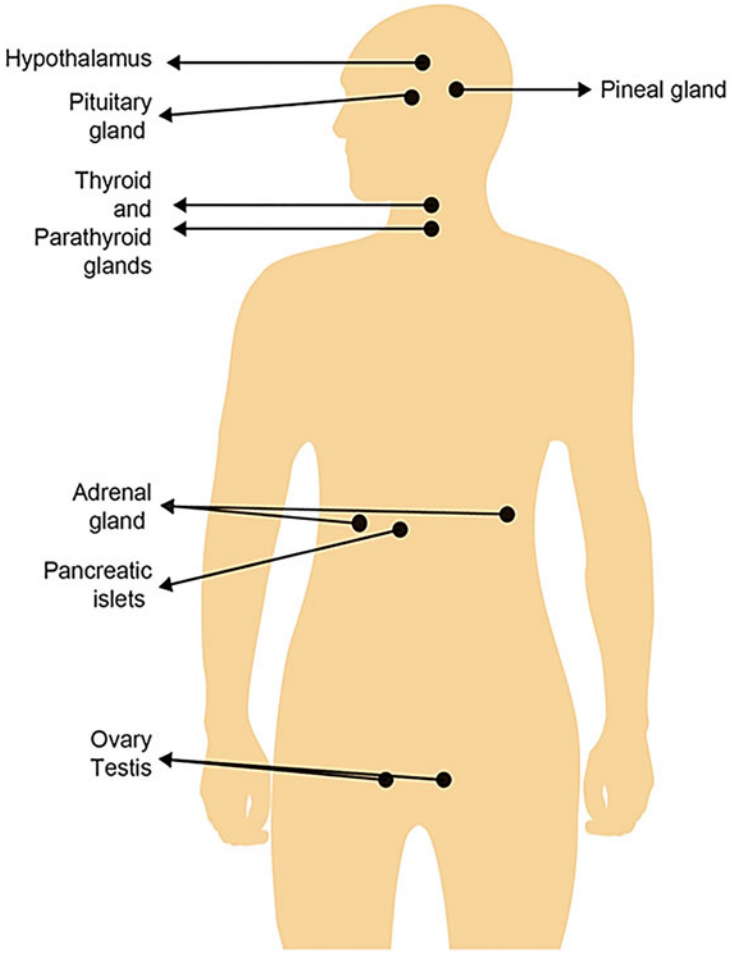

Fig. 1.1 The endocrine glands in human body, distribution of the principal endocrine glands in the body. In addition to hormone-producing tissues in other organs like skin and adipose tissue and autocrine hormone-producing cells

different delivery signals. In this chapter, mechanisms of hormones deliveries, enables cross-talks and signalling pathways with other cells. Underlying biological mechanisms, hormones signalling with trials of developed biomarkers may help in potential management for many diseases.

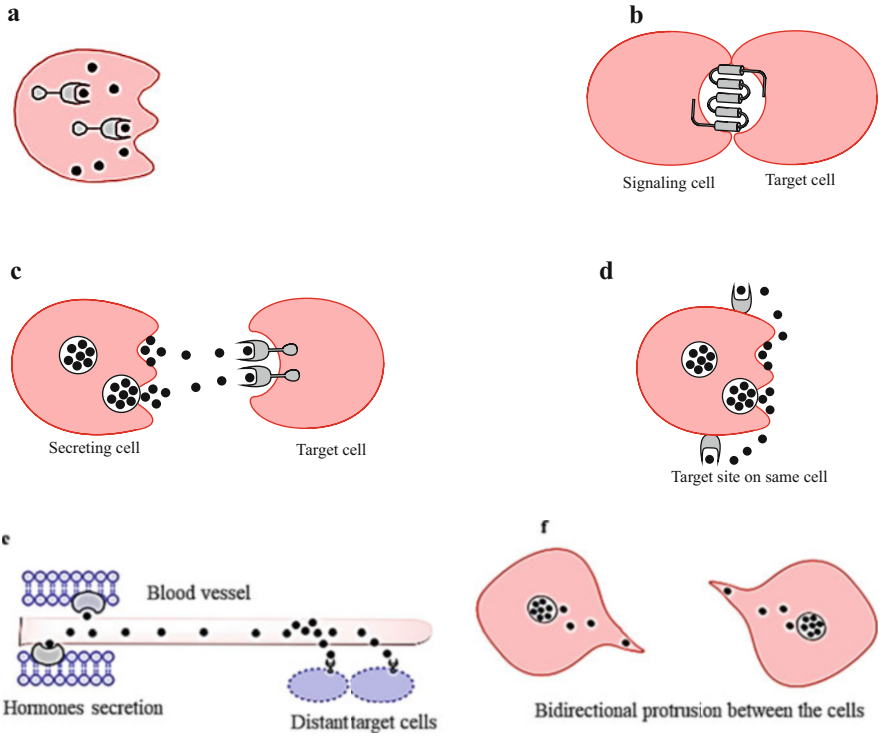

Fig. 1.2 Hormone signalling pathways. Hormone utilizes different mechanism of cell signalling to produce their biological effects, they are: (**a**) Intracrine signal, signals into the cell, (**b**) Juxtacrine signalling (signal between juxtacrine cells), (**c**) Paracrine signalling (signals between cells and its neighbouring cells), (**d**) Autocrine signalling (signal produces from a cell and received by the origin cell), (**e**) Endocrine signalling (signal between the sender cell to target cell via blood circulation), (**f**) Protrusions signalling (mechanism has been specified which utilizes cell protrusions to communicate biochemical signals by frontal contact through long distances)

1.2.1 Intracrine Signal

It could be defined as signalling of the hormone within the cell of origin. Richard et al. identified intracranially as the knowledge of the intracellular functional actions, regulation, trafficking and responding to extracellular peptides and proteins signalling (Re 2014). Intracrine signalling is a way of communication involving the direct action within the secreting cell. This type of signalling pattern is based on internal autocrine loop between the growth factor and intracellular receptors. For example, importance of both sex steroids and immune activity has been recognized in metabolic regulation. Endocrine classic model of sex steroid signal is released from the gonad to receptor cells, including immune cells. This endocrine model manages the broad capacity of immune cells to metabolize and produce sex steroid hormones, permitting the production of the steroids to intracrine signal—means it produces sex

steroid and signals it within the cell of origin. Intracrine function model permits highly cell-independent regulation for exposing of sex steroid. Secretion of sex steroid by immune cells can enable paracrine signalling actions in adjacent cells within metabolic tissues. This indicated that immune cell intracranially expressed sex steroid production using either intracrine or paracrine signalling have been well established. This has promoted its role in autoimmune diseases, cardiovascular system and cancer as reported by Rubinow (2018).

1.2.2 Juxtacrine Signalling

Juxtacrine signalling is intercellular communication pathway, in which the receptor (protein) of the signal as well as the ligand (protein) is anchored in the cell plasma membrane, so juxtacrine signalling depends on direct contact between the membranes of the communicated cells (Rozante et al. 2007).

Juxtacrine signalling mediates three types of interactions between the adjacent cells. First, direct interaction of ligand from one cells and receptor on the adjacent cell. Second, binding of receptor to its secretory ligand by another cell. Third, the signalling takes place through diffusion between adjacent cells. Peptide hormones can act by juxtacrine signalling because peptides can bind to the cell membrane as well as juxtaposed with cell receptors. Buckingham et al. (2006) found that annexin 1 acts as a paracrine and juxtacrine mediator of glucocorticoids in the neuroendocrine system (Re 2014). Juxtacrine signalling is actionable in many key cellular processes particularly in the development process. A good biological model framework has been implemented to develop a novel three-level distinct model for the neurogenic network and its contribution in neuroblast separation (Rozante et al. 2007). Juxtacrine signalling supported release of many growth factors such as angiogenic factor vascular endothelial growth factor (AFVEGF) in direct cocultures, additionally, paracrine signalling promoted release of another growth factor (arteriogenic factor platelet-derived growth factor (AFPGF) in indirect cocultures (Buckingham et al. 2006) and (Santoro et al. 2020).

1.2.3 Paracrine Signalling

Hormones that are secreted by adjacent cells are known as paracrine secretion. In this type of signalling, hormones can pass through or exert an effect over short distances by diffusing across the intracellular space to act as regulatory substances between adjacent cells like glucagon. Within the pancreatic islet, endocrine hormones also compose a complicated paracrine connection with other supporting endothelial, immune cells, nerve terminals and signalling molecules controlling cellular functions. Modification of these signals has possible outcome for diabetes development, progress and curative intervention. Damage of beta cells, decreased endogenous insulin release and dysregulated glucagon hormone secretion are hallmark properties of both type 1 and 2 diabetes that not only influence systemic control of

glucose, but also participate in the physiological functions and cells survival within pancreatic islet. Recent researches have revealed new physiological roles in the islets and identified previously unknown paracrine signalling and mechanisms (such as somatostatin and ghrelin paracrine functions) and to what extent the paracrine signals regulate islet endocrine function and its survival, its effect on the disturbance that happens in diabetes and prospect therapeutic plans to maintain beta cell cluster and physiological function (Hartig and Cox 2020).

1.2.4 Autocrine Signalling

This type of signalling involved the production of an extracellular mediator/hormone by a cell followed by the binding of that mediator/hormone to receptors on the origin/same cell to trigger transduction signalling leading to cascade of responses in the cellular functions. Autocrine and paracrine signalling mechanisms are difficult to research classically because of the limited techniques and the very low concentrations that are implicated. Computational model and a microfluidic cell culture platform could be carried out as alternative tech and can control the removal of molecular agents released by cells into the media. The existence of soluble autocrine/paracrine secretion participates in their viability in in vitro culture. Multiplex microfluidic stage was developed to constantly strip the autocrine/paracrine secretions to downregulate diffusible signalling. By comparing cell growth and differentiation in side-by-side chambers with or without addition of cell-secreted factors, they found that autocrine/paracrine signalling pushes neuroectodermal obligation (King 2007; Kang 2013). Also, activity of the prostaglandin is regulated by autocrine signalling. In the ovary, the proteolysis of the extracellular matrix is energetically controlled by plasminogen activator inhibitor (PAI). Activin (hormone released by the ovary) upregulated the expression and promoted the production of PAI-1 in an autocrine/paracrine signalling communication (Chen et al. 2020).

1.2.5 Endocrine Signalling

In this type, signalling hormones are sent into the bloodstream (endocrine secretion) and act on distant target cells. Endocrine glands such as the pituitary gland, pineal, thyroids, parathyroid, adrenals, ovaries, testis depend on this type of signalling. They play essential and vital physiological functions in the body; however, disturbance or inhibition of one of their endocrine signal leads to subsequent disturbance in the target organ functions. Signalling of hormones of pituitary, thyroid and adrenal is essential for life survival as they regulate. While signalling of ovary and testis endocrine hormones is essential for regulating growth and reproduction. Transfer of the endocrine signal via circulation for distance exposes it to all cells but no one can receive it except those cells that express specific ligands on its receptors, this triggers cellular transduction. Therefore, endocrine signals stimulate responses in slow mode in the receptor cells but influences longer time.

1.2.6 Protrusions Signalling

Interestingly, a surprising information exchange mechanism has been specified which utilizes cell protrusions to communicate biochemical signals by frontal contact through long distances. These protrusions signalling can transfer signals in both opposite ways, from sender cell to target cell and vice versa. Knowing the morphology and mode of function of these coding protrusions in many tissues may force scientists to review contact-dependent cell communication. The researchers focused on protrusions, cytonemes in addition to tunnelling nanotubes. The protrusions signalling arise as essential constitutional component of a vibrant and vital communication network for physiological growth and tissue homeostasis (Mattes and Scholpp 2018). Side signals can be intermediated both by junctional connect between neighbouring cells and through cellular protrusions that permit non-neighbouring cells to react with another different at a distance. Hadjivasiliou et al. (2016) reported how exactly these distinct types of cell–cell contact can be signalling intermediated physically and contribute in the production of complex modality without need of diffusible morphogens or pre-modality. A model has been developed of lateral signalling that depends on a single receptor/ligand couple as example by Notch and Delta. Based on this pattern, in which Delta can isolate Notch, a range of modalities similar to those ideal of reaction–diffusion systems is noted, significantly, these models are self-organizing, thus that local interactions push tissue-scale model. Protrusions can mainly produce types of patterns that contribute to many signalling and to pattern improvement. Interestingly, protrusions can, initially, produce various types of modalities as well as contribute to long-term signalling and to improve the pattern.

Summing up, endocrine system exerts its multiple actions through paracrine, juxtacrine, intracrine, autocrine and endocrine in addition to protrusions signalling in a particular microenvironment as well as in distant parts of the body.

1.3 Endocrine Glands: Location and Functions at Glance

Endocrine system includes classic endocrine glands and those newly identified as hormone secreting organs/tissues/cells that play main and comprehensive functions to enhance the regulation and haemostasis. They are functioning in harmonious, exquisite and precise mechanisms. Science continuously provides more consistency in each systematic, cellular and molecular functions. Disfunction in hormone signalling pathways has been related to multiple disorders.

Recent data regarding the role of long non-coding RNAs (lncRNAs) in tumour originated from organs that play endocrine's functions such as pituitary, adrenal, pancreas, prostate, ovarian and testicular cancers. Data extremely supports the role of lncRNAs in the pathogenesis of tumours initiated from these organs. Furthermore, specific genomic position within lncRNAs has been associated with risk of these tumours. Clearly, lncRNAs are putative biomarkers for tumours originated from organs which act as an endocrine function (Ghafouri-Fard et al. 2020). The main

glands of the endocrine system have been summarized in Fig. 1.1 which includes the following:

1.3.1 Pituitary Gland and the Hypothalamus Control

Pituitary gland (hypophysis) is the master endocrine gland situated on hypophysial fossa of the sphenoid bone in middle cranial fossa of brain. It plays vital role in controlling several body functions and related endocrine glands. The gland has structural and functional relationship with hypothalamus. The three parts of pituitary gland based on their origin and functions are divided into Adenohypophysis, Neurohypophysis and Stem cells marginal zone. Pituitary gland resides in the brain and regulates the function and production of other endocrine hormones by secreting its own 'stimulating' hormones such as gonadotropins (LH and FSH), growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin, antidiuretic hormone and oxytocin. The pituitary gland works in close proximity with central nervous system through the hypothalamus of the brain to control body functions. Since the hypothalamus releases releasing/inhibiting hormones to control pituitary functions. These hormones are divided into two hypothalamic groups; the first group that passes through special portal blood vessels towards anterior pituitary, while second is neurohormones group produced by the hypothalamus and released by posterior pituitary. On the other hand, there are organized structure and function networks of the endocrine cells of the pituitary that coordinate response of endocrine cells to stimulant; these cellular networks are created during foetal growth, they maintained or exposed to modification in adulthood, participating to gland's plasticity. Abnormality in any of the developmental processes of pituitary may drive to inborn hypopituitarism (reduced hormones secretion) that includes series of disturbances either isolated or collective hormone deficiencies including syndromic disorders (Alatzoglou et al. 2020).

1.3.2 Thyroid Gland

Thyroid gland sits in the front of the neck, it controls metabolism and body homeostasis by secreting thyroid hormones (T4 and T3). It works through coordination by TSH from pituitary gland through a feedback mechanism. Thyroid gland is a highly vascularized organ consisting of two lobes connected by isthmus and located in neck. One of the lobes lies at the left and another at the right to fourth tracheal rings and inferior to larynx. The shape of thyroid varies depending on the individuals. The gland is composed of basic functional unit follicle also known as acinus. Follicles shape and size variation occurs with thyroid-stimulating hormone (TSH) activation or inhibition. The main role of thyroid gland is to produce iodothyronines in the form of the hormones T3 and T4. The hormones bioactivity is different, derived from amino acid tyrosine and is bound to iodine. Thyroid hormones metabolism or deiodination is demonstrated in Chap. 5 along with stem/

progenitor cells of the thyroid gland, thyroid follicles, thyrocytes and C cell differentiation.

1.3.3 Parathyroid Gland

Parathyroid glands are also located in the neck behind the thyroid gland and regulate some blood minerals and vitamin D levels through parathyroid hormone. Parathyroid hormone, C cell (parafollicular cell) hormones (calcitonin) and gonads hormones in combination with other hormones are main regulators for free calcium and phosphorus concentrations in the blood. Parathyroid glands are composed of small sized four glands. Parathyroid hormone plays essential function in many physiological functions by participating in regulation of minerals like calcium and phosphorus, also in combination action with the active form of vitamin D. Recently, it has been evidenced that parathyroid hormone has pharmacological beneficial effect and could be a potential therapeutic utilization for bone formation in case of osteoporosis. Chapter 6 discusses the location, tissue structure of parathyroid glands functions, PTH hormone on the ionized calcium concentrations.

1.3.4 Adrenal Glands

Adrenal glands are paired gland located on the upper pole of each kidney where they produce a number of different hormones. The outer part known as adrenal cortex produces cortisol, aldosterone and sex hormones, whereas the medulla part known as adrenal medulla makes adrenaline. Secretion of adrenaline is regulated by central nervous system. In addition to the essential functions of the gland's cortex and medulla regions, the adrenal functions antagonistically to enable melatonin from the pineal gland to protect against heat. Characteristics of adrenal cortex hormones, different stages are shown in the synthesis of adrenal cortex hormones. The three adrenal cortex zones (zona glomerulosa, zona fasciculata, zona reticularis) are briefed in Chap. 7 with detailed physiological functions of the zona fasciculata hormones with regulation of the adrenal cortex. Recent information on adrenocortical stem/progenitor cells was listed including localization in the adrenal capsule, subcapsular region, juxtamedullary region, or between the zona glomerulosa and the zona fasciculata as well as their functions.

1.3.5 Pineal Gland

Pineal is a neuroendocrine gland with pineal size and structural features. Pineal gland produces group of hormones, the main one is melatonin. Pineal gland functions and the physiological roles of melatonin are explained in Chap. 7. Melatonin plays key functions to control various physiological systems and programs puberty's timing. Original melatonergic systems are irritated by new lifestyles of

humanity via changed circadian entrainment, severe suppression by light and self-management of melatonin medication (Gorman 2020).

1.3.6 Pancreas

Pancreas gland located in the upper abdomen region, it plays two important roles as digestive exocrine gland and hormones releasing endocrine gland. Exocrine gland composed of acini secretes enzymes for digestion. It mainly controls blood sugar levels in the circulation through insulin, glucagon and somatostatin. The pancreatic islets are the main endocrine tissue in the pancreas, it is an intensive cellular component include various cell types with endocrine/paracrine functions play vital physiological roles in the regulation and metabolism of glucose, fat and protein homeostasis. Endocrine pancreas are clusters or islets that are responsible for important hormones secretion such as peptide hormone insulin, somatostatin, glucagon and pancreatic polypeptide. Dysfunction in pancreatic islet leads to metabolic disorders including diabetes mellitus. Chapter 8 describes the cells of pancreatic islets (alpha, beta and gamma cells), physiological and metabolic functions of insulin, correlation between immunity/insulin imbalance, cardiovascular functions with insulin imbalance. In particular, secretory vesicles of beta cells secretions play roles in glucose transportation, carbohydrate metabolism in liver, muscle tissues, adipose tissue and protein metabolism in liver and muscle, fat metabolism in muscles and adipose tissue. There are many factors that influence insulin secretion.

1.3.7 Ovaries

Ovaries are located inside the female pelvis and responsible for the production of sex hormones such as oestrogen and progesterone. The endocrine, genetic and metabolic processes imply female reproduction is sophisticated, exhibiting complex functional development during female lifetime. Normal functions of ovaries require strict surveillance of germ cell meiosis and the quantitative stimulation or wastage of ovarian follicles from the primordial follicle aggregation over female's reproductive lifespan. The mechanics regulating the activation of specific subsets of primordial follicles function in prolonged period are complex, it requires coordination of multiple molecular signalling. Ovarian follicle demonstrates variable phases from first formation in embryo stage to stimulation, development and endocrine regulation through the normal reproduction in lifespan. Ovarian hormones are required not only for regulating reproductive process but also for growth, female characters and differentiations and fertility. The most prominent event in female reproduction is ovulation, and synchronous alterations in the endometrium and other ovarian hormones-sensitive organs and tissues. As the goal of this physiologic advancement is to achieve ovulation and gives sufficient environment for ova implantation, gestation, the completion of female fertility (Rojas 2015; Cordeiro et al. 2015).

1.3.8 Testes

Testes are hanging in the male scrotum and control male characteristics through production of testosterone. Reproduction is an important biological process of species evolution; it leads to new offspring from parents. Pituitary gland in coordination with hypothalamus plays a key role in reproductive system, differentiation and different physiological functions in the entire stages of life and its circadian rhythm in both male and female. Chapter 9 describes the roles played by brain, endocrine system and gonads axis via complex communicating signals. Male gonads have many physiological functions performed by testis, interstitial tissue (Leydig cells) and peritubular myoid cells. Also, Sertoli cells act as nurse cells. Spermatogenesis and spermiogenesis are necessary processes for sperms maturation. Gonad's steroid hormones (androgens) characteristics play roles in male reproduction, biological actions along with the regulator hormones from hypothalamic–pituitary–Leydig cell axis. Ovaries are female reproductive glands. Chapter 9 also describes the tissue zones of ovaries and two main functions (exocrine and endocrine) regulated by the hypothalamus and the pituitary. Female sex hormones in pre-puberty and post-puberty are important in growth also. Steroid hormones act as primary role in endometrium, regulation of ovarian functions, puberty as well as by immune system. Different phases and processes happen in the ovarian cycle to regulate gonadotropins, follicular growth, steroid synthesis, non-functional corpus albicans (infertile ovum). The ovarian cycle includes pre-ovulatory phase, ovulation phase and post-ovulatory phase. Synthesis of ovarian hormones steroids after puberty is discussed in Chap. 9 with important functions of progesterone, regulatory roles of inhibin, activin and follistatin in physiology of testis and ovary. The menopause in elderly women and andropause in men is regulated by endocrine and immune systems. After the prime reproductive period, ageing starts, and menopause occurs because of the immunoregulatory changes that lead to cessation of neo-oogenesis and follicular renewal in vivo despite the existence of germline stem cell precursors.

1.3.9 The Secondary Endocrine Organs

The endocrine function is an important feature which is involved in each organ in addition to the classic endocrine glands and tissues. Apart from these some other secondary endocrine organs such as heart produce atrial natriuretic peptide and brain natriuretic peptide. All hormones coming to lung through venous blood are exposed to qualitatively and quantitatively contribution in their flow condition in arterial circulation. In addition to its excretory functions, kidney produces two types of hormones renin and erythropoietin. Renin regulates blood pressure regulation, whereas erythropoietin regulates red blood cells production under hypoxic conditions or haemorrhage. Vitamin D (1–25 dihydroxy vitamin D3) is converted to its active steroid form in kidney. Furthermore, stomach's wall produces gastrin, while gut releases glucagon-like peptide 1 (GLP–1) and ghrelin regulates

metabolism and appetite. Liver produces and releases group of hormones such as insulin-like growth factor-1 (IGF-1) which is known as somatomedin, Angiotensinogen (the precursor of Angiotensin), Hepcidin, Thrombopoietin and Betatrophin. Intestinal hormones. Spleen has an endocrine as alternative function for protein metabolism. Adipose tissue hormones and some neuropeptides are recognized in salivary glands, lingual epithelium and in the saliva itself. Adipose tissue regulates metabolism and energy by releasing a number of hormones such as leptin, adiponectin, resistin and visfatin. Another example is thymus; the immune gland produces thymopoietin and thymosin. Skin produces vitamin D3. Bone secretes osteocalcin.

So, it could be concluded that in addition to the known endocrine glands, most if not all other organs in the body have a secondary endocrine function in addition to its primary function.

1.4 Update on Ectopic Hormone Secretion

Abnormal hormonal secretion could be defined as described by Lloyd (1990).

- Ectopic Hormone Syndromes: Ectopic inconvenient hormone synthesis (paraneoplastic endocrine syndrome) is the production of hormones by tumours derived from tissues that are not normally hormones-secreting tissues.
- Eutopic or entopic hormone synthesis by tumours derived from precursor tissues that normally produce this hormone.
- These definitions were valid until recent advances reported that numerous non-neuroendocrine tissues and derived tumours can also synthesize polypeptide hormones with several directional discrimination.

The term ‘ectopic hormone production’ is referred to hormones produced by tissues that are not endocrine physiological origin, in a way enough to give rise clinical effects. Ectopic hormones are hormones generated by tumours originated from tissues that are not usually involved in the synthesis of that hormone. So, it is not limited to the well-known endocrine tissues that produce hormones, but all cells keep the genetic ability to produce hormone, it is progressively known that malignant cells can express genetic hormonal active peptides but in an unusual mechanism used in normal hormone-producing tissues, since the produced peptide is a fragment or precursor of the normal hormone. The production of ectopic hormones is usually looked as inconvenient and pernicious, as these hormones can lead to dysfunction of many metabolic physiology that depend on that hormone/s. The ectopic hormones are released by unusual sources such as pancreatic islet cell carcinomas that release ACTH, which normally released by the pituitary. Another example is the unsuitable (ACTH) production by some small cell carcinomas of the lung. The most common example of ectopic hormone secretion is PTHrp, which is secreted by 10% of tumours and leads to hypercalcaemia of malignancy (Hinson et al. 2010). A sequence of selective venous sampling (SVS) parathyroid hormone followed by localization by 4D-computed tomography can specify the accurate site of ectopic

parathyroid adenomas in a patient when classic non-invasive images technology search goes wrong or failed (Suntornlohanakul and Leelawattana 2020).

A molecular form of the hormone might circulate differs from that produced from the eutopic tissue. One notion proposes that some essential alterations happen at the genetic level permitting new gene expression for that tissue. Thus, neoplastic alteration will lead to definite genes to turn on (mutate), while other genes to turn off. Another notion proposes that the neoplastic cell is generated from a stem cell that was able to express the gene in its early phase then it is suppressed later, which is followed by neoplastic transmutation, the cell suffers de-differentiation and recovers some of its growth features. It was suggested that some very expressed genes that have been transcribed but not translated at physiological situation may, as a result of neoplastic transmutation, be magnified and translated because of the effect of various supporters (Wassif and East 2014). Various hormonal production such as increased level of morning cortisol, higher tumour grade and also in diabetes mellitus were associated with shorter overall survival. Ectopic Cushing's syndrome happens as a result of (ACTH) production from neuroendocrine tissue (neoplasm) which is a rare and defy disease. Progress of Ectopic Cushing's syndrome in patients with a non-functioning neoplasm may point to tumour's progression. Various hormones production has to be looked like as an ill prediction, marker in Ectopic Cushing's syndrome patients and should lead to massive treatment plan (Lase et al. 2020). ACTH-based Cushing's syndrome, produced by a pheochromocytoma is very rare also, but must be looked as a potential source for ACTH release. The diagnoses defy of this case can be achieved if a rigorous protocol is done for detecting the source of ACTH (Krylov et al. 2020).

Although ectopic hormone production is well known, but an ectopic production of prolactin is rare. A new case of a 47-year-old woman showed hyperprolactinemia has been recently reported. Cabergoline medication did not lower the prolactin concentration absolutely, but removal of a big uterine leiomyoma recovered both bad effects of that ectopic prolactin production; the high level of prolactin and the hypogonadism. The eradicated leiomyoma tissue showed immunostaining for prolactin, assuring for the first time that a uterus leiomyoma was the reason for hyperprolactinemia. This status explains the necessity to look to an ectopic origin of prolactin production in hyperprolactinemia case that it is related to a massive sellar bloc that did not response at all to cabergoline's medication (Sachdev et al. 2020).

1.5 General Characteristics of the Endocrine Glands

Endocrine glands of the body exert important and pervasive effect in regulation of number of processes including metabolic processes through secretion of chemical messengers into bodily fluids and blood vessels, as well as complementing the nervous system. Hormones play role in gene transcription. Receptors of all types of hormones regulate gene transcription either by stimulating transcription agents or by functioning as transcription agents. In addition to that transcription is not a plain

process which a receptor binds to DNA and activates RNA polymerase at an inception location, but also needs a group of enzymes (complex of holo-enzyme), before transcription is started down-flow of the promoters and factors, so, a steroid receptor, for example, may have transcriptional action only when promoters/repressors link with of the molecule in specific part. These factors may function separately of ligand binding, others need ligand linking before activating (Nussey and Whitehead 2001).

The nature and functions of endocrine glands is highly marvellous. Life is present via maintenance of networks of dynamic balances that work forever challenging the intrinsic and extrinsic factors and environmental stressors. Consequently, stress is known as a factor threatened homeostasis that must be re-adjusted through a complex process of physiological and adaptive responding functions. Hormones play critical role to coordinate in both normal and threat homeostasis. The endocrine system is a 'careful, marvellous and wisdom' since it consolidates its actions to reset body homeostasis and to advance the chances of maintenance and survival (Chrousos 2007). Main functions of endocrine system can be summarized as follows.

The ductless glands are called endocrine (came from the Greek *endon* means 'inside'). These glands contain both duct-free secretion. It flows directly from the cell to the interstitial spaces or into the blood circulation directly. In 1905, the British physiologist Ernest H Starling, discussed with Cambridge authorities, called these secretions 'hormones' (from the Greek *hormao*, means 'to excite') (Sengoopta 2005). Endocrine gland is not similar to the exocrine gland that secretes its secretions into ducts to reach its cavity or out of the body (Fig. 1.3a, b).

- To carry out their functions efficiently, the endocrine glands have a small size and an abundance of nearby blood vessels and capillaries into which they can directly secret hormones.
- Endocrine glands are rich in blood vessels and capillaries, also, hormones are dynamically attracted to the cells by fenestrated condensed capillaries to produce pulsation, this pulse is decoded by target cell to trigger the biological response. To produce hormone pulses, endocrine system has improved mechanisms of actions to restrictedly control blood and oxygen perfusion, control hormone utilization, manage endocrine cell reactions to secretory signalling and from the perivascular area into the blood circulation. This blood richness expedites its flow and coordinates cell activities and outcome either in normal physiological or pathological states of the glands (Schaeffer et al. 2011).
- A complex interaction is involved between the endocrine and nervous system to regulate the number of hormones directly or indirectly the body to function in a balanced and regulated manner. For example, mammary glands growth and milk production are not only a result of the action of growth hormone and prolactin but also involve other hormones secreted by the pituitary, gonads, thyroid and other glands. Without this complementarity, the organs of the body would not be able to perform their functions (Rochel and Belorusova 2017; Tritschler et al. 2017; Cerf 2013; Ghorbani and Naderi-Meshkin 2016).

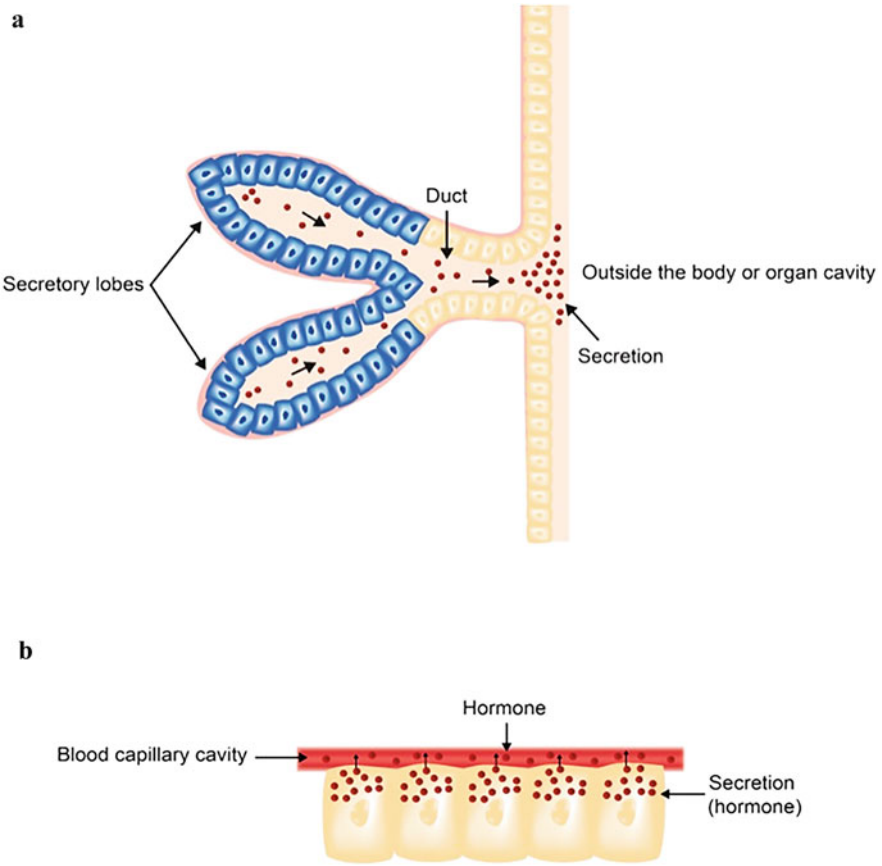

Fig. 1.3 (Upper—**a**) The glands with external secretion (exocrine), note the direction of the movement of the secretion (inside). (Lower—**b**) Cells from a gland with internal secretion (endocrine), note the direction of movement of the secretion directly into the bloodstream without any ducts

- The endocrine glands are highly plastic organs, displaying plasticity to cope with different conditions such as external or internal stresses as well as challenges like temperature, metabolic syndrome by altering their endocrine commitment. Endocrine glands have the ability to differentiate and regenerate continuously by different mechanisms (feedback mechanism/signal transduction) during stress conditions. There is compelling evidence that islet cell modifies its mass, morphology and function (islet plasticity) in various metabolic conditions. Islet cells are actively differentiated to adopt with physiological or pathological conditions such as obesity and pregnancy to maintain normoglycemia (Tritschler et al. 2017). In line with this, insulin resistance has been shown to impact islets by increasing the proportion of β-cell size in the hyperglycaemic conditions as compared with insulin-sensitive control subjects (Cerf 2013).

- Studies have also shown the contribution of endocrine stem cell populations in tissue homeostasis and adaptation to internal or external environment. Stem cells have the ability to proliferate and differentiate to form the multifunctional endocrine system (Ghorbani and Naderi-Meshkin 2016). Growth factors and androgens-dependent proliferation and differentiation of Nestin-positive stem-like cells into chromaffin cells have been reported in stress conditions (Steenblock et al. 2019). Also, stem cell population can respond in diet-induced obesity via Shh signalling in Gli1-positive progenitors (Swierczynska et al. 2015). However, imbalance in plasticity or adaptation can cause various diseases such as adenomas, dysplasia and inflammatory diseases. Endocrine plasticity is of vital importance since hyper- or hypoactivity of hormones has been implicated in the pathogenesis of various diseases in humans (Tritschler et al. 2017; Steenblock et al. 2019; Swierczynska et al. 2015).

1.6 Chemical Classification of Hormones

Generally, hormones are divided into many categories according to their chemical structure, producing source, mode of actions. For example, they are four different categories according to their structural and functional differences. The categories of hormones are peptide, protein and glycoprotein, steroids, amino acid derived hormones and finally fatty acid derivatives (eicosanoids). They are further explained in Figs. 1.4 and 1.5. Steroid hormones can be also categorized according to the gland that produces them, thus this category is classified as sex hormones, adrenal cortex hormones and placenta hormones category, while peptides are produced by many glands, so they are divided according to the producing glands such as pituitary, parathyroid and pancreatic islets hormones. Releasing hormones are categorized

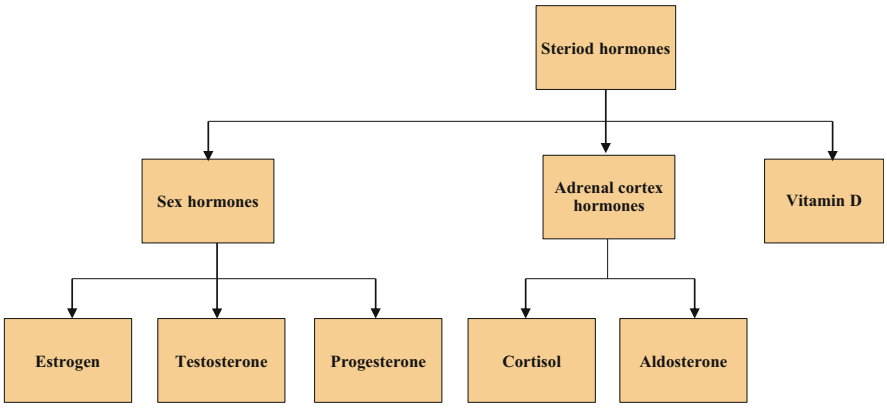

Fig. 1.4 Steroids are group of hormones produced by many endocrine glands including sex steroids (oestrogen, oestradiol, progesterone and testosterone), adrenal cortex hormones (cortisone, cortisol, deoxycorticosterone, aldosterone) and secosteroids (vitamin D)

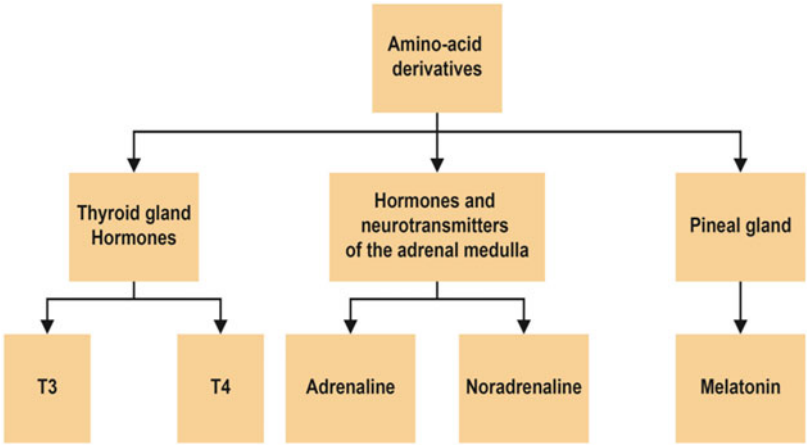

Fig. 1.5 Amino acid derived hormones group includes epinephrine and norepinephrine from medulla of adrenal glands and thyroxine and triiodothyronine synthesized in thyroid gland, melatonin from pineal gland and dopamine

based on their releasing action such as hypothalamic releasing hormones such as luteinizing hormone-releasing hormone and so on. While eicosanoid hormones are synthesized from fatty acid derivatives. Prostaglandins group is the most known group.

1.6.1 Peptides, Proteins and Glycoprotein Hormones

These kinds of hormones are variable in size, depending on the peptide sequences ranging from a few amino acids in a linear chain (peptide hormones) to a larger chain molecule, categorized as protein. Amino acids are substantial, ingredient for peptides and proteins, they work as signal transmitters. Many amino acids such as L-amino acids, D-amino acids, such as D-serine, D-aspartate, D-alanine and D-cysteine have been believed and diverse in humans. Physiological functions of these D-amino acids are gradually revealed in the endocrine system and the nervous system as well. H_2S generated from D-cysteine reduces disulphide bonds in receptors and potentiates their activity. Furthermore, D-amino acids are uncovered in the endocrine glands, such as the hypothalamus, pineal gland, pituitary gland, adrenal, testis and pancreas. D-Aspartate is being studied for the regulation of hormone release from various endocrine organs (Kiriyama and Nochi 2016).

Peptide hormones are polymers of a few amino acids ranging from less than ten to few hundreds, it could be said they are small proteins. It includes wide spectrum of hormones such as interior pituitary hormones (GH and prolactin), posterior hormones such as vasopressin, oxytocin, gastrointestinal hormones, pancreatic hormones (insulin, glucagon and somatostatin), hypothalamic hormones such as

follicle-stimulating hormone-releasing hormone (FSHRH) belong to this group of hormones. Peptide and protein hormones are gene transcription. They change extremely in size, after its release and post-translational modification. This category varies from peptides of short chain (three amino acids) to large chain (multi-subunits proteins) or linked with glucose such as glycoprotein hormones. Peptide hormones can be considered as the intracellular signalling. In addition to their actions into the cells, they also act systemically. So, they can multiple signalling to perform their actions in the target cells. Most protein hormones are synthesized in many steps in its producing cell starting with prohormones, then proteolytically snipped to produce the complete form. In another way, the hormone is originally present as a major precursor, then passes through various proteolytic cleavages to be released. Class B G-protein-coupled receptors (GPCRs) are receptors for some peptide hormones (parathyroid hormone, calcitonin and glucagon), These receptors are engaged in many physiological actions, such as metabolic and stress regulation to growth and maintenance of the skeletal system. Class B GPCRs are classified into two domains: an extracellular domain (ECD) and a helical pack that includes seven transmembrane helices (TM domain). The ECD one is involved for the high affinity and specificity to bind with hormone, while the TM domain is engaged for activation its receptor and signal conjugating to downstream G-proteins (Pal et al. 2012). Protein and peptides are secreted in more than one way. The first way of protein and peptides secretion is the common way, which is Controlled Secretion: The cell keeps hormone in its secretory vesicles and releases them in eruptional way when it receives stimulation. This keeps the endocrine cell release considerable amount of hormone in a short time. The second way is Constituent Secretion: The cell secretes the hormone from secretory vesicles once it synthesizes it without storing it earlier.

1.6.2 Glycoprotein Hormones

Apart from these, glycoprotein hormones are conjugated protein bound to carbohydrate which includes galactose, mannose, fructose. Examples of this group are thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone and human chorionic gonadotropin (hCG) produced by placenta. Glycoprotein hormones are the most complex molecules that have hormonal activities. Glycoprotein hormone has alpha and beta subunits, the alpha subunits of these pituitary and placental hormones are identical, while the different functional features of these four glycoprotein hormones are specified by the distinctive beta subunit in each one of them. Mutually actions of the non-covalently bound of the subunits are necessary for complete biologic activity of the hormones.

1.6.3 Steroid Hormones

Steroid hormones are derived from cholesterol and secosteroids. They are essential for life. This group covers various hormones that include, for example, sex steroids

(oestrogen, estradiol, progesterone and testosterone), adrenal cortex hormones such as (cortisone, cortisol, deoxycorticosterone, aldosterone) and vitamin D forms which called secosteroid shown in Fig. 1.4. Steroids such as oestrogens and testosterone play key roles in hormonal programming for sexual direction, metabolic and reproductive programming and in the neuroendocrine mechanisms required for some pathological syndromes. Furthermore, steroid hormones are important for the protective activities of progesterone on neurodegenerative diseases and the signalling mechanism involved in the origin of oestrogen-induced pituitary prolactinomas (Zubeldia-Brenner et al. 2016). Steroid hormones group plays a curial role in the body functions since they are involved in many main physiological functions including stress's survival, harm and illness, immune functions, metabolic mechanisms, inflammation, minerals and water balance, growth and evolution of sexual characteristics. In addition, steroid hormones, cortisol, is responsible for adaptation to stress and environments changeable factors. The synthesis and secretion of steroid hormones are regulated by the anterior pituitary hormones (except activated forms of vitamin D) (Kiriyama and Nochi 2016).

1.6.4 Amino Acid Derived Hormones

The amino acid-derived hormones are derived from the amino acid tyrosine and tryptophan, they are small molecules. Amino acid derived hormones are chemically modified form of amino acids by removing carboxyl (COOH) group and retaining amine (NH_3^+) group remains. Since it is amino acid-derived, its name has to be ended with *–ine*. For example, amino acid derived hormones group includes epinephrine and norepinephrine from medulla of adrenal glands and thyroxine and triiodothyronine synthesized in thyroid gland. Both of melatonin and serotonin are amino acid tryptophan produced by pineal and the gastrointestinal tract by enterochromaffin cells as well as dopamine (Fig. 1.5).

1.6.5 Fatty Acid Derivatives Hormones (Eicosanoids)

Eicosanoids are hormones derived from polyunsaturated 20-carbon fatty acids. Eicosanoids act as autocrine, paracrine signalling chemicals and hormone. Eicosanoid hormones are made up of small fatty acid derivatives with a variety of arachidonic acid. They are represented by multiple eicosanoids, include mostly from the prostaglandins, thromboxane, leukotriene, resolvins, lipoxins and eoxins. Prostaglandins are prominent example of this group.

Eicosanoids are synthesized from intake essential fatty acids and rapidly degraded within the body naturally, therefore allowing only cell-specific actions. Many eicosanoid metabolites can be secreted in urine. NSAIDs suppress the cyclooxygenases (COX-1 and COX-2), but not the lipoxygenases. Adrenal corticoids (glucocorticoids) inhibit PLA2 activity, thus inhibiting the availability of arachidonate to form eicosanoid and they also inhibit COX-2 action. TXs are

synthesized in blood platelets, once they release, platelets are aggregated and vascular smooth muscle is constricted. Prostacyclin (PGI2) are produced by vascular endothelial cells and usually suppresses the function of thromboxanes. Thrombin, PAF and PGI2 boost vascular smooth muscle relaxation. Omega-3 as polyunsaturated fatty acids provides series 3 prostanoids and the series 5 leukotrienes. Thrombin, ADP, collagen, PAF and serotonin (5-HT) boost aggregation of platelets (Engelking 2015). Eicosanoids are a family of bioactive lipid intermediators that regulate a wide spectrum of physiological functions and pathological effects and show pro-inflammatory property. Moreover, lipid-metabolizing enzymes and rate-limiting step in lipid-controlling and lipid-making metabolic series became objectives for development of many drugs (Yuan and Xu 2016).

1.6.6 Terpenes Hormones

Terpenes or terpenoids are also known as isoprenoids. They are a large family in nature, active organic hydrocarbon chemical complex, which are generated by an assortment of plants from the five-carbon isopentenyl diphosphate compound isoprene structure bulk. They present a massive structural variety. The isoprene polymers are named terpenes (Trevor 2019). Around 60% of famed natural products are terpenoids (Jackson 2010). It is recently reported that triterpenoids extracted from birch have antitumour and anti-human immunodeficiency virus effects (Yin et al. 2020). Terpenes are varied in its structure and functions and contain retinoids, carotenoids, dolichols, steroid hormones, aromatic metabolites. The steroids as well as sterols are biologically formed from the precursor terpenoid which connects to proteins to promote their attachment to the cell membrane. Synthesis of isoprenoids is stimulated by a family of enzymes called prenyltransferases (Chang et al. 2021). Synthesis of nitrogen-containing bisphosphonates (N-BPs) like zoledronates is a novel strategy targeting new triazole bisphosphonate-based isoprenoid biosynthesis inhibitors which showed noteworthy antiproliferative effect versus many human tumour cell lines include lines from pancreas, breast and lung with 4–12 times more efficiency than zoledronate (Legigan et al. 2021). N-BPs have antitumour merits through suppressing farnesyl pyrophosphate synthase (FPPS) (Dunford et al. 2001). N-BPs does not only suppress FPPS, but also deteriorates the biosynthesis of more longer isoprenoid compound (Kavanagh et al. 2006).

1.7 Conclusion

Endocrine system and central nerve system are two types of communication system between different parts of the body through chemical and electrical signals to keep the body homeostasis against internal and external environmental changes. Endocrine system controls important functions such as metabolism, reproduction and homeostasis by regulating secretion of molecular messengers known as hormones from glands located throughout the body. This chapter defines the location and

function of endocrine glands and explains how coordination between endocrine and nerve cells regulates secretion of hormones, neurotransmitters, cytokines and electrical signals. Hormone has been defined primarily as a stimulant, inhibitor, or chemical messenger that after releasing in the systemic circulations imparts specific change in cellular activity of targeted cells. Generally, hormone is an organic molecule synthesized biochemically and secreted by hormone-producing cells and deliver the message to the target cells in different mechanisms including one or more of these signalling: endocrine, intracrine, juxtacrine, paracrine, autocrine and protrusions signalling. In addition to the known endocrine glands, most if not all other organs in the body have a secondary endocrine function in addition to its primary function. Hormones be classified into three chemical classes: peptides and proteins including glycoproteins, steroid and secosteroids hormones and amino acid derivatives. Also, they can be categorized based on secretion pattern and mechanism of action. Hormones play critical roles in gene transcription, so dysregulation of hormone production, signalling pathways, or utilization by target cells has been related with metabolic, inflammatory disorders including cancer, diabetes, neurological and cardiovascular diseases.

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Biological Synthesis of Hormones in Endocrine Cell

2

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Abstract

Hormones are chemical molecules released by various specific cells into the bloodstream or through other signaling and exert biological effects. Hormones are categorized on the basis of synthesis such as derived from amino acids, tyrosine (catecholamines, dopamine, and thyroid hormones), tryptophan (serotonin and melatonin), histidine (histamine), cholesterol (steroids), and phospholipids (eicosanoids), as well as terpenes. Each hormone has its own cycle that includes synthesis, secretion, signal, utilization, and degradation. Their synthesis, half-life, reception, and degradation are controlled wisely to regulate the body functions. The path from synthesis until degradation is a very precise, specific, and timely process. The degradation and downregulation of hormone and its receptors, respectively, are utilized currently as therapeutic management in some disease such as diabetes type 2 and some tumors.

Keywords

Preprohormone · Prohormone · Synthesis · Elimination

Abbreviations

ACTH	Adrenocorticotropic hormone
Ca^{2+}	Calcium ions
E	Epinephrine
FSH	Follicle-stimulating hormone
hCG	Human chorionic gonadotropin
I_2	Molecular iodine
MSH	Melanocyte-stimulating hormone
NE	Norepinephrine
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid-stimulating hormone

2.1 Introduction

The protein and peptide hormones undergo various transcriptional and translation modifications of the specific amino acid, consequently producing more than one prohormone from a single gene such as (calcitonin and calcitonin-gene related peptide). These prohormones are followed by posttranslational process to produce more biologically distinct peptide fragments for different functions (pro-opiomelanocortin). The production of steroid hormones is not mediated by gene expression, but their synthesis takes place through specific enzymes that convert cholesterol into the appropriate steroid in mitochondria and endoplasmic

reticulum (Greenspan and Forsham 1986; Gardner and Shoback 2007, 2011; Koopmans et al. 2009; Salisbury and Arthur 2018). Studies have shown the presence of different enzymes in steroid secreting cells, involved in the synthesis of various steroids hormone such as cholesterol for steroid synthesis in response to tissue-specific tropic hormones (Gardner and Shoback 2011; Koopmans et al. 2009; Salisbury and Arthur 2018). The amine hormones such as the catecholamines, melatonin, and serotonin are synthesized by side-chain modifications of tyrosine or tryptophan molecule, whereas eicosanoid family of hormones such as prostaglandins is formed from lipids. This chapter highlights the chemical nature of the members of various hormonal classes and the various stages of their synthesis during their production in cell organelles. Briefly, synthesis, secretion, signal, utilization, and degradation of various hormones from each group are discussed (Koopmans et al. 2009; Salisbury and Arthur 2018).

2.2 Group One: Proteins and Polypeptides Hormones

The production of proteins and peptides involves three important stages: synthesis of the preprohormone, production of the prohormone, and secretion of the hormone. Simply, prehormone is translated from its mRNA at the endoplasmic reticulum of the cell. It is then transported to the Golgi apparatus, where it undergoes modifications to form the prohormone. The prohormone is then packaged in the Golgi apparatus to be released as the hormone. These stages of synthesis are shown in Fig. 2.1 and explained under the following headings:

2.2.1 Synthesis of the Preprohormone

A preprohormone molecule is protein's precursor to one or more than prohormones, which then act as precursors to peptide hormones. The rough endoplasmic reticulum of protein-hormone producing cell produces the prehormone (Fig. 2.1a), upon receiving a genetic signal from the nuclear DNA. For example, the arginine-vasopressin preprohormone (AVP-NpII) is a typical demonstrative of a polyprotein. Polyproteins processing is initiated by proteolytic enzymes that are directed by couples of basic amino acids. The development can be complemented by alterations of the bioactive peptide. For example, reaction of amidation of the arginine-vasopressin preprohormone needs a glycine residue C-terminal to the hormone and is found in several precursors to amidated peptides (Richter and Schmale 1983).

At the molecular level neuronatin (is a protein coding gen required in brain development in mammalian) increases cleavage of insulin signal peptide by connecting to the signal peptidase compound to ease translocation of the growing preprohormone. Damage of neuronatin gene expression in beta cells decreases insulin amount and reduces glucose-induced insulin release (Millership et al. 2018). This shows the importance of the preprohormone as a potential role for peptide production.

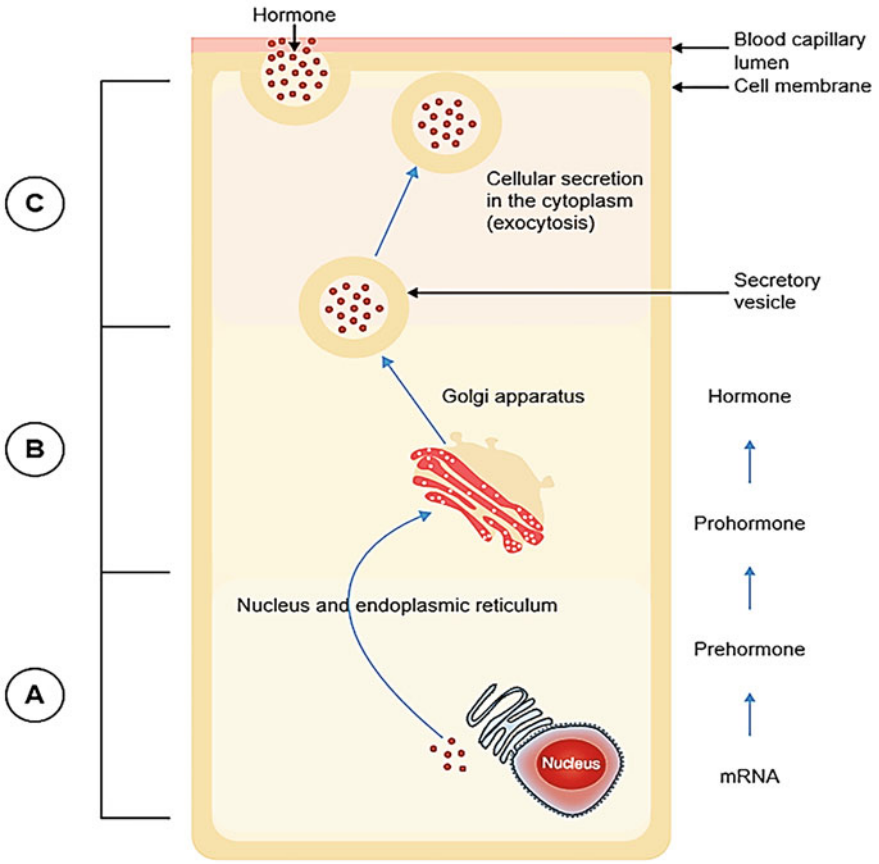

Fig. 2.1 The stages of the production and secretion of protein and polypeptide hormones in an endocrine cell. (**a**) Preprohormone is synthesized in the ribosomes on the endoplasmic reticulum. (**b**) Prehormone is transferred to the Golgi complex where it exposes to several modifications including the addition of sugars. (**c**) Hormones are released from the Golgi apparatus in the form of secretory granules. Once this cell receives stimulator, hormones move and fuse with the cell membrane. The secreted or exocytosed hormones then enter the blood circulation

2.2.2 Production of the Prohormone

The prehormone is transferred to the Golgi apparatus where it undergoes several modifications including the addition of sugars. Hormones that are formed by the addition of sugars to their prohormones are called glycoproteins such as thyroid-stimulating hormone (TSH), human chorionic gonadotropin (hCG), and follicle-stimulating hormone (FSH). After modifications, the modified hormones are then packaged into granules thereby becoming semi-active prohormones (Fig. 2.1b). Greenspan and Forsham (1986) have reported that prohormones are polypeptide including pro-opiomelanocortin, the cleavage of which in the pituitary gland and

hypothalamus gives rise to various hormonal peptide molecules such as melanocyte-stimulating hormone (MSH), β-endorphin, and adrenocorticotropic hormone (ACTH). The cleavage of all prohormone proteins is completed by enzymatic processes (the family of prohormone-converting enzymes) within the Golgi complex of cells (Habener 2011).

2.2.3 Release of the Hormone

Hormones are released from the Golgi apparatus in the form of secretory granules. Peptide hormones can be stored for days or even months in secretory granules after synthesis before release. Hormones stay in the secretory granules, until and unless they receive the signal for secretion out of the cell; once this signal is received, hormone is sent to the cell membrane where it fuses with the help of calcium ions (Ca^{2+}). The secreted or exocytosed hormone then enters the bloodstream (Fig. 2.1c).

2.3 Group Two: Amino Acid Derivatives Hormones

The compositions of amino acid derivatives are many types. They deliver key roles in the physiological functions. For example, catecholamines are a group of amino acid derivatives that derived from one amino acid (tyrosine). Dopamine, norepinephrine, and epinephrine are physiologically effective molecules named catecholamines. Catecholamines work as signaling neurotransmitters and hormones to maintain the homeostasis of the body.

Another prominent main role of amino acid derivative is performed by thyroid hormones that are derived from iodine-bound tyrosine; they are the unique molecules in the body that contain iodine. In addition to the role of thyroid hormones in regulating the energy in all cells of the body, they also regulate the functions of the immune system (Muthusami et al. 2020).

L-Tryptophan is the single protein amino acid firmness. In live cells, it participates in both processes to keep its chemical molecules or to break it by producing a set of bioactive molecules. Derivatives of L-tryptophan have pleiotropic effects on homeostasis processes. Pathways of L-tryptophan indole derivatives include the synthesis (5-HTP), the direct precursor of serotonin which acts as neurotransmitter and hormone. Serotonin is a precursor of melatonin hormone. Both serotonin and melatonin are synthesized by the pineal gland. Tryptophan indole ring breakdown is known as the "kynurenine shunt" which generates cell-response transformer as kynurenic, L-kynurenine, and quinolinic acids or the coenzyme nicotinamide adenine dinucleotide (Taibi and Landis 2009; Palego et al. 2016).

Histamine is a local hormone released mainly by the stomach in endocrine cells (called enterochromaffin-like cells), as they are peptide hormone-producing cells. Histamine is also produced by neurons, basophils, mast cells, and lymphatic tissues. Histamine is synthesized by decarboxylating the amino acid histidine via histidine

decarboxylase. Then histamine is kept in cytoplasmic granules of its producing cells. Many stimulator signals stimulate release of histamine, for example, Enterochromaffin-like cells respond easily to gastrin and acetylcholine to release histamine and its resynthesis, therefore, the enterochromaffin-like cell fulfills main conditions of a physiologically related histamine group. In mast cells, histamine production is antibody IgE dependent, while in the nervous system, a nerve impulse stimulates histamine secretion. Histamine is quickly and greatly metabolized in plasma by *N*-methyltransferase and diamine oxidase. In urine, limited amount (2–3%) of histidine is converted to histamine (Håkanson and Sundler 1991; Bylund 2017).

2.3.1 Synthesis of Adrenaline and Noradrenaline (Epinephrine, Norepinephrine, and Dopamine)

Catecholamine is synthesized into the chromaffin cells of the adrenal glands medulla and regulated by tyrosine concentration. Tyrosine endures hydroxylation process through the enzyme tyrosine hydroxylase to convert to Dopa, which then endures decarboxylation into dopamine which can be released directly to the circulation or undergoes next hydroxylation into noradrenaline (norepinephrine). Norepinephrine could be released into the circulation or exposed to more modification by a methyltransferase to adrenaline (epinephrine) and then released in bloodstream. Glucocorticoids in a significant way upregulate methyltransferase action to promote the production of epinephrine. In addition to its key role in metabolism, catecholamines group performs a major role in immune response. Recently, it is clear that adipose tissue can synthetize catecholamines lightening novel functions for these amines' derivatives in obesity. The enzymes tyrosine hydroxylase and phenylethanolamine, *N*-methyltransferase, and catecholamines are expressed over preadipocytes differentiation in normal and obesogenic conditions.

Catecholamine degrades to its metabolites by two enzymes: (1) monoamine oxidase existing in the outer membrane of the mitochondria and (2) catechol-o-methyltransferase existing in the cell systole. Both enzymes break down dopamine to homovanillic acid while epinephrine and norepinephrine to vanillylmandelic acid to be excreted in urine (Ferreira et al. 2019; Sarkodie et al. 2019; Taylor and Cassagnol 2019; Maestroni 2020; Dutt and Jialal 2019; Akinaga et al. 2019; Gomes et al. 2020).

- There is compelling evidence that L-tyrosine and l-3,4-di-hydroxy-phenylalanine (l-DOPA) enter the adrenal chromaffin cell through L-type amino acid transporter system that linked to the cell membrane (Koopmans et al. 2009; Salisbury and Arthur 2018) (Fig. 2.2a).
- These precursors metabolize to dopamine, which is packed into secretory vesicles via the vesicular monoamine transporter (Koopmans et al. 2009, Salisbury and

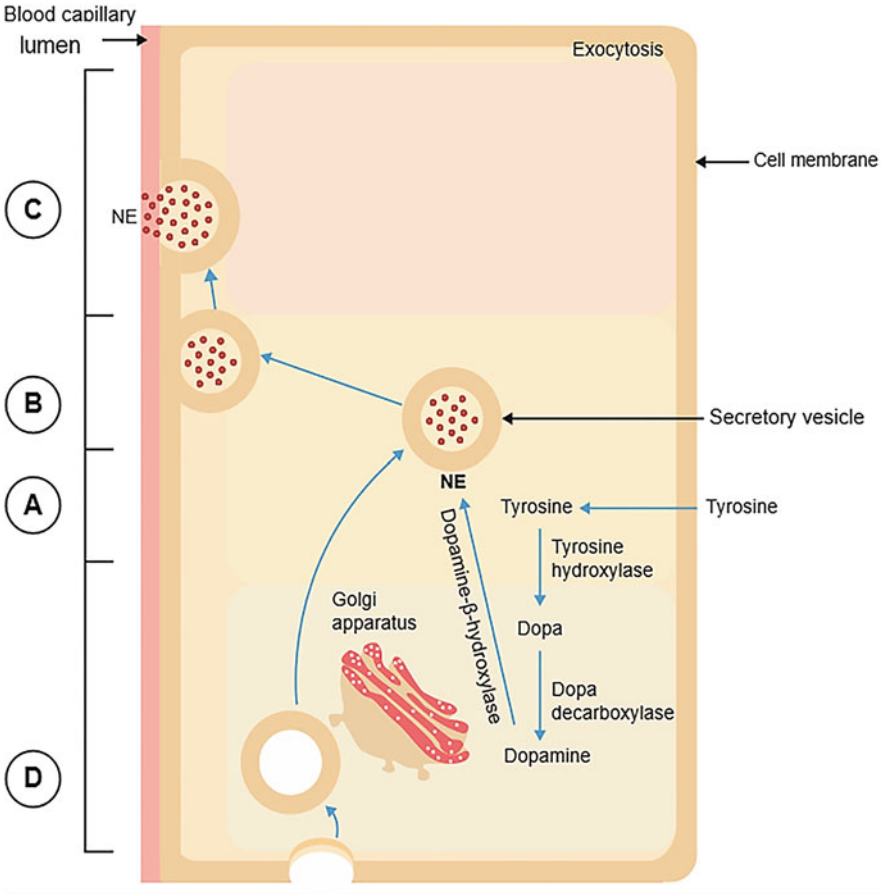

Fig. 2.2 Stages of the synthesis of amino acid derived hormones. Catecholamine (epinephrine, norepinephrine), and dopamine are synthesized into the chromaffin cells in the medulla of adrenal glands. (**a**, **b**) Tyrosine enters the chromaffin cell and exposes to hydroxylation process through the tyrosine β-hydroxylase to convert to Dopa, which then decarboxylated into dopamine. (**c**, **d**) Dopamine is released directly in the circulation or exposes to next hydroxylation process to transform to noradrenaline (norepinephrine)

Arthur 2018). In these vesicles dopamine can be further metabolized to epinephrine and norepinephrine in granules by an enzyme dopamine-β-hydroxylase (DBH) (Fig. 2.2b).

- Except for the enzyme DBH, all the other enzymes involved in catecholamine synthesis are found in the cytoplasm of the adrenal chromaffin cell. The syntheses of dopamine, norepinephrine, or epinephrine depend on intracellular expression of enzyme DBH (Fig. 2.2a, b).
- The secretory granules store and secrete the end hormonal products. More than 95% of epinephrine is essentially synthesized in the adrenomedullary chromaffin

cells and acts as an endocrine hormone secreted into the blood circulation directly (Fig. 2.2c). Reversibly, blood norepinephrine is at most come from influx of the neurotransmitter from sympathetic nerve terminals with chromaffin cell production in the adrenal medulla representing a less than 10% of the whole production (Richter and Schmale 1983; Richter and Schmale 1983).

- For the same reason, due to the location of phenylethanolamine-*N*-methyltransferase (PNMT), norepinephrine has to passively diffuse into the cytosol for conversion to epinephrine, by the PNMT enzyme. Lastly, these final products re-transport again using noradrenalin and dopamine transporters. The empty vesicle could be recycled into the cell (Fig. 2.2d) (Koopmans et al. 2009; Salisbury and Arthur 2018; Eisenhofer et al. 2001; McCarty 2016).

2.3.2 Synthesis of Thyroid Gland Hormones

Thyroid hormone is synthesized unparalleled histological structures named the thyroid follicles. It is one cellular layer of follicular epithelium surrounding a follicular lumen, these cells are also called (thyrocytes or thyroid follicular cells). Thyroid hormones are synthesized from the colloid precursor (thyroglobulin). Thyroid hormones are highly received and utilized by all the cell for energy and development regulation.

2.3.2.1 Thyroglobulin

Thyroglobulin is the protein backbone for production of thyroid hormones. Thyroglobulin is a large glycoprotein and substrate for thyroid gland hormones synthesis and the prohormone phase in which T3 and T4 are stored in the gland. Follicular cells in a spherical arrangement form a follicle, and hundreds of follicles are contained in the thyroid gland. The follicular lumen is a central cavity filled with a sticky fluid called colloid, a concentrated solution of thyroglobulin and the site of synthesis of the thyroid hormones (T4 and T3). Coscia et al. (2020) detected the fine structure of human thyroglobulin of thyroid glands by using the cryo-electron microscopy. That vicinity, elasticity, and solvent exposition play key advantages of its hormonogenic pairs of tyrosine.

2.3.2.2 Glycoprotein Role in Thyrocyte

The main responsible proteins for hormones production in the thyroid gland are glycosylated. Thyroglobulin is a heavy N-glycosylated protein. Oligosaccharides influence the physiological functions of glycosylated proteins significantly. Both pituitary-TSH and TSH receptors on the membrane of thyrocytes include N-glycans that play key role in its function. N-oligosaccharides act a function in thyroglobulin transportation into the follicular cavity, where T4 and T3 are synthesized, as well as in thyroid follicular cells, where hyposialylated thyroglobulin degrades. N-glycans of the transporters of cellular membrane (pendrin and sodium/iodide symporter) are required to transport iodide. Alterations in glycosylation lead to abnormal function of the thyroid as well changes in the clearance rate of the hormones leading to

pathological process such as development of thyroid cancers and autoimmunity (Ząbczyńska et al. 2018).

2.3.2.3 Synthesis of Thyroid Hormones in Follicular Cells

Thyroglobulin is the immediate protein precursor of thyroid hormones through many steps including the iodination, coupling of pairs of amino acid tyrosine, thyroglobulin proteolysis. Tyrosine closeness within thyroglobulin is to allow the coupling reaction. Triiodothyronine (T3) processes three atoms of iodine, while thyroxine (T4) contains four atoms of iodine, as iodine represents 65% of T4 weight. Once thyroid-stimulating hormone (TSH) from pituitary gland binds with thyroid cells, it induces the uptake of iodide through the transporter of sodium/iodide, to enable iodide to diffuse against its level gradient into the thyroid follicular cell while also keeping electroneutrality via the commitment of a positively sodium ion's charge. Then the iodide molecule is moved to the apical part of the follicular cell through an iodide–chloride transporter named pendrin. Vesicles can fuse with the apical membrane of the cell, the iodide is oxidized into the vesicles and bound covalently with tyrosine residues forming the mono basic unit called (monoiodotyrosine residues), the necessary unit for building T3 and T4 (Rousset et al. 2000; Núñez et al. 2017; Mallya and Ogilvy-Stuart 2018).

Details of the steps are listed as the following (Greenspan and Forsham 1986):

- The thyroid follicular cells capture iodine that enters from the base of the cell by active transport as shown in Fig. 2.3a.
- Meanwhile, endoplasmic reticulum of the thyrocyte synthesizes two important proteins, thyroid peroxidases, and thyroglobulin. After the uptake of iodine into the follicular lumen, iodine is transported as I^- toward the apical membrane through a hydrophobic membrane protein via pendrin (Gomes et al. 2020). Iodine raises to the top of the cell and is transformed from an iodine molecule (I_2) into two iodine atoms (Eisenhofer et al. 2001) by the enzyme thyroid peroxidases as well as linked to thyroglobulin tyrosine residues by covalent bonds (Fig. 2.3b).
- First iodination of thyroglobulin provides monoiodotyrosine (MIT) and di-iodotyrosines (DIT). Furthermore, iodination pairs two molecules of DIT that still in peptide link to form the thyroid hormone T4, fundamentally at residual 5 into the thyroglobulin chain. The coupling of two molecules of di-iodotyrosines produces T4, while, with minimum level, monoiodotyrosine combines with diiodotyrosine to form T3 in lysosomes (Fig. 2.3c).
- Thyroglobulin (and not thyroxine) is synthesized on ribosomes, glycosylated in the cisternae of the endoplasmic reticulum, translocated to the Golgi apparatus, and packaged in secretory vesicles, which discharge it from the apical surface into the lumen as shown in Fig. 2.3d.
- Post coupling of iodotyrosine, thyroid hormones does not separate from the thyroglobulin found in the follicular lumen. When T4 or T3 is required, and under TSH stimulation, then thyroglobulin-thyroid hormone compound is exposed to endocytosis or micropinocytosis into thyrocytes as shown in Fig. 2.3e. Thyroglobulin internalizes at the top end of thyrocyte, then transfer

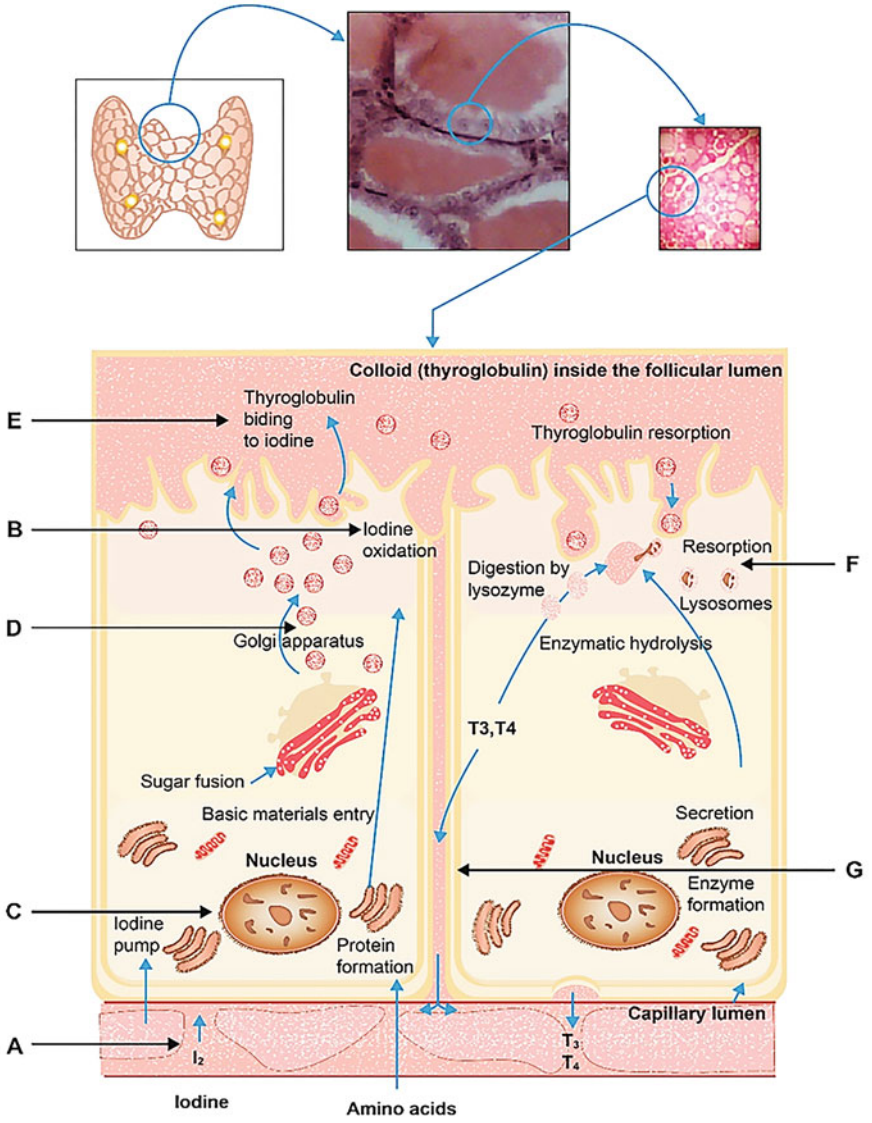

Fig. 2.3 The stages of thyroid hormone formation and release by the thyroid gland cells. (**a**) The thyroid follicular cells capture iodine that enters from the circulation, (**b**) iodine transportation as I^- toward the apical membrane via pendrin, (**c**) formation of thyroid hormones from the basic unit (monoiodotyrosine) in endoplasmic reticulum, (**d**) thyroglobulin forms in the rough endoplasmic reticulum into its ribosomes and glycosylates in the cisternae of the same endoplasmic reticulum, (**e**) endocytosis of the thyroglobulin-thyroid hormone complex into follicular epithelial cells, (**f**) thyroglobulin molecules are reabsorbed by the polarized thyrocytes and then transferred to lysosomes for proteolysis releasing T4 and T3 from their peptide links, (**g**) secretion of thyroid hormone into the blood circulation by exocytosis or/and simple diffusion

to lysosomes and to be exposed to digestion by lysosomal enzymes such as proteases, especially the endopeptidases cathepsins and exopeptidases.

- Endocytosis is followed by hydrolysis of the thyroglobulin-thyroid hormone complexes as shown in Fig. 2.3f. Thyroglobulin molecule is taken up at first by polarized thyrocyte (Fig. 2.3) and then move to lysosomes for proteolytic analysis to separate the hormones T4 and T3 from their peptide likes.
- Thyroid hormones are secreted into the bloodstream by transporters. Thyroid-stimulating hormone (thyrotropin) stimulates thyroid hormone synthesis and secretion by one or both two ways: (1) T_3 and T_4 are broken down inside the follicle and the follicle fuses with the membrane and bursts, releasing its contents by exocytosis. (2) The follicle is broken down by enzymes and releasing T_3 and T_4 into the bloodstream from the cell by simple diffusion (Fig. 2.3g).

2.4 Group Three: Steroid Hormones

Steroids are fat-soluble group of hormones derived from cholesterol, which regulates reproduction developmental and metabolic functions of the body. In mammals, there are six groups of steroids, namely progesterone, estrogens, androgens, glucocorticoids, mineralocorticoids, and vitamin D compounds. The steroids differ from the other groups as they are never stored in the producing cells and also they do not synthesize and/or secrete until an appropriate signal is received. The synthesis takes these steps:

- Steroid hormones are synthesized from cholesterol (Fig. 2.4a) in the adrenal gland and gonads under stimulation of specific tropic hormones such as LH, FSH, or ACTH that induce gonadal or adrenocortical steroidogenesis in the mitochondrial and microsomal compartments of steroidogenic cells.
- In the mitochondria, the initial process of steroidogenesis happens, where the cytochrome P450 side-chain cleavage enzyme separates the aliphatic tail of cholesterol molecule. The pregnenolone is the end product of all steroidogenesis pathways (Fig. 2.4b).
- Pregnenolone forms from cholesterol; it can endure 17-α-hydroxylation to 17OH-pregnenolone to synthesize cortisol and aldosterone in the adrenal cortex cells, while pregnenolone converts to progesterone in the ovarian theca and granulosa cells and converts into testosterone in the testes. 3β-hydroxysteroid dehydrogenase (3βHSD) converts pregnenolone to progesterone (Fig. 2.4c).
- Testosterone is synthesized through complex pathways involving different enzymes. Compounds like cytochrome P450 oxygenase family are essentially contributed to the production of steroids. Other enzymes also involved include 3β-hydroxysteroid dehydrogenase/Δ5-Δ4 isomerase, 17β-hydroxysteroid dehydrogenase, and cytochrome P450 17α-hydroxylase/17,20 lyase (Hammar and Petersson 1986; Rey et al. 1995).

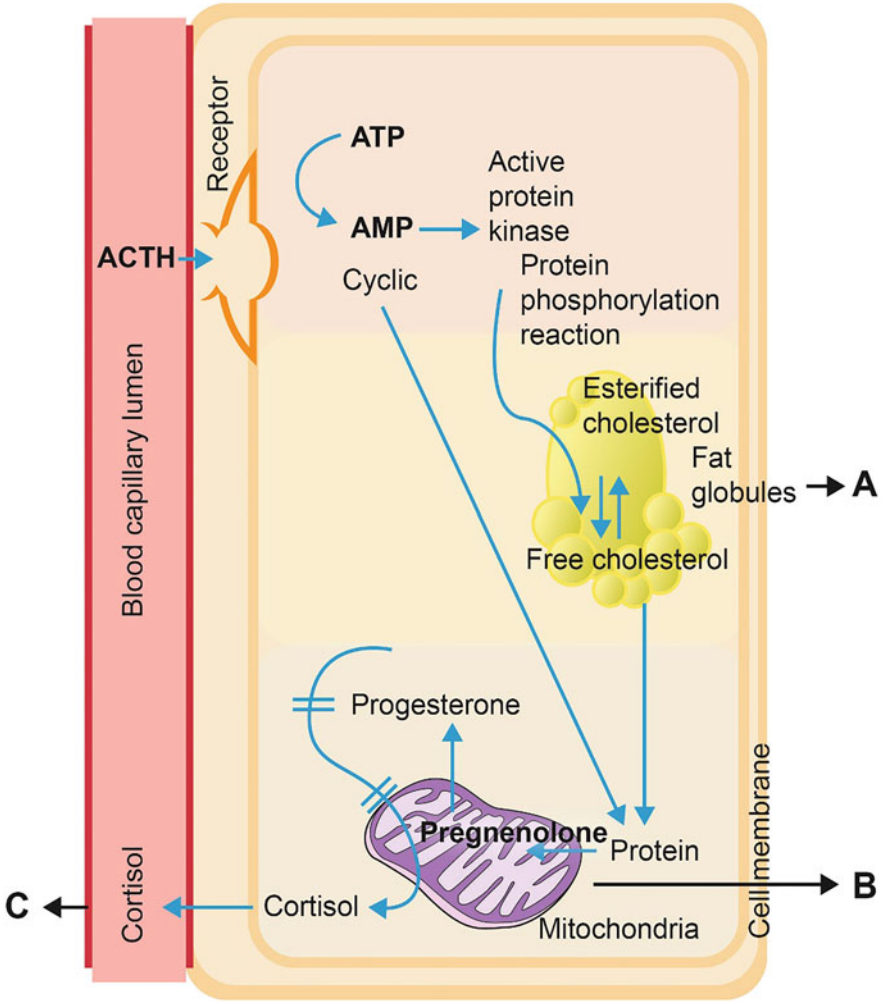

Fig. 2.4 The stages of the formation of steroid hormones in the endocrine gland (steroid-producing cells). (**a**) Steroid hormones are synthesized from cholesterol. (**b**) The end hormone of this first phase to steroidogenesis is the pregnenolone. (**c**) Steroids are not released from secretory vesicles like other types of hormones but are released immediately to the blood circulation after production

- Steroids are only synthesized and secreted when the body needs them, therefore not released from secretory vesicles like other types of hormones but are released immediately to the blood circulation after production (Fig. 2.4c).

Steroid-producing cell contains cholesterol droplets which act as prohormone. In general, steroid hormones are formed from conversion of cholesterol molecule to

pregnenolone (the common steroid precursor). Each steroid hormone is synthesized by a specific steroid-producing cell once it receives stimulating hormones.

Estrogen synthesis is mediated by family 19 of the P450 super family that converts androgenic steroids to the estrogens by aromatization reaction. This reaction requires transformation of the delta4–3-one A-ring found in the androgen molecule to the identical phenolic A-ring distinctive for estrogens (Rey et al. 1995).

2.5 Group Four: Terpene Hormones Synthesis

Biosynthesize of triterpenoid compounds is essential for the structure and function of cell membrane, including signaling molecules of steroid hormones and their receptors, Ninkuu et al. (2021) reported useful information on terpenes, their types, biosynthesis, and their protecting roles for the improvement of friendly environment. In 1939, in chemistry field Nobel Prize had been granted to Leopold Ruzicka (1887–1976) as he had studied molecular construction of higher terpene that includes the first synthesis of male sex hormones. His achievement topic was the "biogenetic isoprene rule" that clarified the biosynthesis of terpenoid. Ruzicka's rule reports that terpenoids are enzymatically cyclized compounds from chains of alkene containing a unique number of linear concentrated of C_5 isoprene units. The number of repeated isoprene units defines the class of synthesized terpenes. For example: 2 units of C_5 isopren = monoterpene (C_{10}); 3 units of C_5 isopren = sesquiterpene (C_{15}); 4 units of C_5 isopren = diterpene C_{20}, etc. In triterpenes, 6 units of C_5 isoprene units are combined providing C_{30} squalene, then it is cyclized to be one of the catachrestic carbon structures from which high numbers of triterpenoid compound could be derived, such as sterols and steroids. Ruzicka also had focused on terpenoids as origin of life, but unfortunately the essential functions of terpenoids have mostly been overshadowed by sugars, amino acids and nucleobases. Hillier and Lathe (2019) reported the above possible abiotic compound of isoprene, the critical part that terpenoids (polyprene) presented in cell life. Endocrinology of all live subjects is based on Ruzicka's central vision of terpenes' function and structure. Figure 2.5 shows the synthesis of terpenes according to Leopold Ruzicka insight.

2.6 Principal Characteristic of Hormones

- Hormones are signaling molecules of various chemicals nature such as steroids present in male and female sex hormones, made up mainly of esterified cholesterol. Proteins and polypeptides are secreted by hypothalamus and modulate pituitary hormones as well as amino acids derivatives such as thyroid hormones.
- Hormones can be produced and secreted in endocrine cells inside (in vivo) or outside the body (in vitro) and (ex vivo).
- Hormones can be carried from the endocrine gland through the bloodstream or other means such as paracrine, autocrine, etc. (mentioned in Chap. 1) to act as

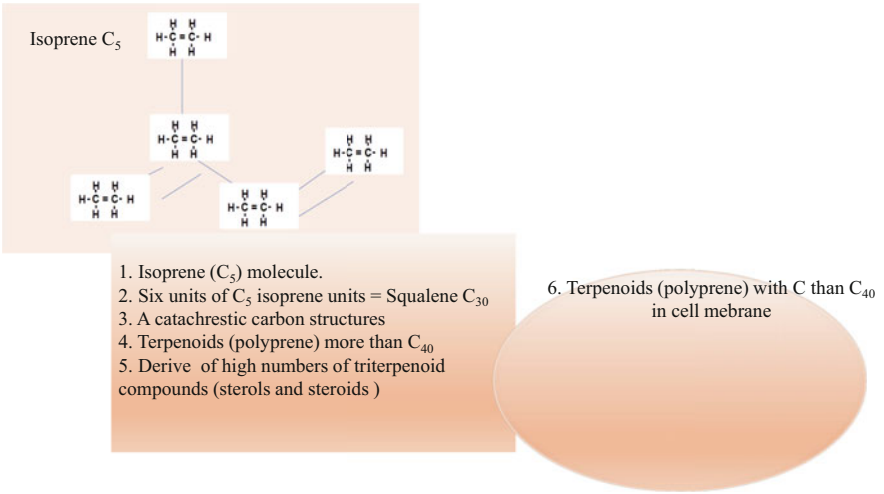

Fig. 2.5 The scheme of synthesis of terpenoids. Terpene synthesized as the following $(C_5)n$ since (C_5) is isoprene molecule, while (n) is number of isoprene unites as explained by Leopold Ruzicka

chemical messengers that have a specific effect on specific receptor cells, tissues, or organs.

- The effect of hormones secreted by endocrine glands is dependent on their ability to form strong covalent bonds with receptors in target cells or tissues; this results in the formation of a highly specialized system between endocrine glands and cells or tissues targeted by hormones.
- Many hormones are metabolized soon after their release. Some types of hormones such as steroids are transported through bloodstreams bound to special carrier proteins. This extends their half-lives to a few hours. Thyroxine secreted by the thyroid also binds strongly to a carrier protein; this extends its half-life to up to 7 days. Catecholamines, such as adrenaline and noradrenaline, are free and unattached to carriers; therefore, they have very short half-lives of only a few seconds in the blood.
- Hormones only act as regulators and they do not initiate or end any physiological function as they do not supply energy or build compounds. Their role is only to control and balance the body's functions. Hormones regulate growth and increase energy production, differentiation, immune and metabolic activities in their receptor cells by acting on the ion pumps that regulate membrane permeability and by regulating enzyme activation and inhibition.
- Despite their low concentrations in the blood and other body fluids, hormones are highly efficient. For example, steroid hormones and thyroid hormones are effective at plasma concentrations as low as 10^{-6}–10^{-9} mol/L, while peptides are more efficient and can act at even lower plasma concentrations of 10^{-10}–10^{-12} mol/L.

- Hormones are secreted in a pulsatile and inconsistent manner, and their secretion rate can vary throughout the day. This is because hormone secretion follows the body's circadian rhythm and also controlled by central nervous system. Pulsatile secretion is a biological phenomenon spotted in several types of bioactive molecules, in which the molecules are released in a regular pattern. The most common biochemical products reported to be released in this pattern are intercellular signaling molecules like hormones and neurotransmitters. The important known hormones that are secreted in pulsatile manner are insulin, growth hormone, thyrotropin, prolactin, thyrotropin, and gonadotropin-releasing hormone as demonstrated by the following examples:
- Thyroid hormone levels increase when the weather is cold, and this increases the activity of important physiological processes, such as those involved in energy production.
- It is difficult to measure the levels of the hormone ACTH because of its pulsatile and variable secretion throughout the day, which is reflected in the role it plays.
- Growth hormone and prolactin levels increase during deep sleep. Growth hormone and insulin are released alternatively according to intervals of the intake meals.
- Melatonin levels increases in the darkness and decreases with the onset of light.
- Insulin levels in the blood are at their lowest in the morning before eating.
- Cortisol levels fall at dusk.
- Response time: Response time is the period between the moment when the hormone is triggered (signal) and the response to it is generated. Response times for hormones can be in seconds, minutes, hours, or days, being much slower than the durations of nerve impulses, which occur within milliseconds. For example, the response to adrenaline, involving effects such as increased heart rate and breathing, face flushing, slowing down of digestion, occurs a few seconds after adrenaline release following exposure of any of the senses to a frightening situation. While the effects of thyroid hormones can last for several days.
- Modification of hormones after secretion: A hormone undergoes many modifications after it is released. These can be in the form of partial cleavage into peptides or enzymatic transformation as seen in steroid and thyroid hormones. These modifications can take place at many locations after secretion and at various distances. The modifications aim to transform the hormones into more active forms and can take place in the liver, kidneys, bloodstream, and sometimes in the receptor-containing tissues themselves (Simpson et al. 1997).
- Forms of hormones in the bloodstream: Hormones in the blood are in either free or bound state. Bound hormones only dissociate from carrier proteins when they are needed and have longer lifespans because: (1) it is difficult for the kidney to remove bound hormones. (2) The metabolism and breakdown of bound hormones in the liver are reduced. (3) It facilitates its circulation in the blood. Blood capillaries do not allow large or protein-bound particles to pass through; however, there are special openings in the membranes of blood capillaries through which only free hormones can pass. Therefore, free hormones are more biologically

active than bound hormones. Free hormones can easily interact with receptor on cell membranes from the capillaries and can be broken down in specialized tissues.

- Hormone receptors: Hormone receptors are subsets of biochemical molecular compounds that are utilized by all cells for communication and transportation between the cells as well as with the external environment. Based on their cellular location, hormone receptors can be categorized to external fixed receptors, internal mobile receptors, and internal nuclear receptors, whereas, based on their molecular structure and mechanism, hormone receptor types are nuclear receptors, kinase-coupled receptors, G protein linked receptors, ligand-gated ion channel receptors. Hormone binds to its G protein linked receptors, results in stimulation of adenylate cyclase generating cAMP, and stimulates cAMP dependent protein kinase (PKA). These compounds (receptors) combined with hormones through electrostatic powers include hydrogenic bond, hydrophobic interaction, and other factors to form a hormone receptor complex that can stimulate responses in cell organelles. Different kinds of hormone receptors include:
- **External fixed receptors** cause the breakdown of protein and amine hormones after they bind to receptors present on the surface of the plasma membrane.
- **Internal mobile receptors** cause the breakdown of steroid hormones after they bind to internal receptors in the cytoplasm (internal mobile receptors), in addition to binding to receptors on the membrane of the target cells as seen with steroids.
- **Internal nuclear receptors** are present within cells that have high affinity for steroid and thyroid hormones and certain other molecules.
- In some cases, hormones exert effects to change the environmental conditions in the body and thereby induce a macrophage response, which may benefit immunity (Curi et al. 2017).
- Hormones can interact by different mechanisms such as endocrine and paracrine-autocrine molecular interactions. These signals associated with progesterone release during the human corpus luteal phase as well as being critical for the luteal growth, maintenance, and regression (Curi et al. 2017).
- There are clear structural and functional interactions and relationship between hormones and minerals and vitamins. Thyroid hormone utilizes carotene and converts it to vitamin A.
- Degradation of hormones and reduction of their levels is controlled by negative feedback mechanisms.
- The bloodstream eliminates hormones after their role. Blood eliminates some hormones after the required amount of hormones has bound to the receptors in cells and tissues.
- Any remaining hormone is eliminated through the liver, kidneys, and muscles. The most important elimination pathways for hormones involve enzymatic mechanisms including dissolution in water, oxidation, hydroxylation, methylation, decarboxylation, or binding to a sulfur group (Simpson et al. 1997).
- It is well documented that large peptide hormones such as insulin, calcitonin, somatostatin, glucagon, and secretin metabolized and degraded within 5 min.

However, smaller peptide hormones such as desmopressin, vasopressin, oxytocin, leuprolide, goserelin, buserelin, gonadorelin, deslorelin, and nafarelin metabolized and degraded very tardily (Wang et al. 2015).

- There is a small percentage (less than 1%) of all hormones that are excreted in the urine or feces without undergoing modification (Wang et al. 2015; Waugh and Grant 2006; Bick et al. 2005; Bullock and Grossberg 1991).

2.7 The Various Phases in the Life Cycle of a Hormone from Synthesis to Elimination Are Summarized as Follows

The hormones are always stored till released and the storage time depends on the hormone and environment. While hormones like steroids are not stored as they are released once the stimulant induces steroid-producing cell. The hormone goes through several stages which are:

- Accumulation of the basic and raw materials making up the hormone in the hormone-producing cells.
- Production of prohormones occurs in the rough endoplasmic reticulum for proteins and thyroid hormones and in the cytoplasm for steroids.
- Biochemical modification takes place in the Golgi apparatus or in the cytoplasm that converts preprohormone into the prohormone.
- Secretion with or without secretory granules.
- Existence of the hormone in its final form, which can be before secretion or after secretion and at any location in the body.
- Exocytosis or simple diffusion from the producing cell.
- Circulation in the blood or in the space between cells.
- Binding of hormones to receptors in the target cells.
- Completion of hormone activity and elimination.

2.8 Emerging Strategy for Hormones/Receptor Degradation as Therapy

Gastrointestinal duct peptides hormones like (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)) are the known hormones released by the superior (GIP, K cells) and inferior (GLP-1, L cells) in the gut as a response to food intake as well enhance insulin release as a result of hyperglycemia. Incretins are the reason of a two- to three-fold increase in insulin level response to oral administration of glucose in comparison with intravenous way. In diabetes, incretins influence decreased/canceled as a result of a reduction effect of GIP on the diabetic endocrine pancreas. However, the insulin-promoting and glucagon-inhibitory actions of GLP-1 are present in type 2 DM to the level that therapeutical stimulation of GLP-1's target receptors clearly decreases glucose and ameliorates glycemic regulation in circulation. Based on that, it has become an essential

compound of incretin-depend glucose-lowering effect medicine such as GLP-1 receptor agonists and suppresser of dipeptidyl peptidase-4 or (DPP-4). Additionally, GLP-1 acts other roles, it reduces appetite, then weight loss with long term, because the gut of obese impaired in GLP-1 secretion, indicating its contribution in obesity' pathophysiology. Also, GLP-1 is stimulated when food reaches to distant part of the small intestines where (L cells) are present abundantly. This may explain loss of weight and improvement of glycemic regulation post bariatric surgery. GIP and GLP-1 have effects in adipocytes, skeleton, and the cardiovascular systems. GLP-1 receptor agonists (liraglutide) decrease cardiovascular issues and expand life in high-risk of type 2 diabetes (Nauck and Meier 2018). GIP and GLP-1 are instantly deactivated essentially through N-terminal analysis via dipeptidyl peptidase IV (DPP IV, CD26), a specific enzyme found on some cells such as endothelial, epithelial cells. While their cleavage via neprilysin (neutral endopeptidase) is a rare way of regression. Also, kidney can eliminate incretin hormones. So, DPP IV inhibitors and DPP IV-resistant incretin analogues are used as a type of drug for treating type 2 DM but there is potential side effect (Mentlein 2009). Incretin hormones have a key physiological role and pathophysiology roles in obesity and type 2 diabetes, as well as they act as therapeutic agents for a well physiological activity.

Conversely, decreasing hormone receptors components such as estrogen receptor (ER) is a promising way for suppressing breast cancer. It has been found that combination of tamoxifen with selective estrogen receptor degrader (SERD) acts as a potential therapy for breast cancer. Elacestrant (SERD) may act as an endocrine corner stone for reasonable combination to conflict resistance. It has been reported that there is a possible therapeutic use of elacestrant as a singular or in a combination medicine, for both early and late-stage ER+ tumor. It possesses an antitumor effect in several ER+-derived xenograft types of breast cancer patents (Bihani et al. 2017; Patel et al. 2019). Bioavailable chromene-dependent selective estrogen receptor degrader shows strong effect in a model of tamoxifen-resistant breast cancer (Nagasawa et al. 2018). Raised degradation of ER alpha via the ubiquitin-proteasome system led to reducing the transcriptional effect of ER modulation that assured through the decrease in the activity of estrogen receptor components along with downstream of related genes expressions. Combination of tamoxifen with MHO7 (6-epi-ophiobolin G) extracted from mangrove fungi acts as a new down-regulator agent on ER alpha which differs from the common molecules in ER+ in breast cancer's cells (Zhao et al. 2019). It was reported that estrogen receptor degrader such as ERD-148 suppresses the development of ER-positive breast cancer through downregulation of ER alpha to a degree in comparison with Fulvestrant's potentiality with marginal non-specific toxicity (Gonzalez et al. 2020).

2.9 Methods for Studying the Functions of the Endocrine Glands

- Studying various aspects of the stem cells of the endocrine glands in vitro and in vivo.
- Investigating the regulatory role of the endocrine system for the stem or progenitor cells of all body organs.
- Examining the role of the endocrine system in tissue regeneration and maintenance.
- Administration of different doses of hormones at different concentrations and studying their effects over time, their cumulative effects, and the organism's rates of their clearance.
- Extracting hormones such as bacterial insulin, human chorionic gonadotropin (hCG), and pregnant mare gonadotropin, and studying their characteristics and effects by administering them to experimental animals or examining the possibility of using them for other medical objectives.
- Studying the body's physiology of experimental animals before and after removal of the endocrine gland or its inactivation in another way.
- Culturing endocrine tissues and cells in vitro and studying their physiological products under normal conditions and the effect of changes in internal and external culture conditions.
- Study on hormones receptors.
- Measuring hormone levels in fluids inside and outside the body to ascertain hormone concentrations under both normal and pathological conditions.
- Administering hormones that are expected to treat certain medical conditions such as diabetes in experimental animals and studying the results.
- Conducting hormones simulation studies.

Since the pituitary gland is the key to many physiological functions, it is attracted to be engaged in machine learning. There is a collaborative work between endocrinologists and engineers of machine learning in the expansion of interpretable high-performance machine learning models and several algorithms. All is considered as root for the required alteration by machine learning and artificial intelligence to solve many issues in endocrinology and metabolism, along with real improvement clinically. Endocrinologists will keep playing a major role in this domain as they analyze and explain in scientific rigor way. Studies highlight potential methods for prospective machine learning applications utilizing diverse modalities of images can develop the clinical carefulness of patients of pituitary disorders (Hong et al. 2020; Peng et al. 2020; Saha et al. 2020).

2.10 Conclusion

Hormone is a chemical messenger that interacts, communicates, and carries information from one cell to another or within the same cell, typically via extracellular fluids or blood. Hormones are categorized into several classes such as peptides and proteins, monoamines, steroids, and secosteroids. Based on complex nature of hormone, a number of different signals are involved in hormonal activation to produce their cellular effects. Hormones are entirely different from each other based on their chemical compositions and synthesis in endocrine cell (preprohormone, prohormone, and hormone). Hormones are derived from amino acids tyrosine (catecholamines, dopamine, and thyroid hormones), tryptophan (serotonin and melatonin), histidine (histamine). But cholesterol acts as prohormone molecule for steroids, while phospholipids revealed eicosanoids. Differences in the chemical groups affect properties, distribution, and interaction with receptors as well as functions of hormones. This chapter highlights the stages of production and chemical nature of different hormone's classes as well as explains the complex mechanism that governs the synthesis, secretion, signaling, utilization, and degradation of hormones.

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Mechanism of Hormones Secretion and Action

3

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Abstract

Endocrine system has vital roles and is influenced by complex factors and signaling to achieve accurate rhythm and patterns of hormone secretion and effects. The endocrine system effect is slow to start but it can take long-term actions. Endocrine system is an integrated communicative tool for the human body, performing various functions through its hormones as chemical messengers. The pituitary gland is the master regulator of the endocrine system, which coordinates and controls the function of other glands in the body through secretion and signals of stimulating/inhibiting hormones. The signal transduction mechanism of the hormones is mediated by binding with cell surface receptors and stimulating multifactorial downstream targets including second messengers involving cyclic adenine monophosphate (cAMP), calcium ions, and 3-cyclic guanosine monophosphate (cGMP), to induce cellular response and physiological functions. Hormones govern receptor regulation and number, regulate ion transport and membrane permeability, regulate substances and minerals in the blood and cells. Due to their highly restricted functions, the elasticity and plasticity of human endocrine system suggest a powerful history of adaptation to changing environments. The main axis such as hypothalamus-pituitary-adrenal under stress, hypothalamus-pituitary-gonadal and -pineal axis play key roles over important periods. The circadian clock acts carefully to regulate each level of the pituitary-hypothalamus axis ensuring proper compatibility of physiological functions during daylight, either under normal or abnormal conditions. Additionally, the endocrine system plays a key role in maintenance, regeneration, and remodeling the tissues by governing stem/progenitor cells, sexual and mental maturation. It is also overcoming some limitation of stem cell's treatment. This chapter details the hormone secretion mediated cellular events and wide spectrum of its functions.

Keywords

Endocrine system · Cell signaling · Messengers · Hormone · Stem cell · Permeability · Circadian rhythm · Growth · Receptor · Stress · Hypothalamus · Pituitary

Abbreviations

1,25(OH)2D	Calcitriol
ACTH	Adrenocorticotropic hormone
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
Ca^{2+}	Calcium ions
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CNS	Central nervous system
FSH	Follicle stimulating hormone
FSHRH	Follicle stimulating hormone releasing hormone
GH	Growth hormone
LH	Luteinizing hormone
Ni	Inhibitory protein
Ns	Stimulating protein
PTH	Parathyroid hormone
T3	Triiodothyronine
T4	Thyroxine

3.1 Introduction

Endocrine system is effective, dynamic, and controlled by complex regulations and feedback signaling to produce accurate modes and patterns of hormone secretion in order to optimize regulation of cellular and physiological functions (Kauffman and Hoffmann 2020). There is compelling evidence that imbalances in the hormones mediated signaling pathways are responsible for a number of endocrine diseases including developmental disorders. Alternation in cell signaling results from the environmental stress and physiological challenges (Bullock and Grossberg 1991; Bullock et al. 2001; Waugh and Grant 2006). Hormones perform several functions that regulate the tissue homeostasis by positive and negative feedback to cope with internal cellular stress and external environmental fluctuations (Bullock and Grossberg 1991; Bullock et al. 2001). Hormones signaling controls functional coordination, changes in cellular receptor regulation, ion and metabolite transport, membrane permeability, regulation of the level of substances and minerals in the circulation and cells, completion of growth, sexual, mental maturation, behavioral activities, differentiation processes, and the daily variations and circadian rhythm

(Bullock et al. 1991, 2001; Burkitt et al. 1996; Gardner and Shoback 2011). Therefore, the success and sustainability of any therapeutic regime are highly dependent on its interaction with multiple hormones in at least one cell signaling cascades (Guyton 1986; Guyton and Hall 2016). The hypothalamus and the master endocrine gland (pituitary gland) play a key role in regulating the function of endocrine system including response to internal and external stress. It is known that anterior lobe of the pituitary gland (adenohypophysis) secretes different hormones into the hypophyseal portal system through specialized cells; consequently, modulate the function of endocrine and other target organs. The endocrine system not only regulates the entire body physiological functions but also controls the tissues regeneration and maintenance because it governs the physiology of stem/progenitor cells till the maturation in every organ in the body (Nakhla et al. 1989; Guyton and Hall 2006; Gancz and Lilach 2013; Gribble and Reimann 2017).

Also, for non-classic endocrine glands, the communication is a principal feature. It is now known that the heart behaves as a real endocrine organ, since it can modify the functions of other tissues. The heart can communicate with one of the distant organs such as visceral fat, it seems that cardiokines and adipokines are involved in bidirectional crosstalk between fat tissue and the myocardium which is vital role to maintain the normal functions in both of them. Hormones released by the heart are now well-known to impact the metabolic function of adipose tissue and other tissues and modify the periphery secretion of metabolic substrates and signaling molecules. Dysregulation of heart cardiokines and adipokines influences cardiovascular health (Jahng et al. 2016)**.** To highlight the underlying mechanism of cell signaling, we underpin the basic aspects of cell signaling, factors controlling hormone secretion, hormone interaction, and functions of the endocrine system. Role of endocrine system on stem cells is summarized.

3.2 Mechanism of Target Cell Signaling

Hormones are **the first chemical messengers** to reach the target cell where they bind to receptors found in or on the cell. This stimulates second messengers, which induce cellular responses in the following manner (Waugh and Grant 2006; Bullock and Grossberg 1991; Bullock et al. 1991, 2001; Burkitt et al. 1996; Gardner and Shoback 2011; Guyton 1986; Guyton and Hall 2006, 2016; Nakhla et al. 1989; Gancz and Lilach 2013; Gribble and Reimann 2017; Salonia et al. 2005; Feillet 2010; Lin et al. 2015; Ghorbani and Naderi-Meshkin 2016; Parikh et al. 2017; Odle et al. 2018; Salvatore 2018).

3.2.1 Second Messengers

- **Cyclic Adenine Monophosphate** (cAMP): This is used by many hormones such as follicle stimulating hormone (FSH) and luteinizing hormone (LH).

- **Cyclic Guanosine Monophosphate** (cGMP): This is involved in certain endocrine cell signaling pathways. In cultured fetal pituitary and growth hormone (GH)-secreting adenomas, nitric oxide stimulates h-growth hormone. cGMP, which is a primary regulator, mediates this hormonal process (Rubinek et al. 2005). cGMP is also involved in endocrine, metabolic, and neuropsychiatric diseases (Friebe et al. 2015).
- In addition to their signaling role, both cAMP and cGMP have beneficial effects such as their involvement in preventing kidney failure. Serelaxin is a pregnancy hormone that acts by increasing the kidney's cGMP concentrations, which could be considered a new signaling approach for treating kidney fibrosis (Schinner et al. 2015; Zbrojkiewicz and Śliwiński 2016).
- **Ca^{2+} Roles in Hormone Secretion**: Ca^{2+} are found inside cell organelles. They also play a role in cellular exocytosis processes, binding and are used by numerous hormones such as oxytocin and insulin. Calcium, whether endogenous or exogenous, stimulates the endocrine glands, in the pituitary or other glands, in several ways. Calcium plays an active role in regulating basal and stimulating secretion of hormones of endocrine glands. Basal secretion of hormones in the body takes place in the physiological levels of ionic calcium whether inside the cell organelles and cytoplasm or in the intracellular fluids and blood (Wollheim and Sharp 1981). Moreover, in enteroendocrine cells, calcium ions are involved in the exocytosis process. The site of action of a gene specific to calcitonin hormone was identified, which came into play when changes occurred in intracellular calcium levels in vitro in the cells of new born and adult rodents (Bick et al. 2005). It has also been shown that the effect of calcitonin on the sex glands may take place indirectly through the higher centers or directly on the reproductive glands. The effect of calcitonin on the steroid hormones may be mediated by a messenger such as Ca^{2+}. A gradual decrease in Ca^{2+} concentrations in cell culture from 1.5 ml to under 0.01 ml lowers the concentrations of both the estrogen and androgen hormone receptors. Increasing the Ca^{2+} concentration to normal levels (1.5 ml) restores the steroid hormone receptor levels to their normal value (Nakhla et al. 1989). Figure 3.1 shows the levels of some regulatory and other sex hormones in adult male animals before and after calcium injection.
- **Prolactin**: There are also unknown details about messengers that mediate the action of certain hormones in the cell, such as prolactin. There is no tissue that could not express any mRNA/protein of PRL receptors (PRLRs), which largely distributed enabling PRL to do more than 300 actions such as endocrinology and metabolism, control of water and salt balance, growth, regulation of reproduction. Several isoforms of the human PRLRs act to intermediate its effects in the immune system. Additionally, some pathological states, such as cancer and autoimmunity, are related to high level of PRL, which could affect by endocrine, paracrine, autocrine signal, or through high sensitivity to PRL itself (Bole-Feysot et al. 1998). The first step for PRL's mechanism of action is to bind to a receptor's cell membrane. The ligand (one PRL molecule) binds with two receptors on the cell: (1) site 1 of PRL's molecule binds to one receptor molecule, (2) then a second receptor molecule binds to site 2 of PRL, forming a homodimer PRLR

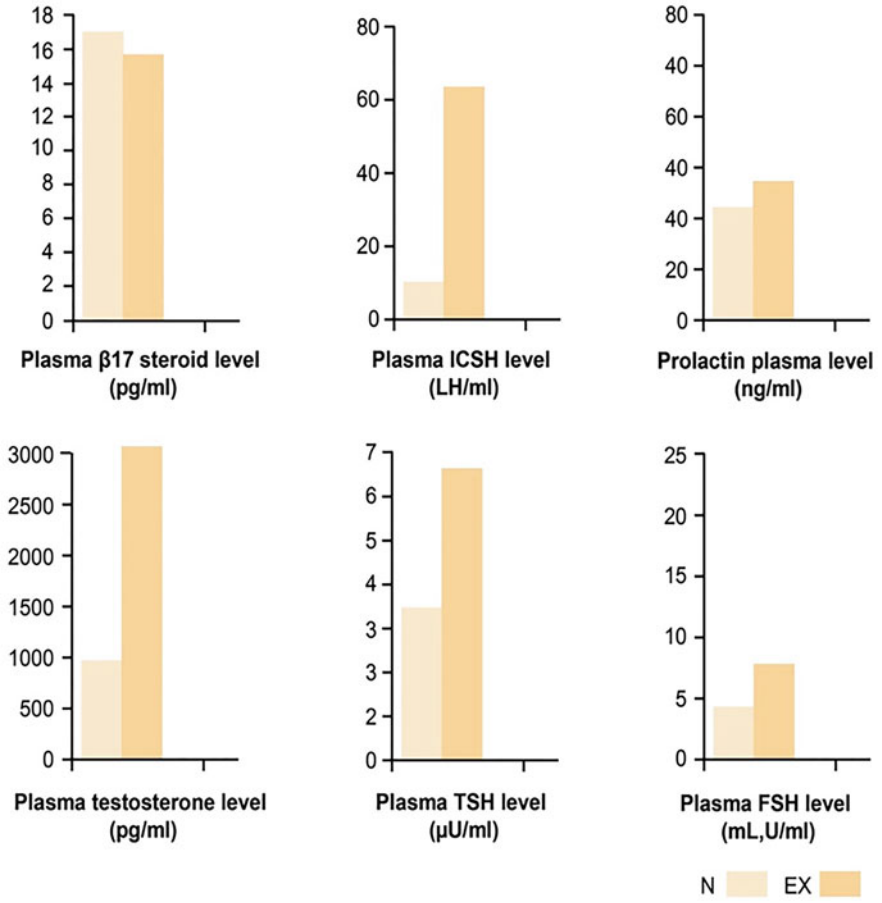

Fig. 3.1 The levels of some regulatory and sex hormones in adult male animals before (N) and after injection with calcium (E)

complex compositing of (PRL molecule + two molecules of receptor). This PRLR connects with a tyrosine kinase, JAK2 in the cytoplasm, phosphorylates, and then receptor's phosphorylation. Other receptor-associated kinases of the Src family have also been shown to be activated by PRL. Other pathways of signaling are required to phosphorylate cytoplasmic Stat proteins, which themselves dimerize and bind to specific promoter factors on PRL genes in nucleus. Additionally, PRL stimulates pathway of Ras/Raf/MAP kinase which may be required in the proliferative activities of PRL (Bole-Feysot et al. 1998; Clevenger and Kline 2001). Alterations in the proportion between isoforms of prolactin receptor, signalization, and ending of main mediators of prolactin should be accurate in multiple organs and tissues. Some factors should be taken in consideration such as molecular functions of the mediators and the proportion of isoforms in health

or illness. Abramicheva and Smirnova (2019) explained the potential therapeutic tactics needed to correct deterioration in prolactin signaling. PRL as a pleiotropic hormone plays functions in the brain. Molecular signaling, such as NF-kappa B, PI3K/AKT, and JAK2/STAT5 are studied to be employed in the molecular pathways that clarify PRL effects in excitotoxicity, behavior as well as PRL neuroprotective effect which could be helpful in the therapeutic effect in certain neurological disorders (Molina-Salinas et al. 2021).

- Insulin receptor substrate (IRS) such as IRS-1, IRS-2, IRS-3 and IRS-4 may act as regulators of insulin-like growth factor 1(IGF-1) pathway in several steps (Tsuruzoe et al. 2001).

3.2.2 The Mechanism of Action of Hormones in the Target Cell

Hormones bring about their various effects through their specific receptors on the cell membrane. This can be demonstrated through the mechanism of action of peptide hormones. Peptide hormones bind to their specific receptors on the plasma membrane, called cell membrane receptors. Figure 3.2 shows that the effect of the peptide hormones on the target cell is achieved through several mechanisms. The first messenger binds to its receptors on the cell membrane forming a hormone–receptor complex via the enzyme adenylyl cyclase, which triggers the loss of phosphate from ATP, changing it into cAMP. This results in a temporary increase in the secondary messenger cAMP in the presence of Mg^{2+}. This process takes place in the plasma membrane and can also be triggered by GTP and prostaglandins. Following this, cAMP acts on protein kinases and has a stimulating protein (Ns) and an inhibitory protein (Ni). Thus, stimulatory hormones are mediated by Ns, while inhibitory hormones act through Ni. The stimulatory hormone can break down the stimulating proteins (Ns) into two component units, one of which is a regulatory component and stimulates the phosphorylation of ATP. This is followed by reactions that lead to a cellular response to the hormone. The enzyme nucleotide phosphodiesterase stimulates the cytoplasm to inhibit cAMP and eventually inhibits all subsequent stimulatory mechanisms. Calcium ions bound to calmodulin also stimulates this enzyme (Greenspan and Forsham 1986; Gardner and Shoback 2007; Molnar and Gair 2019).

3.3 Main Functions of the Endocrine System

Hormones in the body perform many functions that regulate the body's internal environment in accordance with internal changes and external factors. They perform their role through these physiological functions. The distinctive characteristic of the endocrine system is that its effect is exerted by route of numerous substances. Chemically, the hormones are varying groups; the range of compounds represented includes steroids, amino-acid derivatives, peptides, and proteins. The combined specific feature is that they are synthesized in specific organs or in circumscribed

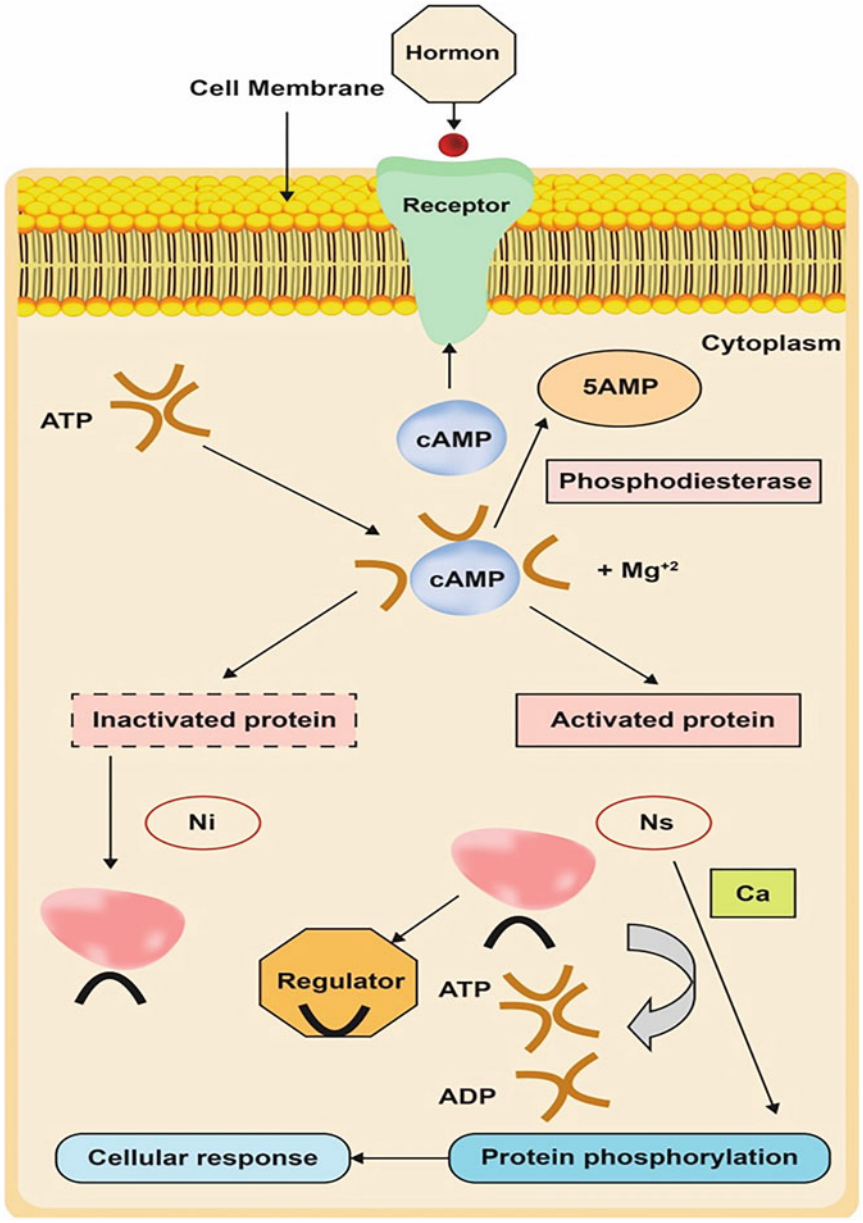

Fig. 3.2 The mechanism of action of hormones in the cell. The first messenger (hormone) binds to the receptor on the cell membrane which stimulates adenyl cyclase to form hormone–receptor complex, this triggers the release of cAMP; the secondary messenger cAMP in the presence of Mg^{2+}. cAMP acts on protein kinases and has a stimulating protein (Ns) and an inhibitory protein (Ni). The stimulatory hormone can cleavage the stimulating proteins (Ns) into two component units, one is a regulatory component that stimulates the phosphorylation of ATP. This is followed by reactions that lead to a cellular response to the hormone. The enzyme nucleotide phosphodiesterase activates the cytoplasm to suppress cAMP, then inhibits all next stimulatory mechanisms

cell's groups. For example, there are many endocrine cellular groups such as Leydig's interstitial cells in the testes, the islet cells of the pancreas, cell groups in the stomach (gastrin), the duodenal mucosa (secretin), and others. The hormones signalling are variable into wide range order to meet specific actions on the receptors of the target cells. Each hormone's action is performed only on its particular target cell. A moreover distinctive is that each endocrine organ exclusively synthesizes and release specific hormones (Brück 1983).

3.3.1 Endocrine System Coordinates Physiological Functions of the Body

The nervous system and the endocrine system function in a complementary manner, and hormones also complement each other's actions to give the body the best results without inducing conflicting effects. Hormones govern maintenance of a complex dynamic homeostasis and balance that is permanently challenged by essential/internal or external counter stressors or drives. Hormones play main action in the coordination of both fundamental and threatened stable equilibrium. The endocrine system integrates its actions to readjust homeostasis and to ameliorate the stressors, then increases the survival of life which used to clarify this integration. The adaptive reaction to stress exerts its action on the main endocrine axes. Many modifications in the regulation of the adaptive hormonal response are done in different physiological and pathophysiological situation (Chrousos 2007).

3.3.2 Endocrine System Controls Stem Cells System in the Body: The Missing Link

Endocrine system not only regulates the entire body physiological functions but also controls the tissues regeneration and maintenance because it governs the physiology of stem cells in every organ in the body. Stem cells are detected in a certain dynamic microenvironment named as a niche. The endocrine signals control the response of stem cells to environmental factors such as exercise, hypoxia, and nutrition. Most organs in the body are exhibited to environmental stress and physiological challenges. To adapt, they change tissue size, contents, or signals. These changes arise from tissue-specific stem cells and their specific environment. As the endocrine system is a main effector and responsible of physiological changes, so the system could control and change stem cell behavior in many ways. Hormones regulate all stages of stem cell life. For example, adrenocorticotropin and growth hormone, insulin, thyroid and parathyroid hormones, glucocorticoids, erythropoietin, and gastrointestinal hormones regulate most of the activities of stem cells (establishment, survival, proliferation, expansion, differentiation, maintenance, migration, and homing) (Ghorbani and Naderi-Meshkin 2016). Moreover, a single hormone can influence one type of stem cell differentially in its various stages or influence diverse types of stem cells in many ways. The wide complexity and variability in response of

stem cell to hormonal signal allows endocrine system's hormones to control the body's response and reaction to physiological challenges. More functions could be regulated by the hormones to control stem cells, for example.

3.3.2.1 Effect of Endocrine and Hormonal Signals on Stem Cell in Different Life Stages

Endocrine system and hormonal can greatly affect stem cell functions in fetal, postnatal, and adult tissues. During life, various types of stem cells take part in tissue generation, repair, plasticity, and maintenance. Their capability to secrete growth factors, to propagate and differentiate to sundry cell lineages, and to immigrate and reside into the deteriorated tissues made them attractive factors for cell medication and tissue engineering. Normal function of stem cell is restricted to the cell intrinsic pathways and extrinsic signals coming from the surrounded circulation or microenvironment. Knowledge of the signals that regulate stem cell functions is major to understand organogenesis, tissue repair, and plasticity in normal physiological functions and to improve the therapeutic efficiency of stem cells in regenerative medicine (Ghorbani and Naderi-Meshkin 2016). Expression of possibility stem cell markers like nestin, as well as topographical residency in the peripheral area around the pituitary cleft has been believed to specified pituitary stem cells. A side population has been identified in the *postnatal* pituitary which in several other tissues appear a stem cell-enriched part (Vankelecom 2007). In addition to the niches of stem cell, elderly also impacts signals that immediately or indirectly influence the functions of stem cells in the tissue. These signals contain secreted soluble molecules by different tissues, like hormones, growth factors, cytokines, exosomes, and circulating mRNAs (Carlson et al. 2009). The endocrine system coordinates a wide-ranging array of body functions chiefly through secretion of hormones and their actions on target tissues. Collective efforts by geneticists, developmental biologists, and stem cell biologists have produced resources of knowledge concerning involving of stem/progenitor cells to both organogenesis and self-renewal of endocrine organs. Pathways controlling pivotal steps in both growth, expansion, and stemness maintenance, and that are recognized to be significantly modified in a wide spectrum of endocrine disturbance, such as cancer, are also defined. This growing of knowledge is being directed to develop potential new cell-based remediation plans for endocrine-related disease (Mariniello et al. 2019).

3.3.2.2 New Role: Endocrine System Helps in Designing and Overcoming the Limitation of Stem Cell Therapy

Recent evidences provide the potential of manipulation of stem cell behaviors in order that ameliorate their curative changes. The endocrine system is believed as an essential regulator of stem/progenitor cells in the physiological status. Hormonal signals modify appearance of stem cell behaviors including survival, propagation, differentiation, immigration, and residency. The modifying impact of hormones has pharmacological potentials to boost the regenerative efficiency of stem cells existing in the tissues in addition to increasing the efficiency of cell-based treatment. Furthermore, the endocrine system is a route that could be used by environmental

effectors such as exercise, hypoxia, and nutrition can adjust stem cells functions (Gancz and Lilach 2013; Ghorbani and Naderi-Meshkin 2016). For example, thyroid hormone is a key determinant factor for tissue functions in vivo. The family of deiodinase regulates the tissue-specific activation/inactivation of intracellular thyroid hormones. The regulation of T3-dependent transcriptional program is required by several cell's systems, particularly the stem cells. There is a strong relationship between thyroid hormones and different signal mechanisms involved in the control of stem cell functions. The deiodinases may take a role in the biology and physiology of stem cell. Stem cells possess an unlimited self-renewal capability and the potency to differentiate into multiple types of mature cells (Salvatore 2018).

In pancreas, one of the difficulties facing in vivo's studies of maturation of human embryonic stem cells/induced pluripotent stem cells-derived cells (hESC/iPSC) is the low survival average post-transplantation, despite encapsulation of implanted pancreatic cells to avoid the immune reaction. It has been reported that generation of islet-like organoids could be derived from hESC/iPS, but it still needs vascularized structure to be applied in regenerative medicine (Shahjalal et al. 2018). After implantation of human induced pluripotent stem cell-derived pancreatic endocrine progenitor cells in insulin-deficient diabetic in mice, there is upregulation of the insulin-producing capability by growing the endocrine cell's number including insulin-producing cells without affecting the bloc of graft, which revealed helpful thought in diabetic medication by stem cell-derived pancreatic cells (Mochida et al. 2020).

3.3.3 Hormones Govern Receptor Regulation and Number

Hormones work with their specific receptors to regulate organ function by controlling the number of receptors according to the amount of hormone in the blood. Regulation of receptors is a critical role of endocrine/hormone functions through up- or downregulation of the number of its receptors and by desensitization of the receptors. Hormone acts to increase or decrease receptor synthesis, by internalization of membranous receptors after binding with ligand, or by desensitization (deconjugation of the receptor from its signal transduction path). It generally requires phosphorylation of the receptor. Several hormones can regulate their own receptors (homologous regulation) such as regulation of hypothalamic GnRH on the pituitary to release gonads regulating hormones (FSH and LH), while other receptors are regulated by different hormones (heterologous regulation) such as estrogen that regulates oxytocin's receptors. Coupling between hormone and its receptor relies on the number of receptors, the level of circulating hormone, and the affinity of the hormone for the receptor. The affinity is known as a hormone concentration that occupies half the total number of receptors and the higher the affinity the lower the concentration of hormone demanded. The specific hormone–receptor in the target cells decreases their surface's receptor numbers, while the opposite happens when hormone concentrations are low, in which case the receptor cells bind strongly to the small amount of hormone circulating in the blood. Usually, a ratio of less than 5% of hormone is occupied by receptors at any one time with achieving maximum

biological responses when only a part of the total number of receptors are occupied. These two factors are critical for defining response of the target cell to a hormone although there is low occupation of receptors (Nussey and Whitehead 2001; Molnar and Gair 2019).

3.3.4 Hormones Regulate Ions Transport and Membrane Permeability

Hormones regulate ion permeability and transport processes across the cell membrane. This consequently has an effect on the rate of energy production, processing, and secretion of substances, as well as on the transfer of nutritional elements such as amino acids, glucose, and fatty acids, all of which are vital processes for the body. In addition, they regulate the transport of substances across the epithelium and activate enzymes in the cell membrane, cytoplasmic mitochondria, and numerous other enzymes necessary for cell reactions.

The permeability of cell junction is upregulated via rise of the level of cAMP. Many cell lines such as rat glioma C-6 cells, with β-adrenergic receptors, were treated with catecholamine, also human lung WI-38 cells, with prostaglandin receptors, were exposed to prostaglandin E1. Junctional permeability, the ratio of cell interfaces transferring the probes, increased after treating with hormone. The rise in permeability required many hours to improve and it was related with a rise in the particles number of membranous gap-junction. This communication between junctional intercellular and hormonal may give physiological regulation mechanism for junctional communication and physiological symmetry of cell's responses in target organs and tissues to hormone (Radu et al. 1982). Hormone induced changes in cAMP can modify human red blood cells (RBC) proportional ionic permeability of chloride. Elevated plasma concentrations of epinephrine or norepinephrine elevated relative ionic chloride permeability IN uremic RBC (London et al. 1993). Vasopressin and other hormones increase cytosolic Ca^{2+} and stimulate protein kinase C elevated permeability through the nuclear membrane. Moreover, centralized release of retained Ca^{2+}—which is close to the envelope of the nucleus—produced a local increase in the permeability of the nucleus. However, neither stimulation nor suppression of protein kinase C influenced nuclear permeability. Hormones binding to certain G protein-coupled receptors elevate nuclear permeability through cytosolic Ca^{2+} (O'Brien et al. 2007).

3.3.5 Hormones Regulate Substances and Minerals in the Blood and Cells

Hormones regulate the blood and cellular levels of substances and salts to preserve and maintain balance in the body's internal environment. This process takes place through hormonal integration. This is demonstrated through the set of hormones responsible for carbohydrate metabolism in the case of hunger and satiety (insulin,

glucagon, growth hormone, etc.). Also, the system is responsible for water and mineral metabolism (antidiuretic hormone, parathormone, calcitonin, and adrenal mineral corticoids). The homeostasis brought by hormones is not the sole result of internal metabolism, such as that of glucose, phosphorous, calcium, and other substances, since there are external factors such as temperature, dryness, and psychological factors that lead to the appropriate hormones responding physiologically by adjusting their secretion.

Another example for maintaining balance is aldosterone, the steroid hormone belongs to a group of hormones called mineral corticosteroid that regulates ion and water concentrations. Aldosterone released by the adrenal cortex is responsible for adjustment of electrolyte levels in extracellular fluids. In contraindication to ADH, which supports the reabsorption of water to keep the required water balance, aldosterone acts on kidney tubules by stimulating Na reabsorption and K release from extracellular fluid of the cells (Molnar and Gair 2019). Many factors can stimulate aldosterone release such as decrease in blood sodium concentrations, blood hypotension, or blood volume, or a rise in blood potassium concentrations. It also suppresses the loss of Na in exocrine excretion such as saliva and sweat and gastric juice. The reabsorption of Na also leads to the osmotic reabsorption of free water, then returning blood volume and pressure to normal. The mechanism that blood hypotension stimulates aldosterone release could be explained by triggering a series of chemical release. When blood pressure decreases, the renin–angiotensin–aldosterone system is stimulated. Cells of the juxtaglomerular apparatus, which control the functions of the kidney nephrons, are alarmed and release renin instant. Renin, a hormone, circulates in the bloodstream and interacts with angiotensinogen (inactive plasma protein produced by the liver). Angiotensinogen is cleaved by renin and converts it to an active form called angiotensin I, which is converted into angiotensin II in the lungs. Angiotensin II acts as a hormone which causes the release of aldosterone hormone, leading to increased Na reabsorption, water reservation, and an elevation in blood pressure. Angiotensin II that also acts as a potent vasoconstrictor leads to an increase in ADH which increased thirstiness, to raise blood pressure and volume.

3.3.6 The Circadian Rhythm of the Hypothalamus–Pituitary Axis

Lot of functions of human behavior and physiology are governed by daily circadian rhythms (24-h) that effectively play a key role in the health and well-being, such as the cycle of sleep-wake, functioning patterns, attentiveness, and various daily hormones profiles and coordination. These rhythms are naturally created by an internal regulator point "pacemaker" in the hypothalamus, where diurnal light exposure to the retina of human's eye is involved to sustain synchrony of these circadian rhythms either with internal or external environments. Individuals that have normal eyesight sense consider this daily concurrence as granted function, although they face several of the difficulties of circadian desynchrony when they travel for long distances or working night shifts (Lockley et al. 2007). The

hypothalamus and the master endocrine gland play a key role in daily variations and physiological functions. The circadian/biological clock acts carefully to regulate each level of the pituitary–hypothalamus axis ensuring proper compatibility of all physiological functions with daylight, either under normal healthy conditions or unhealthy environmental conditions (Lin et al. 2015). Impulsion is an essential feature of the central nervous system and endocrine systems. Circadian clocks are found throughout the central nervous system and periphery, as they regulate several physiological functions as well as mood. These processes involve monoaminergic and glutamatergic transit, hypothalamic–pituitary–adrenal axis function, immune and metabolism function. The pituitary–adrenal axis dynamically regulates the production of corticosteroids in the physiological status and in response to stress. Within the full daily hours, this axis function oscillates with either the ultradian or circadian rhythm. These rhythms show importance for regulating metabolism, inflammation, stress response. Also, mood and cognition undergo circadian genes regulation by molecular and cellular mechanism. The nervous and endocrine systems drive these rhythms in amazing physiological mechanisms, while causing health consequences when they are disordered. There is also a link between disruption of circadian rhythm and regulation of mood (Focke and Iremonger 2020; Ketchesin et al. 2020).

3.3.7 Completion of Growth, Sexual, Differentiation, and Mental Maturation

The thyroid and growth hormones, along with the sex and other hormones, contribute to mental and sexual growth as well as to bodily growth. They also play a central role along with the sex hormones and prolactin in stimulating and regulating growth in general in the organism, since the growth hormone triggers bone and muscle growth among others. It is assisted by sex hormones, such as testosterone and estradiol, in protein synthesis in the tissues and ensuring that the levels of salts such as calcium and phosphorous in the bones are in equilibrium with their levels in the blood. Gonads hormones and growth hormone function in high accuracy during puberty phases to regulate skeletal system growth and to close the epiphysis of long bones at the end of puberty phase through genetical and molecular mechanisms. Estradiol and testosterone hormones play role in the differentiation of gonadal organs of infant during its development in the first semester of pregnancy.

3.3.8 Elasticity and Plasticity of Human Endocrine System

Hormones intermediate developmental flexibilities, the changes in the phenotype that happen during development of embryo. Due to their highly restricted functions, the elasticity and plasticity of human endocrine system suggest a powerful history of adaptation to changing environments. The main axis such as hypothalamus-pituitary-adrenal axis (HPAA) and the hypothalamus-pituitary-gonadal axis

(HPGA) plays key roles over important periods since the produced hormones influence strongly on the development of the brain. These two axis systems have potent characteristics in human developmental plasticity to be reacting to dynamic effectors connected with human society (Ponzi et al. 2020). Also, serotonin is a monoamine that is distributed widely in the brain. It plays a comprehensive role in development process of the immature brain and in adult brain functions during life. During development of the brain, serotonin regulates its own final terminal density (autoregulation) cortical electric circuits development and specified connections between the thalamus and brain cortex. Serotonin is using pharmacotherapy to ameliorate many developmental disorders caused by deficit of serotonin such as autism, sudden infant death syndrome, rare genetic syndromes, and others (Whitaker-Azmitia 2020).

3.3.9 Endocrine Physiology and Adaptation to Stressors

Physiological adaptation to variable conditions of food availability is not only visible at the behavioral level, but also at endocrine system/hormonal level. So, thus, melatonin, adrenal corticosteroids, adipokines (leptin/ghrelin), insulin/glucagon, orexins, and T4, T3 which display rhythmic profiles of release in ad libitum feeding status are sensitive to raise and/or reduction in energy stock. Also, they are influenced when food sources become limited or unobtainable at usual times (Feillet 2010). Stress leaves a constant impression on human and other organisms and change their future responses. Neurons of hypothalamic corticotropin-releasing hormone (CRH) orchestrate endocrine and behavioral reactions to stress as they are very sensitive to adrenal corticosteroids (stress hormones). CRH neurons are stimulated speedily in response to stress. CRH neurons activity highly accustom to reduplicated presentations, but not new stressors. Stress experience and corticosteroids intone and modify special components of CRH neuronal action in order to mediate stress-stimulated adaptations (Kim et al. 2019).

3.4 Factors Regulating Hormones Secretion

3.4.1 Regulation of Hormone Concentration in the Circulatory System by Humoral Factors

The essential role of hormones is to help the body achieve homeostasis. This means that metabolites, salts, and other substances found in the blood have a regulatory effect on hormone secretion. The positive and negative feedback mechanism is one of the most crucial factors in regulating hormone secretion. An example of positive feedback occurs when the Graafian follicle, during the pre-ovulation stage, releases estrogen despite elevated levels of estrogen in the bloodstream, which alerts the pituitary to secrete more of the hormone. Conversely, there is negative feedback, for example, when there is an increase in the cortisol levels in the blood, the pituitary

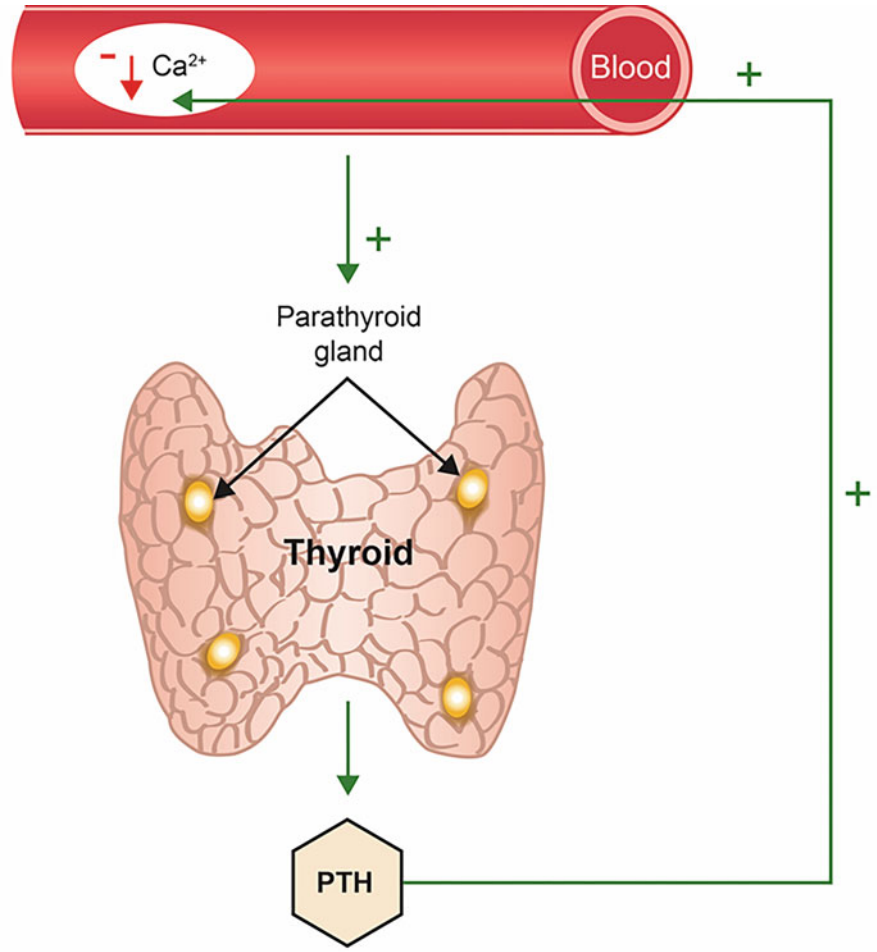

Fig. 3.3 Regulation of free calcium levels in the blood by parathyroid glands in negative back mechanism manner. PTH increases free calcium in the circulation to the normal physiological limit. To avoid higher levels, high level of calcium inhibits the secretion of PTH from parathyroid. In case calcium level decreased, this stimulates the gland to produce PTH

inhibits the adrenal cortex, then cortisol secretion decreases. The reverse happens when cortisol levels in the blood drop below physiological levels. This leads to the release of cortisol into the blood by activation of the pituitary to secrete ACTH (short axis). This alerts the adrenal cortex to secrete the hormone or it alerts the hypothalamus (long axis) to alert the pituitary and so on. Figure 3.3 depicts an example of how metabolites regulate the hormones. Another example of negative feedback mechanism is the regulation that takes place when there is a decrease in the thyroid gland hormones thyroxine (T_4) and triiodothyronine (T_3). The hypothalamus or pituitary is alerted and produces TRH and TSH successively. When the levels of the two thyroid

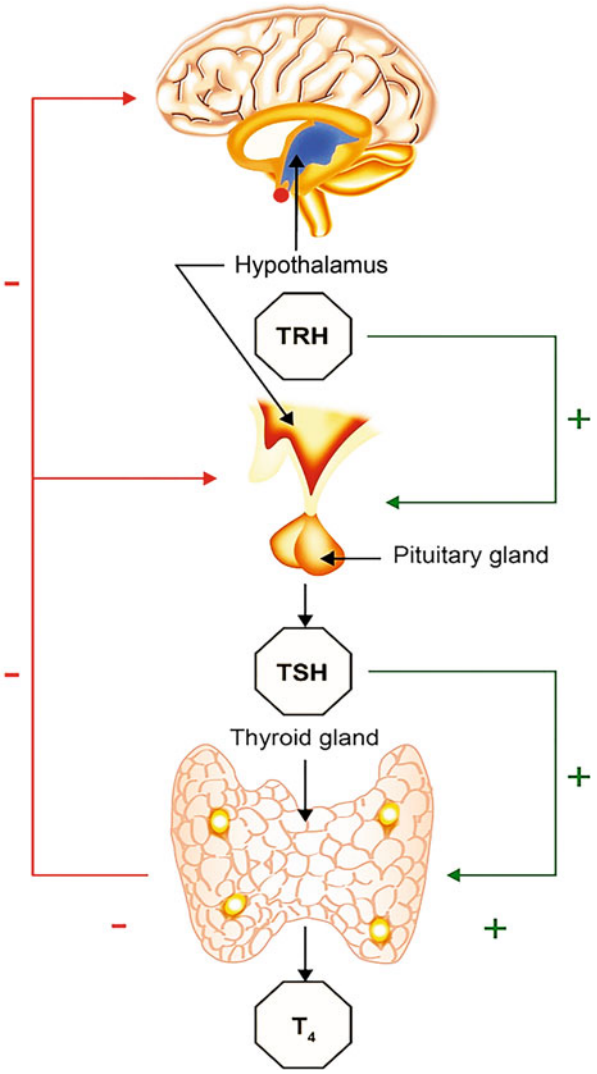

Fig. 3.4 Regulation of thyroid hormones secretion (T_4–T_3–Negative feedback mechanism). TSH increases T3 and T4 in the circulation to the normal physiological limit. To avoid higher levels, high level of T3 and T4 inhibits the secretion of TSH from pituitary as short loop or inhibits production of TRH from the hypothalamus as long loop. In case T3 and T4 level decreased in blood, this stimulates the short or long loop to produce TSH or TRH subsequently

hormones increase, TRH stimulates the pituitary to secrete TSH, which sends a signal to the thyroid to secrete T_3 and T_4 as shown in Fig. 3.4.

3.4.2 Hypothalamic Control of the Pituitary Gland

As will be detailed mentioned in Chap. 4, the hypothalamus controls the function of the two lobes of the pituitary gland: glandular and neuronal lobes:

Glandular Anterior Lobe: This is mediated by neuronal hypothalamic hormones that stimulate the pituitary gland to secrete its hormones such as those that cross

the portal vessels (Fig. 4.1), some of which stimulate and some of which inhibit certain pituitary hormones.

Neuronal Posterior Lobe: This is mediated by neuronal hypothalamic hormones that make up the posterior lobe hormones that stimulate the neuronal part of the pituitary to secrete oxytocin and vasopressin.

3.4.3 Direct Neuronal Stimulation on Endocrine Glands and Cells

The arcuate nucleus (ARC) of the hypothalamus is gathering of neurons in the medio-basal hypothalamus, adjacent to the third ventricle and the median eminence. ARC contains many important populations of neurons that mediate different physiological and neuroendocrine and functions. Kisspeptin is a metastasis inhibitor gene in human which plays an important role in starting release of gonadotropin releasing hormones (GnRH) at puberty (Lee et al. 1986; Skorupskaite et al. 2014). Kisspeptin neuronal fibers originate in the external zone of the median eminence (ME). ACR in the hypothalamus contains populations of kisspeptin neurons project fibers to the ME. There is a direct communication (kisspeptin to GnRH terminal-to-terminal) in the ME, kisspeptin plays signaling role as it receives stimulatory estrogen signals and produces the complete positive feedback of GnRH/LH. Kisspeptin neurons of the ARC extent to the external region of the ME and act onto the GnRH nerve fibers (Schwartz and Zeltser 2013). Balance of energy is done through harmonious actions of nutrition circuits of neural and neuroendocrine, which boost energy in case of limited energy supply. Feeding behavior encourages muscle's contraction of different somatic and visceral tissues that distributed over the head and the upper digestive system in order to digest food, stimulate endocrine and exocrine to release hormones and enzymes, respectively. Neurons contributing to nutrition behavior are centralized in central, peripheral, and enteric nerve system (Schwartz and Zeltser 2013). The endocrine gland has a direct neuronal supply that regulates its secretion, as is the case when the neuronal cortex stimulates the adrenal medulla to produce adrenaline.

There is a set of cells organized in some endocrine glands and other organs include the pituitary, adrenal glands, thyroid (C-cells) and pineal gland, sympathetic nervous system, the intestines, pancreas, melanocytes in the skin, P-cells in lungs, the urogenital canal, and chemoreceptors as type I cells, all of these cells have originated from the neural crest. These cells are called APUD cells which are designed and programmed to act as a neuroendocrine function. This set of cells can be considered as one of the physiological control systems. They produce a diversity of amine and peptide hormones that are characterized by cytochemical features. Its name (APUD) is derived from (Amine Precursor Uptake and Decarboxylation) (Whitwam 1977). APUD does not include steroidogenesis endocrine cells.

3.4.4 Effect of External Environment, Genetics, and Lifestyle on Hormones Secretion

Early life stress elevates the risk development metabolic and cognitive diseases in adulthood (Abbink et al. 2020). Diabetes mellitus (DM) is a group of symptoms for many disorders known by constant hyperglycemia in which genetic and environmental risk factors work synergistically. DM type 1 happens in children and requires contagious, autoimmune, or toxic demolition of pancreatic beta cells that produce insulin, so they depend on external insulin. While DM type 2 occurs in adults in which they secrete insulin partially and ineffective because of insulin resistance. Also, there is another group of unusual types of diabetes in the youth which they inherited as monogenetic disorders. The implied process could be called "genes versus environment" or "nature versus nutrition," DM happens at the interface of the two areas, in addition to the influence of epigenetic heritage. These factors have great effects on chronic health diseases such as diabetes that require change in lifestyle. Also, epigenetic factors can modulate the interaction between environment and genes (Tremblay and Hamet 2019).

3.5 Relationship and Coordination Between Hormones Actions

Hormones act in a complementary and coordinated manner with each other without any conflicts in their respective mechanisms of action. Hormones are signaling molecules spreading through all tissues, thus work on the entire level of organism. Furthermore, a specific hormone influences a set of various biological functions perfectly. Hormones coordinate combined collaboration between the cells and tissues of the body, a phenomenon is named "organismal harmony." Moreover, that hormones mediate life history which is shaped finally by evolutionary stressors to the extent to include decisions at organismal level (van den Berg 2019).

3.5.1 Regulatory and Domination Relationship

This occurs when one hormone is dependent on the secretion of another regulatory hormone. The majority of frontal lobe pituitary hormones are released after secretion of stimulating hormonal factors from the hypothalamus. For example, the pituitary secretes FSH after it receives a hormonal signal called FSHRH, and this is also the case for luteinizing hormone (LH). Another example, insulin suppresses glucose production in direct and indirect mechanisms in the liver since it dominates the acute regulation of hepatic glucose production in the normal dog although the liver is affected by other hormones (Edgerton et al. 2006).

3.5.2 Alternating Relationship

This is where the levels of two hormones in the blood increase in an alternating manner as seen with insulin and GH. Despite the synergistic effect of these two hormones on growth, they work together in alternation; their concentrations immediately after and between meals alternate such that insulin increases immediately after a meal and growth hormone levels decrease, at the time close to the next meal, growth hormone increases and insulin decreases, and so on, in order to maintain steady glucose levels.

Plasma insulin decreases lingeringly through fasting, while plasma growth hormone showed intermittently increased levels. Insulin levels elevated immediately after taking protein food, and growth hormone present higher concentrations than over fasting but this increase correlates with the protein intake followed by the rise of insulin. Exercise gave rise a clear decrease in the protein-stimulated insulin increase and additional rise in growth hormone concentrations (Sukkar et al. 1967).

3.5.3 Antagonistic Relationship

In this relationship, each hormone has an antagonistic effect on the other hormone's function, for example, calcitonin helps deposit calcium and phosphate by stimulating osteoblast, while parathormone acts antagonistically on the bones by reabsorbing calcium through stimulation of the osteoclasts to achieve a steady calcium and phosphate state in the body alongside other mechanisms. Progesterone, which is present in the blood throughout pregnancy, is an antagonist of oxytocin.

The counterregulatory hormones cortisol, glucagon, adrenaline, and growth hormone are produced through hypoglycemia and also in other stress cases. These counterregulatory groups act as insulin-antagonistically effects in the liver and in the peripheral tissues. The insulin–antagonistic action on glucagon and adrenaline is of rapid start, while both cortisol and growth hormone are noticed only after a lateness period of many hours. The counterregulatory hormones cortisol, glucagon, adrenaline, and growth hormone are produced during hypoglycemia and also in other stress cases. These counterregulatory group acts as insulin-antagonistically effects in the liver and in the peripheral tissues. Glucagon is the key hormone for sharp glucose increase. Growth hormone and cortisol participate, to counter regulation through long hypoglycemia, while adrenaline is the most importance in this case. In addition to insulin-antagonistic action on growth hormone, it plays an important role in the control of daily rhythms of glucose metabolism (Lager 1991).

3.5.4 Permissive Action

Permissiveness is a biochemical function, as the presence of a specific hormone is necessary for another hormone to exert its full functions in its target cell. Permissive hormone acts to upregulate the receptors of the anther hormone on its target. The

permissive role of the hormones has been evident. Parikh et al. (2017) suggest this role of combined of glucocorticoid and thyroid hormones during the cardiac differentiation phase. Leptin is acting as a permissive hormone for reproduction. The receptivity of leptin of both the hypothalamus and the pituitary is important. Animals like mice that could not synthesize leptin are infertile (Odle et al. 2018). Prolactin is a major permissive regulator of LH effect in the ovary and of its additional on extragonadal functions (Anne et al. 2013).

3.5.5 Cooperative Relationship

The increase in estrogen levels at the end of pregnancy increases the number of oxytocin receptors in the uterus, and this in turn boosts the effect of oxytocin on the muscle cells of the myometrium during birth, also helps prostaglandin for uterus contracting (Bick et al. 2005). For example, the combination of the effects of the growth hormone from the pituitary, cortisol from the adrenal cortex, adrenaline from the adrenal medulla, and glucagon from the pancreas islets quickly restores low glucose levels. Parathormone (TH) works in unison with the catabolite of activated vitamin D, called calcitriol ($1,25(OH)_2D$) produced by the kidneys, to absorb calcium and phosphorous from the intestines, kidneys, and bones to increase calcium levels in the blood to physiological levels. In addition, the GH, thyroxine, and insulin work together to stimulate growth, especially in the bones. As Al-Makawi (2000) mentioned that estrogen and progesterone work together to bring about an eight-fold increase in the thickness of the lining of the uterus compared to their individual effect if each acted alone.

3.6 Conclusion

Endocrine system is an integrated communicative tool for the human body, performing various functions through chemical messengers in the form of hormones. These hormones are produced by the glands, tissues, and cells, where they regulate and control the functions of targeted organs and cells to maintain homeostasis. The pituitary gland is the master regulator of the endocrine system, which coordinates and controls the function of other glands in the body through secretion and signals of stimulating/inhibiting hormones. The endocrine system plays a key role in maintenance, regeneration, and remodeling the tissues by governing stem/progenitor cells, sexual and mental maturation. The signal transduction mechanism of the hormones is mediated by binding with cell surface receptors and stimulating multifactorial downstream targets including second messengers.

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The Pituitary Gland: Functional Relationship with the Hypothalamus, Structure, and Physiology

4

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Contents

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Abstract

The pituitary gland is the most important endocrine gland as it controls many of the body's functions such as growth, maturation, metabolism, reproduction and coping, responding to stress, daily rhythm, and ageing. The pituitary performs a key role in the regulation of several physiological functions in association and interactions with different hormones and growth factors. The pituitary gland is small in size and is located at the base of the skull within a depression in the sphenoid bone (sella turcica). This site allows for functional and anatomical connections with the hypothalamus via the portal blood system. The pituitary consists of two lobes: the posterior lobe (neurohypophysis) which has a rich supply of nerves and contains pituicytes, whereas the anterior lobe (adenohypophysis) has less of a nerve supply. The adenohypophysis is divided into three parts entirely derived from Rathke's pouch; they are: (1) Pars distalis. (2) Pars intermedia located between the pars distalis and the posterior pituitary. (3) Pars tuberalis, a longitudinal collection of secretory cells with a good blood supply.

The pituitary gland also contains stem cells which play role in turnover, cell differentiation, and response to physiological, pathological, and stress factors and to respond to hormonal signals. The hypothalamus is a neuroendocrine structure in the human brain involved in many body physiological functions, such as pituitary functions, circadian rhythm, stress response, homeostasis, behaviour, growth, and reproduction. This regulation is carried out partially through the hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonads axis, and hypothalamic-pituitary-thyroid axis. The pituitary gland secretes many hormones, the anterior pituitary produces most pituitary hormones such as growth hormones, prolactin, thyroid-stimulating hormones, adrenocorticotrophic hormone, melanocyte-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone, while the posterior lobe release two neurohormones such as vasopressin and oxytocin. In addition, the pituitary gland is also involved in releasing antidiuretic hormone, somatostatin, dopamine, and gonadotropin-inhibitory hormone, appetite-regulating hormone (leptin), and vasopressin. This chapter discusses the topics related to the pituitary gland and its functional relationship with the hypothalamus.

Keywords

Pituitary gland · Hypothalamus · Physiology · Anatomy · Structure · Stem cells

Abbreviations

α-MSH	α-Melanocyte-stimulating hormone
β-LPH	β-lipotropic hormone
β-MSH	β-Melanocyte-stimulating hormone
ACTH	Adrenocorticotropic hormone
ACTHRH	Adrenocorticotropic hormone-releasing hormone
ADH	Antidiuretic hormone
APUD	Amine precursor uptake and decarboxylation
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CRF	Corticotropin-releasing factor
CRH	Corticotropin-releasing hormone
FSH	Follicle-stimulating hormone
FSHRH	Follicle-stimulating hormone-releasing hormone
GH	Growth hormone
GHIH	Growth hormone-inhibiting hormone
GHR	Growth hormone receptor
GHRH	Growth hormone-releasing hormone
GnIH	Gonadotropin-inhibitory hormone
GnRH	Gonadotropin-releasing hormone
GPR147	G protein-coupled receptor 147
GSH	Gametocyte-stimulating hormone

H&E	Haematoxylin and eosin stain
hCG	Human chorionic gonadotropin
hMG	Human menopausal gonadotropin
hTSH	Human thyroid-stimulating hormone
ICSH	Interstitial cell stimulating hormone
IGF	Insulin-like growth factor
IGF-BP	Insulin-like growth factor-binding protein
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
MPOA	Medial preoptic area
MSH	Melanocyte-stimulating hormone
PIF	Prolactin inhibitory factor
POMC	Pro-opiomelanocortin
pre-POMC	Pre-pro-opiomelanocortin
PRL	Prolactin
PVN	Paraventricular nucleus
STAT	Signal transducer and activator of transcription
STH	Somatotrophic hormone
T3	Triiodothyronine
T4	Thyroxine
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone
TSHR	Thyroid-stimulating hormone receptor

4.1 Introduction

The pituitary gland, also known as the hypophysis, is the most important endocrine gland as it controls many of the body's functions, either directly or indirectly. The pituitary performs a key role in the regulation of several physiological functions which is realized by the effects and interactions of different hormones and growth factors that are synthesized and released by more than five endocrine cell kinds and the non-endocrine cells and components that anatomically, functionally, and cooperatively express the complexity of pituitary (Bilezikjian and Vale 2011). It controls and regulates the functions of other endocrine glands and various body functions. In the scientific literature, it is also known as the master gland and controls physiological processes in humans and animals. The pituitary gland plays a key role in steering the essential processes of life such as growth, maturation, metabolism, reproduction and coping, responding to stress, daily rhythm, and ageing. Moreover, it has a stem cells population which is required for its cell remodelling and responding to numerous factors. The secretion of hormones from its anterior and posterior lobes is regulated by the neuroendocrine gland in the brain (the hypothalamus) (Guyton 1986; Trudeau and Somoza 2020). Upon this imaginary framing, the communication

between the hypophysiotropic brain and the pituitary gland is the basis of endocrinology principles. The anatomy and signals of the connexions between the hypothalamus and the pituitary gland are harmonious and reveal various manners of communication with several levels of complication. Various genes in the angiogenesis and axonal direction pathways may be substantial in that communications (Daly and Camper 2020). Many factors for transcription govern the development of the pituitary gland and specify the type of hormone-producing cell. There is an impact of every single gene on the expression of the downstream target. Several transcription factors that play main functions may mutate in patients and cause congenital pituitary diseases (Daly and Camper 2020). The liver is the central target of growth hormone action. So, many functional changes in liver physiology and biochemistry happen in the lack of growth hormone action such as changes in liver enzymes and fatty acids and amino metabolism (Riedel et al. 2020).

4.2 Anatomy and Histology of the Pituitary Gland

The pituitary gland is small in size but is well equipped for its functions because it is located at the base of the skull within a depression in the sphenoid bone (sella turcica). This site allows for functional and anatomical connection with the hypothalamus. In humans, it weighs 500–900 mg and measures approximately $6 \times 10 \times 15$ mm. During pregnancy, it doubles in size. From surface view of the pituitary gland, it seems a simple structure, contains anterior and posterior lobes that are fully imaged and visualized by MRI, while the anatomy and inner functionality are immensely complicated.

Vascular Supply of the Pituitary The pituitary gland is highly vascularized with a blood flow-rate of 0.8 mL/g/min. It is also close to a blood sinus called the sphenoidal sinus, allowing hormones from the anterior pituitary lobe to enter the bloodstream easily. The pituitary gland is connected to the hypothalamus via the portal blood system as shown in Fig. 4.1. The neurohypophysis is less vascularized than the anterior lobe, in accord with its particular function.

Nerve Supply of the Pituitary The posterior lobe has a rich supply of nerves and contains pituicytes, whereas the anterior lobe has less of a nerve supply, as shown in Fig. 4.1 (Bilezikjian and Vale 2011; Bullock et al. 1991; Lechan et al. 2019).

APUD cells As mentioned in Chap. 3, its name is related to amine precursor uptake and decarboxylation. A group of unrelated cells secrete most of the hormones except steroid hormones. It includes both specialized neurons and endocrine cells that synthesize polypeptides and biogenic amines. Its name is derived from the fact that polypeptides production relates to the uptake of a precursor amino acid and its decarboxylation process in the cell to produce an amine. Insulin, corticotropin, glucagon, and antidiuretic hormone are examples for the peptide hormones. Norepinephrine, serotonin are examples for amine hormones. Many hormones pituitary

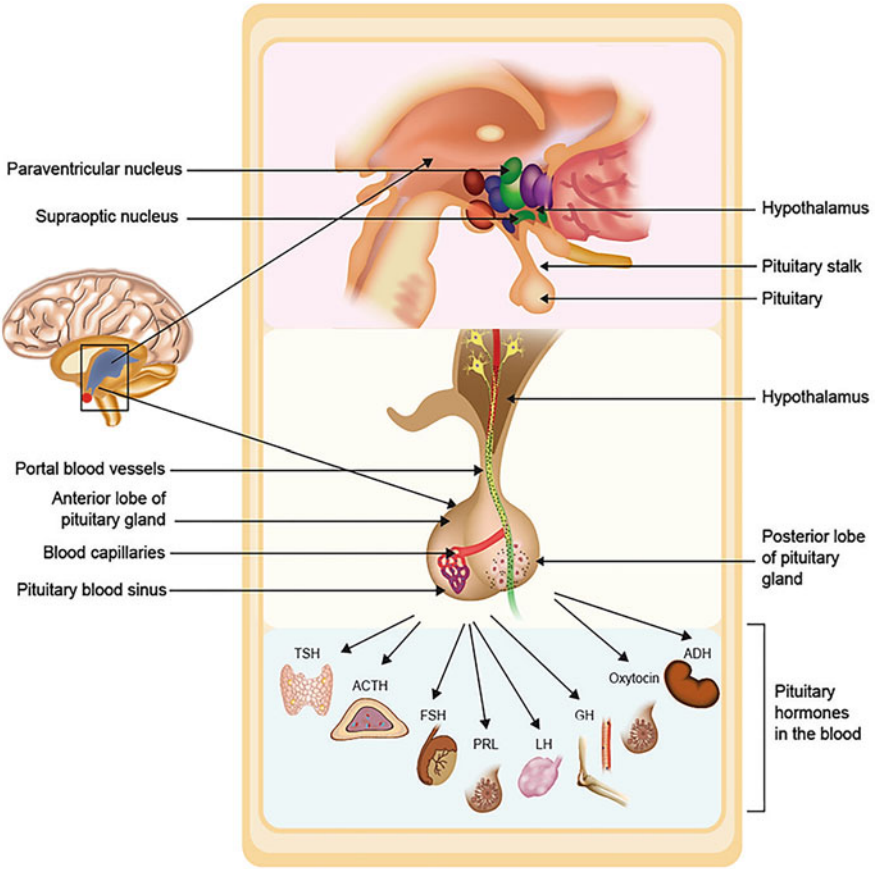

Fig. 4.1 The anterior and posterior lobes of the pituitary and their relationship with the hypothalamus. (2) Blood supply (red) and nerve supply (green): note the relative difference between the two lobes. (3) Neurons (yellow) extend from the hypothalamus to the posterior pituitary. (4) Hormones are secreted from the two lobes into the blood

secreting cells are classified as APUD cells as will be explained below. The pituitary is divided into at least three parts (adenohypophysis, neurohypophysis, and stem cells marginal zone) according to origin and function (Figs. 4.1 and 4.2).

4.2.1 Adenohypophysis

It is called also the anterior pituitary lobe. The adenohypophysis is divided into three parts entirely derived from Rathke's pouch; they are: (1) Pars distalis. (2) Pars intermedia located between the pars distalis and the posterior pituitary. It is the least vascularized of the three areas. (3) Pars tuberalis, a longitudinal collection of

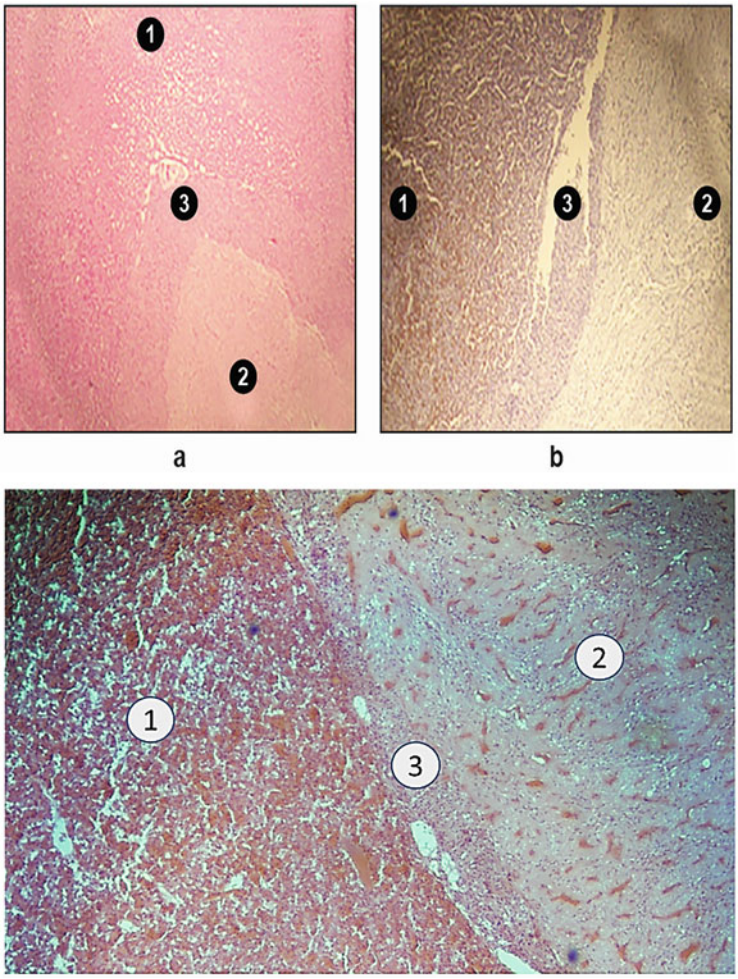

Fig. 4.2 Vertical (**a**) and horizontal (**b**) sections of the pituitary glands H&E ×4 showing (1) endocrine lobe (anterior), (2) neural lobe (posterior), and (3) the intermediate section between them, which sometimes makes up part of the anterior lobe. H&E magnification 10×, 40× and 200×

secretory cells with a good blood supply. Figure 4.3 illustrates the histology of the adenohypophysis.

Pars Distalis Pars distalis constitutes the core of the anterior pituitary in humans and is the most highly vascularized area of the pituitary gland. Its function is boosted by the portal hypophyseal vessel (Fig. 4.1), which carries the neurosecretory hormones from the hypothalamic nuclei to the anterior pituitary lobe. Epithelial cells are grouped here in the form of longitudinal extensions interspersed with blood vessels. These epithelial cells are divided into two types of cells in the anterior lobe:

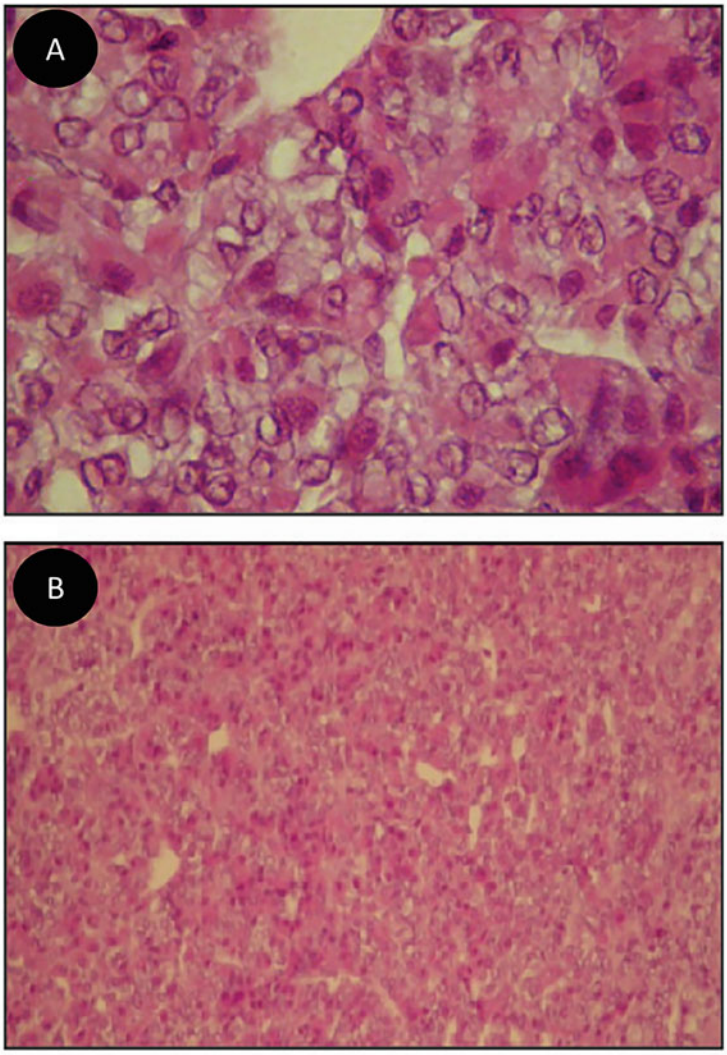

Fig. 4.3 Cross section showing secretory cells in the anterior lobe of the pituitary gland in the form of branched cords. (**a**) H&E 100×; (**b**). H&E magnification 40×

Type 1 Chromophobes which are agranulocyte cells and not chromophile precursor cells play an active secretory role (Fig. 4.4). They have multiple functions: They may be cells that secrete as-yet-unknown hormones. Act as a reserve that can be transformed into acidic or basic cells. Chromophobes may play a supporting role for other cells rather than being secretory. It is believed that they are secretory cells that have released their contents. They play a role in the secretion of adrenocorticotropic hormone (ACTH) (Al-Makawi 2000). They may be present as

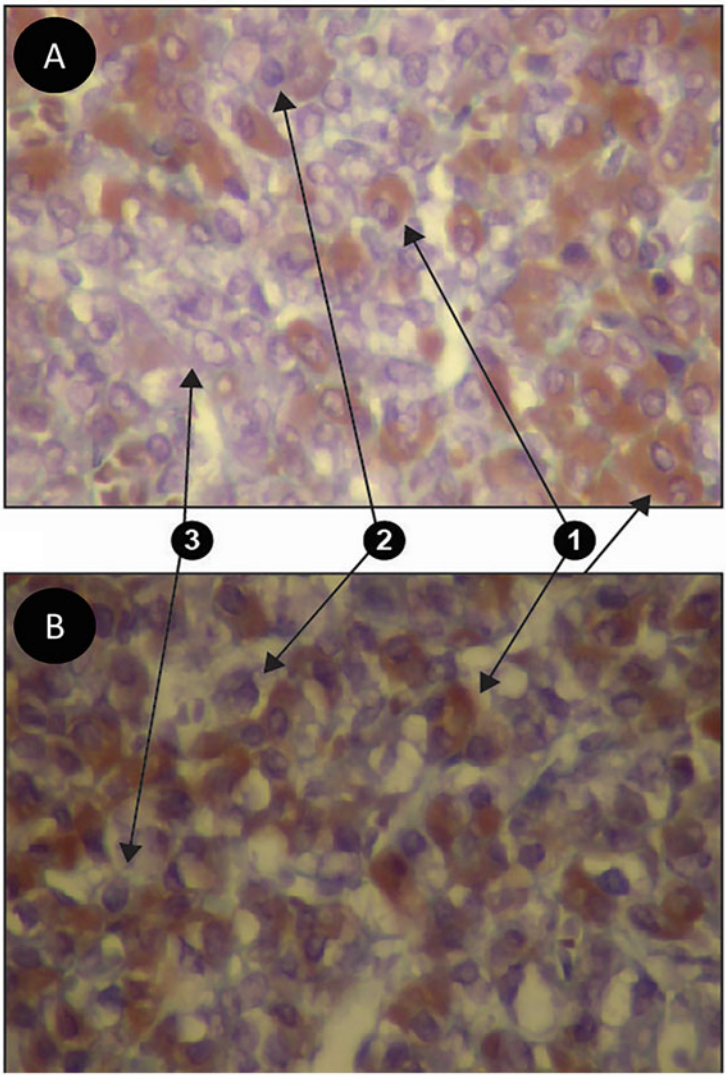

Fig. 4.4 Cross section of the anterior lobe (endocrine) showing (1) acidophils (orange or beige), (2) basophils (blue), and (3) chromophobes (no stain). (**a**): Azan 40× and (**b**): Azan ×100×

potential stem cells in the pituitary gland. Proliferation of pituitary chromophobes and prolactin (PRL)-releasing hormone cells along with the response of birds and rats to gonadal hormones and seasonal photoperiod are used as parameters for clarifying the role of hypothalamic neurons in the regulation of animal reproduction (Pantic 2001).

These secretory cells have granules that stain easily and are divided into two types depending on their staining capacity (eosinophils and basophils): Eosinophils (acidophiles): constitute approximately 80% of chromophiles (Fig. 4.4). These cells are the main cellular source of two kinds of hormones: (1) Somatotrophs secrete growth hormone (GH), also known as somatotropic hormone (STH) or somatotropin. (2) Lactotrophs or mammotrophs secrete PRL. Basophils: constitute approximately 20% of chromophils (Fig. 4.4). They are the source of the hormones below and form an organized network of structures. These cells secrete the following hormones:

- Luteotrophs secrete luteinizing hormone (LH).
- Folliculotrophs secrete follicle-stimulating hormone (FSH). Each of the preceding two cells types is called gonadotrophs and their hormones named gonadotropins.
- Thyrotrophs secrete thyroid-stimulating hormone (TSH).
- Acidophils secrete the hormone β-lipotropic hormone (β-LPH).
- Corticotrophs represent 15–20% of the cells in the anterior lobe (Ivell et al. 1983). They secrete ACTH and are classified as APUD cells.
- The pituitary gland also contains endorphins, such as β-lipoprotein, which are thought to be secreted by ACTH-secreting cells.
- Cells that secrete melanocyte-stimulating hormone (MSH) and which may also secrete ACTH. They are also classified as APUD cells.

Pars Tuberalis It is a collection of secretory cells above and enveloping the infundibular stalk. These cells extend to the base of the hypothalamus and constitute one of the most highly vascularized areas of the pituitary gland (Fig. 4.1).

Pars Intermedia The pars intermedia is found between the pars distalis and the neurohypophysis. It is a remnant structure and considered obsolete, in humans and is relatively well vascularized (Bullock et al. 1991, 2001).

4.2.2 Neurohypophysis

It is called also the posterior pituitary lobe. The neurohypophysis consists of median eminence, infundibular stem, and pars nervosa. The neural lobe is a collection of secretory neuronal axons protruding from two of the hypothalamic nuclei (the supraoptic nuclei and the paraventricular nuclei). These axons are non-medullary fibres extending downwards through the pituitary stalk to the ends of the neural lobe (Fig. 4.1). The neural lobe acts as a reservoir tissue for hormones produced by the bodies of these nuclei until they are released, including vasopressin/antidiuretic hormone (ADH) and oxytocin, which are released on demand, after their arriving from their source of production. The neurons spread through the three different

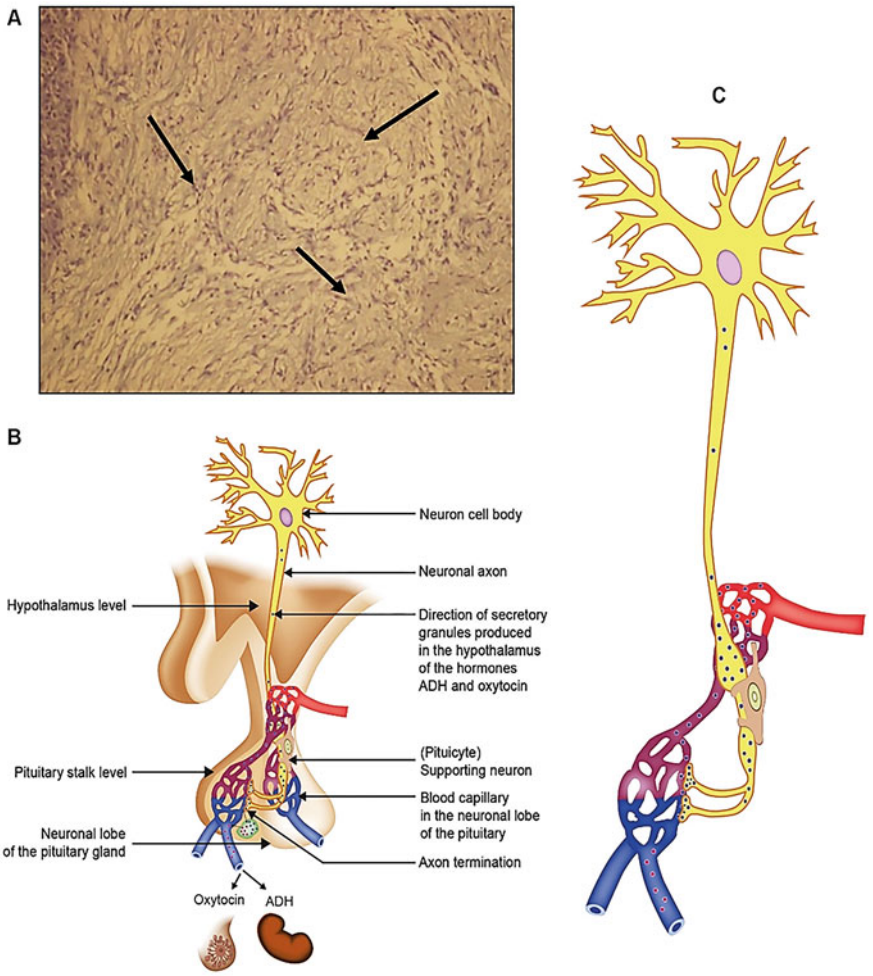

Fig. 4.5 Cross section showing the tissue of the neurohypophysis, the arrows indicate many pituicytes widespread in the tissues (**a**) (H&E ×10). The non-medullary neuronal axons (**b**, **c**) whose bodies are located in the secretory supraoptic nuclei and the paraventricular nuclei in the hypothalamus, the axons are supported by pituicytes whose structure and function resemble that of the microglia. It also shows extension of the neuro-axons from the hypothalamic nuclei via the pituitary stalk into the neurohypophysis and their role in producing and storing antidiuretic hormone (ADH) and oxytocin B. (**b**, **c**: modified from book by Waugh and Grant (2006) Published by Churchill Livingstone) (Waugh and Grant 2006)

tissues (the nuclei, pituitary stalk, and posterior lobe) and are supported by cells called pituicytes (Fig. 4.5) whose role and structure are similar to that of the microglia in the brain (Waugh and Grant 2006).

4.2.3 Stem Cells Marginal Zone and Folliculostellate

The anterior pituitary is not only comprised of three parts, but it includes an expanding group of essential factors required for the anterior pituitary growth. The cell clustering has many functions such as magnification of signals coming from the hypothalamus, local regulation mechanisms via autocrine and paracrine secretion as well as modification through glial-derived cell types, and the stem cells (Lechan et al. 2019). In the postnatal pituitary, a side population was identified in the marginal area around the cleft, which represents stem cells (Vankelecom 2007). Undifferentiated population of pituitary stem cells stays in the anterior pituitary and results into the three major lineages of progenitor, featured with the expression of main transcription factors required for lineage and last differentiation: a subpopulation differentiate into GH/PRL/TSH-expressing cells, another subpopulation cells produce ACTH-releasing cell; however, gonadotropin LH and FSH-releasing cells came from lineage of different subpopulation (Mariniello et al. 2019). Hormone-releasing-cell types also contain lactotrophs and somatotrophs and that produce both prolactin and growth hormone, which are lower differentiated precursors than the real specialized cells producing the hormone (Morris et al. 2012). In addition to stem cell, anterior pituitary contains non-endocrine folliculostellates (FS) which are organized into three-dimension networks communicating intracellularly via gap-junction. Because of their placing along the endocrine cells of the pituitary gland, FS regulates and supports endocrine cells function either mechanically or chemically by forming structural support around the endocrine cells, or through autocrine and paracrine signals by releasing growth factors and cytokines. FS acts as intrapituitary signals between numerous cell types and modifies inflammatory reaction. FS's mechanical support is also shown by its production of metalloprotease suppressor which sustains the basal membrane and supports three-dimension structure. Additionally, FS surrounds endocrine cells, making adjacent contact to provide the growth factors inside the pituitary gland (Morris et al. 2012; Rees 2005; Devnath and Inoue 2008). Also, FS has a phagocytotic activity and that FS cells are nominee of organ-specific stem cells (Inoue et al. 2002). Thus, FS promotes pituitary homeostasis, favouring the maturation of stem/progenitor cells, then stem cells play role in plasticity of the anterior pituitary in postnatal phase. Certainly, the fine adjusting of quantity and functionality of hormones releasing-cell types in diverse physiologic status involves great plasticity of the pituitary that is provided by pituitary stem and progenitor cells that govern cells differentiation. Pituitary stem cells play role in turnover, differentiation, and response to physiological, pathological, and stress factors and to respond to hormonal signals. Plasticity of pituitary provides dynamic and constant cell homeostasis and adjusts its function to either physiological conditions such as increase in growth hormone-releasing-cells during puberty or in prolactin releasing-cell during pregnancy and lactation or at pathological conditions. This requires non-hormonal pituitary stem/progenitor cells that express stem specific cell markers needed for the growth of spheroids (pituispheres) and to differentiate into pituitary releasing cells. For more explanation, for example: The active function of those subpopulations of pituitary stem cell produces generations of new

gonadotropin and ACTH producing cells after gonadectomy or adrenalectomy, respectively (Lechan et al. 2019; Vankelecom 2007; Nolan et al. 1998; Levy 2002; Horvath et al. 2010; Garcia-Lavandeira et al. 2015).

4.3 Endocrine Physiological Functions of the Hypothalamus

The hypothalamus is a neuroendocrine structure in the human brain that adjusts a broad domain of physiological functions, such as pituitary functions, circadian rhythm, stress response, homeostasis, behaviour, growth, and reproduction. This regulation is carried out partially through the hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonads axis, and hypothalamic-pituitary-thyroid axis. The hypothalamus nuclei also secrete neurohormones which stimulate the pituitary hormones that regulate the steroidal hormones involved in sexual maturation.

4.3.1 Hypothalamus Releasing Stimulatory Hormones on the Pituitary

- Thyrotrophic-releasing hormone (TRH), also called thyrotrophic-releasing factor, signals the pituitary to produce TSH from anterior pituitary.
- TRH also stimulates the pituitary gland to produce PRL from anterior pituitary.
- LH-releasing hormone (LHRH) stimulates the pituitary to secrete LH from anterior pituitary.
- FSH-releasing hormone (FSHRH) stimulates the pituitary to release FSH. The latter two hormones from the hypothalamus are jointly referred to as gonadotropin-releasing hormones GnRH.
- ACTH-releasing hormone (ACTHRH), also known as corticotropin-releasing hormone/factor (CRH/CRF), stimulates the pituitary to secrete ACTH from anterior pituitary.
- GH-releasing hormone (GHRH) stimulates GH secretion from the pituitary.
- The hypothalamus also produces oxytocin and ADH, which are secreted by the posterior lobe of pituitary.

4.3.2 Hypothalamus Inhibitory Factors on the Pituitary

- Somatostatin is released by the hypothalamus; it inhibits the secretion of GH in the anterior lobe of the pituitary. Also, the 56-amino acid c-terminal fragment of the prohormone of GnRH inhibits GH from the pituitary.
- Prolactin release-inhibiting hormones (PRIH): It is unanimity that mammalian prolactin release-inhibiting hormones (PRIH) is the catecholamine neurotransmitter (dopamine) that is a functional inhibitor of PRL secretion either in vivo or in vitro. Dopamine is a neurohormone released from the ARC and PERIV nuclei of hypothalamic neurons particularly by the tuberoinfundibular dopaminergic

neurons, then dopamine increases its concentration in the blood portal system in physiological conditions wherever PRL release is suppressed from the pituitary. Also, the 56-amino acid c-terminal fragment of the prohormone of GnRH is PRIH. While GAPA is not a physiologically PRIH because of its poor concentrations in portal or peripheral circulation (Norris and Carr 2013).

- Gonadotropin-inhibitory hormone (GnIH)**:** It is a neuropeptide produced by the hypothalamus, identified in the birds and also in mammals including human as an inhibitor of pituitary gonadotropin synthesis and release suppressing gonads growth and maintenance. As a neuroendocrine hormone, GnIH neurons' cell bodies found in birds locate in the paraventricular nucleus and also in mammals in the dorsomedial hypothalamic area. Its neurons reach the median eminence controlling anterior pituitary functions. GnIH receptor is the G protein-coupled receptor 147 (GPR147). It is believed that it couples to Gαi protein. GnIH receptor (GPR147) is expressed in the pituitary's gonadotrophs (Tsutsui et al. 2010; Takayoshi et al. 2012; Di Yorio et al. 2019).

The Physiological Functions of GnIH

- GnIH acts during various times, ranging from minutes to days.
- GnIH inhibits synthesis and release the gonadotropins from the pituitary.
- GnIH neurons extend to GnRH neurons in the preoptic area, GnIH inhibits gonadotropin production either by decreasing GnRH neurons' activity or/and directly by inhibiting the pituitary's gonadotrophs.
- Melatonin and stress activate the expression and secretion of GnIH through melatonin receptors expressed on GnIH neurons, then GnIH suppresses reproductive behaviour.
- It plays a role in responding to the environmental factors to suppress the physiological and behavioural reproductive functions of mammals and birds.

GnIH has a therapeutic effect in treating reproduction cycle and hormone-dependent disorders, such as early puberty, endometriosis, uterine fibroids, prostatic and breast cancers (Tsutsui et al. 2010; Takayoshi et al. 2012; Ubuka et al. 2012).

4.3.3 Appetite Regulation

Many blood peptides hormones and signalling pathways take key parts in food intake. Leptin is an endogenous peptide that controls the appetite, energy metabolism, and glucose intake in the central nervous system. In the normal healthy status, leptin is released from adipose tissue and transferred through the blood–brain barrier to the hypothalamus to regulate hunger and satiation. It is a prospective therapeutic hormone for obesity (Khafagy et al. 2020). Somatostatin is also one of hypothalamic peptides that controls behaviour of food-seeking, and it is a part in the complicated route of appetite (Kumar and Singh 2020). Oxytocin is a hypothalamic peptide hormone that regulates many physiological functions, some of them are eating and metabolism. Oxytocin is featured on decreasing food intake, bodyweight, and

therapeutic effects on eating disorders through both homeostatic and non-homeostatic eating in some mechanisms such as cognitive, metabolic, and reward (Romano et al. 2020).

4.3.4 Water Balance

Water balance in the body is achieved via the hypothalamic nuclei, the supraoptic nucleus is an aggregate of magnocellular neurosecretory cells existing in the anterior hypothalamus. These cells produce vasopressin (ADH) and oxytocin. Both regulate osmotic, balance blood pressure by exciting aquaporin expression in distal tubules and collecting duct of the kidney to rise water absorption. While stimulation of vasopressin receptors (V1aR, V1bR, and V2R) is required for the vasopressin action on regulating blood pressure and water balance (Borrow et al. 2019; Yu and Das 2020).

4.3.5 Body Temperature Regulation

The hypothalamus also contributes to body temperature regulation via secretion of TRH, which stimulates the production of TSH from pituitary, resulting in stimulation of the thyroid to produce two regulatory hormones to increase energy production through stimulation of the mitochondrial enzymes responsible for oxidation, resulting in an increase in the basic metabolic rate. Also, neurotensin is a neuropeptide neurotransmitter expressed in many areas and lateral hypothalamus in central and peripheral nerve systems. Neurotensin signalling plays roles in body temperature regulation (Torruella-Suárez and McElligott 2020). Signalling of oestrogen receptor alpha (ERα) in the ventromedial hypothalamus (VMH) participates in energy homeostasis via modulation of physical functions and thermogenesis. Chemo-genetic stimulation of ERα-positive VMH neurons activates heat production and movement in male and female. While ERα creates a sex dimorphic controlling bulge of energy spending (van Veen et al. 2020).

4.3.6 Circadian Rhythmicity

Circadian rhythm is around 24-h cell-independent term determined by transcription-translation feedback noose of particular genes, which are named ‘circadian clock genes’. The centric circadian pacemaker in mammals is placed in suprachiasmatic nucleus of the hypothalamus and regulates peripheral circadian clocks. The circadian network system controls substantially the entire physiological functions, which are exposed to modification as a result of variations in the outer environment, for example, light, the timing of food intake and other factors that cause circadian disruption such as dysregulation in sleep-wake rotation, shift work, travel over time zones that has prolonged-term effects on health, it is a key lifestyle participates

in the risk of some metabolic disorders such as diabetes, obesity, mellitus, and cancer (Ikegami et al. 2019).

4.3.7 Resurgent View: Hypothalamic Stem Cells (The Tanycytes)

There are specialized radial glial cells within the hypothalamus called 'the tanycytes' which represent a population of hypothalamic stem cells that regulate exposure to blood born signals. It has two actions, sensors and regulators for the hypothalamic input and output. Hypothalamus's neurogenesis by this very pivotal cell type is a very important and novel knowledge offers possible therapies for related dysfunctions (Rizzoti and Lovell-Badge 2017).

Hypothalamic tanycytes have potential role in controlling feeding and energy balance (Bolborea and Dale 2013), metabolic and neuroendocrine and neurogenic functions (Goodman and Hajihosseini 2015). Hypothalamic tanycytes are known to generate acute hyperphagia through activation of the arcuate neuronal network (Bolborea et al. 2020).

4.4 Hormones of the Pituitary Gland

The pituitary gland secretes many hormones which regulate various body functions directly or indirectly (Fig. 4.1). Up to date, the anterior pituitary produces most of the pituitary hormones such as GH, PRL, TSH, ACTH, MSH, FSH, and LH. While the posterior lobe releases two neurohormones: vasopressin and oxytocin.

4.4.1 Growth Hormone

It is called human growth hormone (GH) or somatropin hormone (STH) which is encoded by the GH1 gene. The growth hormone is the most abundant hormone in pituitary gland. Although GH is very specialized hormone, but it is received and utilized by each cell in the body in vital organs and skeletal and muscular systems. It forms highly specific system with each target cell for its expressed receptors that help in regulating its effects. It participates with PRL in some physiological function for the similarity of chemical structure in both of them. GH, GH mediators, and GH receptors have key roles in the physiology and biochemistry, while their dysregulation may cause pathophysiological conditions.

4.4.1.1 Characters of Growth Hormone

GH is a peptide hormone that includes 191 amino acids (Backeljauw and Hwa 2016). It is released mainly from the acidophils (somatotrophs) and stored in large quantities in the human anterior pituitary gland (Bullock et al. 1991). It is also detected in other regions in the brain (Lim and Khoo 2000). It constitutes 4–10% of the pituitary gland's weight. GH is found in high levels in children and is secreted

daily in high amounts in adolescents, but its levels decrease with age. Also, placenta of pregnant women releases GH in the circulation. Placental GH levels could be detected from 5 weeks of gestation in women and increases during gestation to maximum concentrations (5.9–24.4 ng/mL) at 35–36 weeks of pregnancy. Then it disappears at parturition. GH and PRL are released by the acidophils; they are similar in structure and play a significant role in regulating reproduction according to seasonal changes and period of light. Human GH is highly specialized than other species. The half-life of pituitary GH in the blood is approximately 30 min. Its secretion is pulsatile and occurs every 20–30 min. Its concentration varies according to physiological status (Bullock et al. 1991); while the mean half-life of placental GH ranges (11.5–15.2 min) in pregnant. About 75% of the placental GH disappears from maternal circulation after the first 30 min.

4.4.1.2 Physiological Functions of Growth Hormone

Stimulation of Bone and Cartilage Growth

GH promotes body growth in childhood, adolescence and maintains bone and muscle growth after maturity. The biological impact of GH mostly is not directly on the target tissue but rather through the activation of GH mediators called insulin-like growth factors (IGF) (formerly called somatomedins) such as (IGF-I) and IGF binding proteins (IGF-BPs) which are peptides with numerous physiological functions. IGFs play roles in pre-, neo-, and postnatal development and growth of creatures. GH mediators act on target organs and tissues with the help of the thyroid hormones and insulin. They are primarily produced in the liver (Fig. 4.6) as well as in the plasma, muscles, kidneys, and bone marrow. Mouse bone marrow's stromal cells release both IGF-I and IGF-BPs. GH mediators act to stimulate the cartilage endplate areas in the epiphysis, leading to increased chondrocyte numbers (Fig. 4.7), which encourages the formation of bone cells and, consequently, to increased epiphyseal bone mass (Fig. 4.8) (Bullock et al. 1991; Szewczuk et al. 2009; Mahan and Ayoob 2017).

Longitudinal growth in children is assisted by the action of the growth plates and discs of cartilage existing at the ends of the long bones to lengthen them. Growth plates produce chondrocytes incessantly. The growth plate includes stem cells and a stem cell niche that control the chondrocytes generation in the postnatal growth phase. The niche that permits stem cells to renovate displays in synchronization with the maturation of secondary ossification centre in the bone epiphysis. Therefore, the generation process of chondrocyte varies from neonatal and postnatal phase significantly, i.e., prior and later the establishment of the mineralized epiphyse. Thus, at neonatally, bone growth depends on the utilization of chondro-progenitors phase, while at postnatal phase it depends on the function of the stem cell niche (Chagin and Newton 2019). After fusion, bones grow vertically but not horizontally under the effects of GH. Through its mediators, GH stimulates the cartilage attached to bones and influences muscle connective tissue and adipose tissue (Fig. 4.9). These biodynamic interactions lead to an increase in the number and size of cells, increasing the weight and size of tissues in the body. In addition to its indirect effects, GH has a

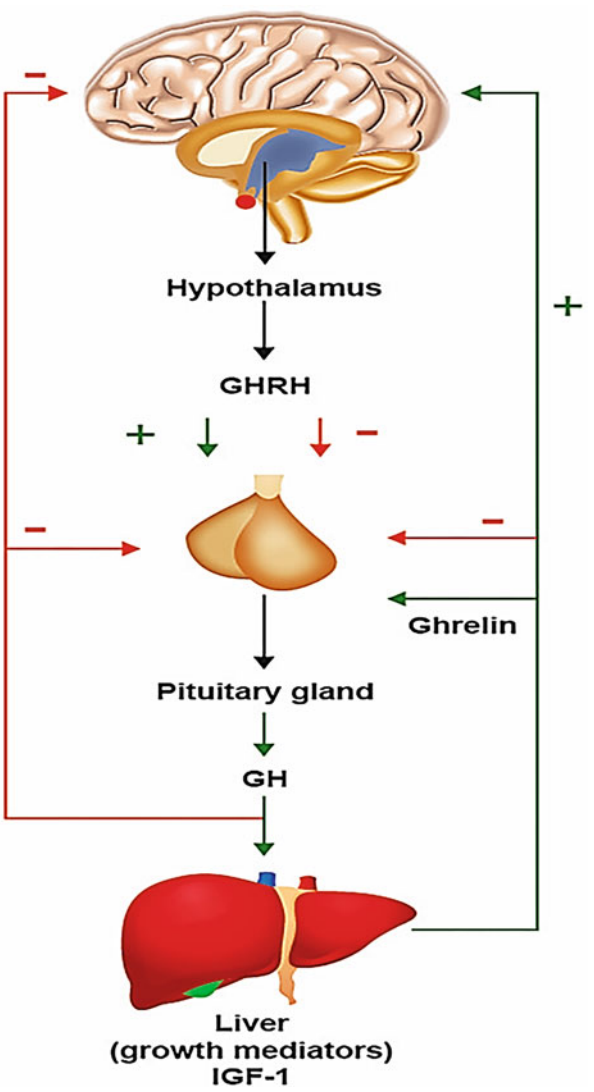

Fig. 4.6 Mechanism of growth hormone (GH) secretion and of insulin-like growth factor

direct effect on the growth of cartilage and bone. Furthermore, there are additional factors that influence longitudinal growth of the bone such as gonads steroids, nutrition, and genetics.

Growth Hormone Regulates Metabolism

GH regulates metabolism in organs such as the liver, muscles, intestines, and pancreas. GH controls many vital activities such as energy reserve and cellular renewal. The liver is a dominant target organ of GH action, liver activates the synthesis of insulin-like growth factor 1 (IGF1) and influences several biological

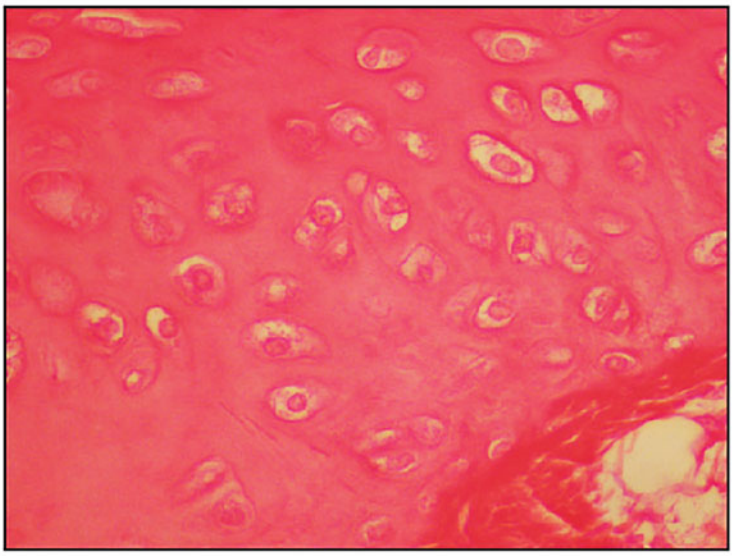

Fig. 4.7 Cross section in the epiphyseal cartilage in the bone. H&E magnification 400×

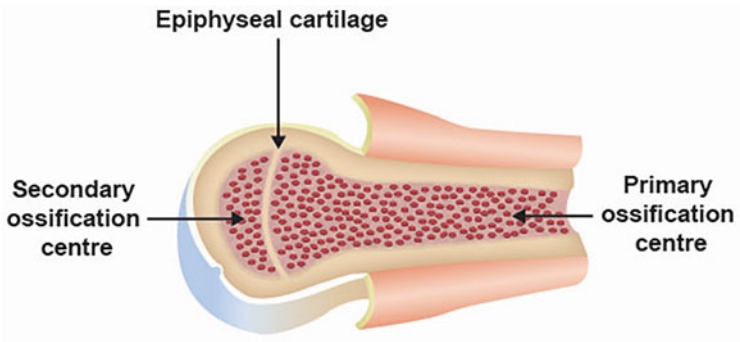

Fig. 4.8 Illustration of epiphyseal cartilage in the bone

pathways. Additionally, GH regulates several features of liver physiology and biochemistry via GH-dependent stimulation of the Janus kinase (JAK) 2—the transcription signal transducer and activator of transcription (STAT) 5 mechanism regulates several physiologic functions in hepatocytes. Failure of GH-STAT5 signalling in multiple experiments correlates with metabolic liver diseases, while GH-activated STAT5 plays a protective role in chronic liver diseases (Kaltenecker et al. 2019).

In general, GH enhances amino acid uptake from the blood to form proteins and dissolve fats in the tissues. It has a lytic effect on carbohydrates in the liver (Fig. 4.9),

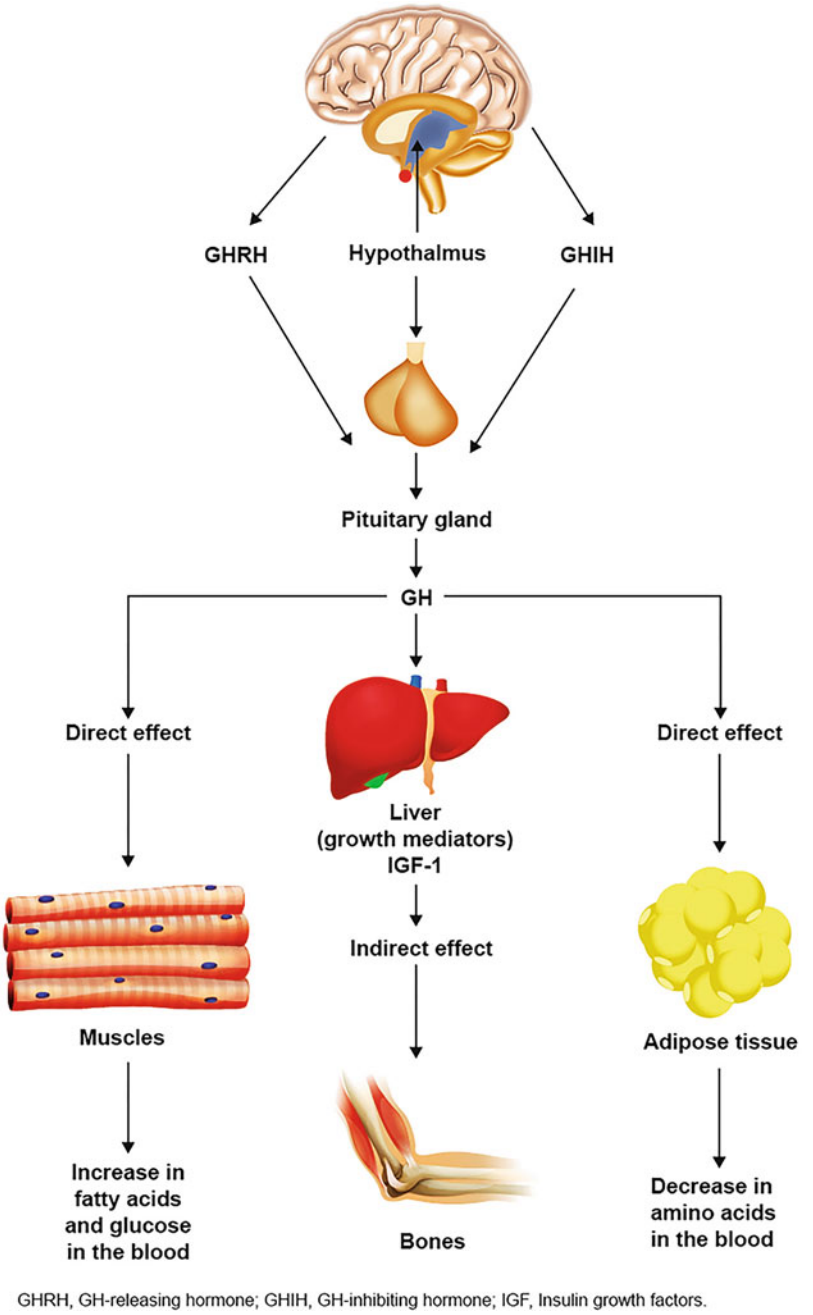

Fig. 4.9 Mechanism of growth hormones (GH) secretion and actions on the target organs

resulting in a decrease in amino acids and an increase in fatty acids and glucose in the blood within the physiological levels. Owing to its stimulation of protein formation and the breakdown of fats, GH helps regulate the use of fats in energy production instead of proteins. It has a catabolic effect on adipose tissue, and the breakdown of adipose tissue, with the help of the catecholamines, reduces its volume leading to the release of more fatty acids from adipose tissue into the blood where they are oxidized (Fig. 4.9). An increase in GH levels tends to increase sugar levels via the blood fats it generates, which counters the effects of insulin. Regular exposure to GH can lead to diabetes with failure of the insulin-producing β-cells due to the constant demand for insulin secretion because this raises the baseline insulin level needed to decrease glucose levels. Diabetes is usually accompanied by acromegaly, which results from excessive GH production after maturity.

Recently, main functions of GH have been identified through its receptors (GHR). Lack of GH receptor is an exceptional model to know the results of GH deficiency GH. In animal models, deficiency or high levels of GH or GHR expression leads to cascades of disturbances in the liver functions such as: lack of GHR leads to disorder in fatty and amino acids metabolism and antioxidants. This lack elevates concentrations of group of enzymes required in many biochemical pathways (amino acid degradation, cycles of urea, and tricarboxylic acid), diminishes beta-oxidation of short-chain fatty acids or elevates degradation of certain amino acids that may elevate concentrations of short-chain acylcarnitines in the liver and in the circulation, reduces activity of carnitine palmitoyltransferase 1A which decreases the capability of mitochondrial to import fatty acids for beta-oxidation, elevates significantly the concentration of mono-unsaturated glycerophosphocholines in the liver. There are different variations in the metabolism of methionine and glutathione, because of the drastic elevation in concentration of glycine *N*-methyltransferase as well glutathione concentrations (Riedel et al. 2020). In contrast, constantly increasing concentration of GH throughout life is related with liver disorders such as hepatomegaly because of hyperplasia and hypertrophy, inflammation, high arachidonic acid in younger age while liver tumours at older animals. These changes are attributed to higher expression in the hepatic enzymes (cPLA2α, COX1, and COX2) which are needed in arachidonic acid metabolism (Piazza et al. 2020).

Growth Hormone Participates in Haematopoiesis

Insulin-like growth factor I (IGF-I) is also known as mediator of many indirect actions of growth hormone (as pervious mentioned). GH participates in haematopoiesis (erythropoiesis) process in bone marrow, through IGF-I which has also a key in the same vital process. IGF receptors are present in both erythrocyte precursors and mature erythrocytes. While the role of IGF-binding proteins (IGF-BPs) in erythropoiesis may modulate the local levels of IGF-I. For the bone marrow, there are two physiological sources of IGF-I either from the serum (as an endocrine signal mechanism) or produced locally within the bone marrow by stromal or other cells (as a paracrine signal mechanism) (Aron 1992).

In in vivo studies on human and animals, GH, IGF-I, II, haematopoietic microenvironmental factors, cytokines and tissue oxygen, as well as colony-stimulating

factor-1 (CSF-1) and interleukin-3 (IL3) in in vitro have a promoting effect on erythropoiesis. It is known that hypocellularity of main lymphoid organs is a characteristic in elderly humans and animals, this is for the limited levels of either GH or IGF-1 in the cells of the lymphoid organs. In in vitro, CSF-1 and IL3 stimulate high expression and production of the IGF-1 in non-adherent bone marrow cells and myeloid progenitor cell lines as the cells differentiate into advanced maturated haematopoietic cells. CSFs factors deficiency leads to apoptosis of both non-adherent bone marrow cell and a myeloid progenitor cell, while adding IGF-1 to these cell lines suppresses apoptosis, since IGF-1 acts as anti-apoptotic factor for haematopoietic progenitors up to 50%. GH insufficiency patients might show moderately weakened propagation in erythyroid that causes anaemia. Noteworthy improvement in erythropoiesis parameters during GH treatment (Kelley et al. 1996; Petri et al. 2007; Ciresi et al. 2018). Signalling of GHR is a key mechanism in a wide-ranging of cellular activities including ageing. In the haematopoietic process, GHR is expressed in a highly and specific way in haematopoietic stem cell (HSC) and it is upregulated significantly throughout ageing (Stewart et al. 2014).

Growth Hormone Participates in Puberty

GH, IGF-1, and gonads steroid hormones altogether significantly rise throughout puberty, their effects are magnified equally as they regulate growth, enlarge muscle mass, and influence the mineralization of the bones. The opposition of androgen and oestrogen functions in the male and female controls the variance timing at the onset of puberty and closing of the height in both sexes. The synergistic activity of these hormones working on perfection of anabolism is important to significantly utilize during the determinate years of puberty (Mauras et al. 1996). To clarify the mechanisms controlling this synergic action of GH and other hormones through pubertal surge, it is good to know that axis of GH/IGF-I is an important factor during different phases of puberty and age. There are variations in both serum IGF-I and growth hormone binding protein concentrations, also in GHR gene expression in blood lymphocytes of females. As there is a significant decrease in IGF-I concentrations in adult female and prepubertal females in comparison to pubertal females. While serum GHBP concentration is significantly higher in prepubertal than pubertal group and adult female. A higher level of GHR gene expression in pubertal girls in comparison with other female groups. Sex hormones can positively impact GHR action through the pubertal phase, in a double manner, as rising production of GHR mRNA and decreasing GHR cleavage lead to variations in growth hormone binding protein (Pagani et al. 2015).

Growth Hormone and Glucocorticoids

GH and glucocorticoids are required in the regulation of essential processes for the maintenance of vital functions including energy supply, growth control, and systemic energy homeostasis, particularly during conditions like physical stress (Mueller et al. 2012). GH and glucocorticoid together increase expenditure of resting energy. Their effect is mediated by leptin, as treatment with glucocorticoid and GH elevates serum levels of leptin which is regulated by glucocorticoids via alteration in

insulin release, impartially of alteration of body fat mass (Berneis et al. 1996). GH plays a role in higher level of control. In the brain arcuate nucleus (ARH), proopiomelanocortin- (POMC) and agouti-related peptide (AgRP)-expressing neurons have central important function in metabolism regulation. These neurons are affected by blood hormones, such as GH and another energy regulating hormone, leptin. GH has direct tropic actions on the growth of POMC and AgRP axons because of GH effect controlling hypothalamus neurocircuits that regulate energy homeostasis (Wasinski et al. 2020).

Growth Hormone Retains Mineral and Water

GH boosts mineral (Jørgensen et al. 1994) and water (Peyreigne et al. 2001) preservation in the body. This is due to re-absorption by the kidneys of minerals such as calcium, phosphate, and sodium. This can be explained as part of GH role in regulating bone formation. Short-term treatment of GH to short normal kids has a temporary slight sodium and a secondary water retention, this is because of improper elevation in plasma renin activity which leads to sodium retention in the early period of GH treatment for those children (Lampit et al. 1998). Though GH has water-retaining actions in subjects at rest, but the exercise-induced GH response is reduced when exercise is done without liquid drinking (Peyreigne et al. 2001).

4.4.1.3 Regulation of Growth Hormone Release

- The release of GH is dependent on GHRH secretion from the hypothalamus, which is produced as a by-product of all the factors with an impact on GH. While GH inhibition is dependent on somatostatin, which is released from the hypothalamus whenever there is a need for it (Fig. 4.9).
- Concentration of the main metabolic products (glucose, amino, and fatty acids) in the circulation plays role in GH regulation: (1) **Glucose**: reduced glucose level in blood (hypoglycaemia) greatly stimulates the release of GH, as do hunger and fasting. To the contrary, increased glucose in the blood (hyperglycaemia) decreases GH secretion. (2) **Amino acids:** Proteins intake or the entry of amino acids into the veins stimulates GH, indicating that GH stimulates the uptake of blood amino acids into tissues. (3) **Fatty acids:** Fatty acids inhibit GH's response to certain activators (Bullock et al. 1991).
- GH levels in the blood vary according to food intake by the body: In the first phase, immediately after a meal, insulin increases and GH decreases. In the second phase, during the normal period between two meals, the GH level increases and insulin decreases. In the third phase, the increased GH levels stimulate a desire to eat/appetite, which will increase blood sugar levels, after which the first phase begins and so on (Al-Makawi 2000).
- The release of GH is also regulated by ghrelin released by the stomach. Ghrelin is a peptide hormone that stimulates the appetite and fat production in the body and bodily growth, leading to excessive consumption of food and weight gain (Fig. 4.6).
- GH is released in pulsatile manner according to diurnal variation. Autoregulation of GH is also undergone a negative feedback mechanism.

- GH is influenced by several factors; psychological stresses increase the secretion of GH positively. GH release is affected by physical exercise, and physical stresses such as fasting and shock such as hyperglycaemia, hypoglycaemia, hypovolemia, and some surgeries process (Lim and Khoo 2000).
- GH secretion shows variances between genders. In male, it is pulsatile secretion while in contrast, female shows continuous secretion. Additionally, the concentrations of GH secretion also decrease with age, a fact named 'somatopause' (Lim and Khoo 2000).
- In humans, GH secretion increases within 2 h of deep sleep.
- GH release is affected by the secretion of other hormones, especially hormones administered pharmacologically (Besser and Martini 2013; Luciano and Besser 1982).

4.4.1.4 Disruption in Growth Hormone Levels

Gigantism is a disorder resulting from high GH levels in childhood. While Acromegaly is a condition that happens when a GH increases inappropriately after maturity. While Acromegaly diabetes is a hyperglycaemia disorder resulting from GH levels continuing to increase associates with Acromegaly. Dwarfism is a condition developing as a result of a deficiency of GH in childhood. Many metabolic disorders in utilization of glucose, amino acids, and fatty acids with high levels of the catalytic enzymes are associated with disturbances in GH or GHR expression.

4.4.2 Prolactin and Its Nature

Prolactin (PRL) is a peptide hormone that consists of a single chain of several peptides. Chemically structure of prolactin is like to growth hormone, it comprises 198 (Bullock et al. 1991) or 199 amino acids. It is synthesized after proteolytically cleavage of a 28-amino acid signal peptide from the prolactin prohormone named pre-prolactin (Jin and Fan 2019; Al-Chalabi et al. 2020; XVth Congress of International Federation of Associations of Anatomists 1999). PRL is produced and released from mammotrophs (pituitary lactotrophs), a type of acidophilic cell found in the anterior lobe of the pituitary and acts as endocrine hormone in the system circulation (Bullock et al. 1991). Recombinant human prolactin could be induced and expressed in bacteria strain, Escherichia coli (Affonso et al. 2018). PRL has several different names; mammotropic hormone as it promotes mammary glands growth. Galactopoietic hormone as it stimulates milk's production and flow. Lactogenic hormone as it maintains lactation (Bullock et al. 1991). Hypophysectomised female rats had about 10–20% lactogenic serum activity in comparison with controls, the lactogenic active action gradually increased to 50% within 2 months greater than controls. This indicates that there are extra-pituitary sites of PRL such as mammary gland, decidua, prostate, and skin. Extra-pituitary sites PRL and GH are acting as autocrine or paracrine sites of PRL and GH action either in health or illness (Ben-Jonathan et al. 1996; Cabrera-Reyes et al. 2017). PRL is also released in brain within—but not outside—paraventricular nucleus (PVN) and medial preoptic area

(MPOA) in response to some physiological stimulus (Torner et al. 2004). PRL has a pulsatile secretion pattern and an increase in its level occurs 60–90 min after falling asleep. Its half-life in humans is around 15–20 min, reaches 30–50 min in blood. Normal concentration is (15–20 ng/mL) (Levy 2002).

4.4.2.1 Physiological Functions of Prolactin

PRL is one of the remarkably multitalented pituitary hormones as it regulates several physiological effects, such as growth, lactation, metabolism, reproduction regulation, immune response, brain function and behaviour and osmoregulation (Affonso et al. 2018; Bole-Feysot et al. 1998; Ben-Jonathan et al. 2006; Grattan and Kokay 2008; Clapp et al. 2009), angiogenesis (Clapp et al. 2009), and food intake (Ladyman et al. 2020).

Action of Prolactin on Mammary Gland and Lactation PPRL has effects on more physiological activities and processes than all other pituitary hormones combined. PRL has a dual function, it acts as a circulating (endocrine) hormone and as a local cytokine. The variation of PRL activities comes from three properties: structural polymorphism, systemic and local production, and forked intracellular signalling mechanisms and target genes (Ben-Jonathan et al. 1996), in addition to its neuropeptide action property. It stimulates growth of the mammary gland tissue and milk production, PRL with prompting hormones acting on mammary glands and lactation, PRL increases during pregnancy and plays an important role along with insulin, cortisol, and human placental lactogen in increasing and boosting mammary gland growth. It is supported by progesterone, which stimulates the follicles while oestrogen stimulates the mammary ducts. But both progesterone and oestrogen prevent PRL from having an effect on lactation (Bullock et al. 1991). The mammary gland emerges as a main PRL target tissue. PRL activates its growth, differentiation, survival of the gland epithelium, milk synthesis. These effects happen based on the growth and retrogression of the mammary gland vascularization (Andres and Djonov 2010) which regulated by PRL and vasoinhibins. PRL supports the expression of VEGF in epithelial cells of mammary glands (Clapp et al. 2008).

PRL is required in the biosynthesis of milk components like lactose, the sugar needed for milk carbohydrate, casein for milk protein and fats. PRL binds to the cellular membrane and stimulates the transcription cascade to synthesize enzymes required for producing milk. Lactogenesis does not happen, but following parturition since high levels of oestrogen and progesterone during pregnancy cause down regulation of PRL receptors in the mammary gland. However, after parturition, the concentrations of oestrogen and progesterone fall quickly. Therefore, their inhibitory action on the mammary gland is disappeared PRL along with cortisol is involved in lactogenesis. PRL stimulates the action of galactosyltransferase, the enzyme needed for lactose production. GH and thyroid hormone also stimulate lactogenesis, but oxytocin is responsible for milk excretion (Bullock et al. 1991; Al-Chalabi et al. 2020).

Growth and Angiogenesis Effects of Prolactin Blood vessels are acting as PRL targets tissues. PRL induces new blood vessels growth (angiogenesis) either in direct manner by acting on endothelial cells or indirect mechanism through upregulation of pro-angiogenic factors like vascular endothelial growth factor. Furthermore, PRL gets antiangiogenic actions after enduring to proteolytic cleavage to vasoinhibins, a family of PRL fragments that have effective antiangiogenic, vasoconstrictive, and anti-vasopermeability actions. For these opposing effects of PRL and vasoinhibins, the control of the proteases that cleavage specific PRL demonstrates a proficient mechanism for regulation growth and function of blood vessels (Clapp et al. 2015). PRL also has growth-boosting effects because of the similarity of its chemical structure to GH. Placental lactogen has also a similar structure to PRL (Bullock et al. 1991).

Osmoregulation Effect of Prolactin PRL has an important osmoregulatory function in all vertebrate classes. The functions include ionic and osmotic elements that contribute to the control of paraneuronal prolactin-releasing cells and actions of prolactin on many epithelial tissues of ion- and water-transporting (Loretz and Bern 1982). C-type natriuretic peptides and prolactin in the pituitary and pancreas have a key function in freshwater acclimatization of euryhaline eel (Katayama et al. 2020). Although PRL plays a significant role in osmoregulation of birds, fish, and mammals, while osmotic regulation of prolactin response and actions on excretion of renal water in human is not clear yet. Supraphysiologic prolactin concentrations have not antidiuretic effects in a vasopressin-free state and that severe changes in tonicity of serum do not influence prolactin secretion in man (Berl et al. 1976).

Prolactin Regulation of Reproduction and Food Intake In humans, PRL does not play a stimulator role in gonadotropic function as it does in some animals, but excessively high level of PRL has a suppressing effect on the production of hypothalamic gonadotropin-releasing hormones (GnRH) that inhibit the anterior pituitary to release FSH and LH in human causing hypogonadism and infertility, since PRL inhibits the circulation levels of both sex hormones oestrogen in woman and testosterone in man. Then the ovulatory cycle in females is inhibited which justifies amenorrhea during lactation. This physiological effect of PRL acts as a normal contraceptive manner and may regulate the time intervals between pregnancies. Correspondingly, PRL in male reduces GnRH release decreasing and infertility and spermatogenesis (Bullock et al. 1991; Raut et al. 2019; Štelcl et al. 2018). PRL plays a role in fat metabolism and hair shedding (Badowska-Kozakiewicz 2012). Pregnancy and lactation in mammalian are escorted by infertility duration that happens with continuous increase in food intake. Certainly, effective female reproduction depends on harmonization of the diverse systems controlling reproduction and metabolism. Increase in lactogenic hormone (prolactin and the placental lactogens) perfectly influences both systems at the suitable time. Also, period and pattern of lactogens exposure is a fundamental factor influencing these hormones to change reproduction and food intake status. But transitory elevation in prolactin, as happens in healthy virgin females and males,

does not apply long-lasting effects. While exposure to chronically high concentrations of lactogens is able to clearly suppress fertility and high food intake. From physiological view, the unique period of suppressing pattern of lactogenic release is sustained in the healthy female happens only during pregnancy terms and lactation period, as these controlling systems begin its synchronization (Ladyman et al. 2020).

Effects of PRL on Brain and Behaviour PRL stimulates proliferation of precursor cells of oligodendrocyte that differentiate into oligodendrocytes, the cells responsible to form myelin of neuron's axons in the central nervous system. Also PRL promotes neurogenesis in the brain of both maternal and foetal (Badowska-Kozakiewicz 2012; Shingo et al. 2003; Gregg et al. 2007; Larsen and Grattan 2012). PRL is released locally within the paraventricular nucleus (PVN) and medial preoptic area (MPOA) which confirms the involvement of PRL as 'novel' neuropeptide in multiple brain functions (Torner et al. 2004) such as neurogenesis, neurodevelopment, neuroprotection, memory, sleep, and learning. The pleiotropic functions of PRL hormone in the brain can be explained by the distribution and expression of PRL and its receptors in several neuronal tissues. Prolactin plays a key role in inducting maternal and caring behaviour in both female and male through molecular mechanism on the brain. Prolactin plays a key role in inducting maternal and caring behaviour in both female and male through molecular mechanism on the brain.

Prolactin Immune-Effect PRL has immunity-related functions and has receptors on the immune cells. It has an immune-protective effect. PRL, GH, IGF-I, and thyroid hormones have critical immune-protective actions which may ensure immune system homeostasis and reduce the susceptibility which may happen in response to stress-induced disease, so these hormones act against the negative effects of immunoregulatory factors, like glucocorticoids which are released during exposing to major stressors (Dorshkind and Horseman 2001). The mechanisms of the immune-protective action of PRL during stress are by stimulating the production of immunomodulating cytokine and lymphocytes-activating factors like interleukin-1 produced by peritoneal macrophages. PRL also abolishes the stress-induced inhibition of proliferation of blood lymphocytes (Fomicheva et al. 2004).

Prolactin Has Potent Multi-Signalling Effect Blood PRL is released by various types of lactotrophs in pituitary and extra-pituitary origin-tissues, it can act in various signals, an endocrine signal as hormone, paracrine signal as growth factor, or autocrine signal as neurotransmitter or immunoregulator. At the cellular level, PRL exerts mitogenic, morphogenic, and secretory activity. Many factors originate centrally and peripherally and are required in the mechanism controlling PRL secretion and concentrations in the blood circulation. The negative feedback mechanism keeps the pituitary lactotrophs to be regulated and not continuously active (Ben-Jonathan et al. 1996; Ciechanowska et al. 2013).

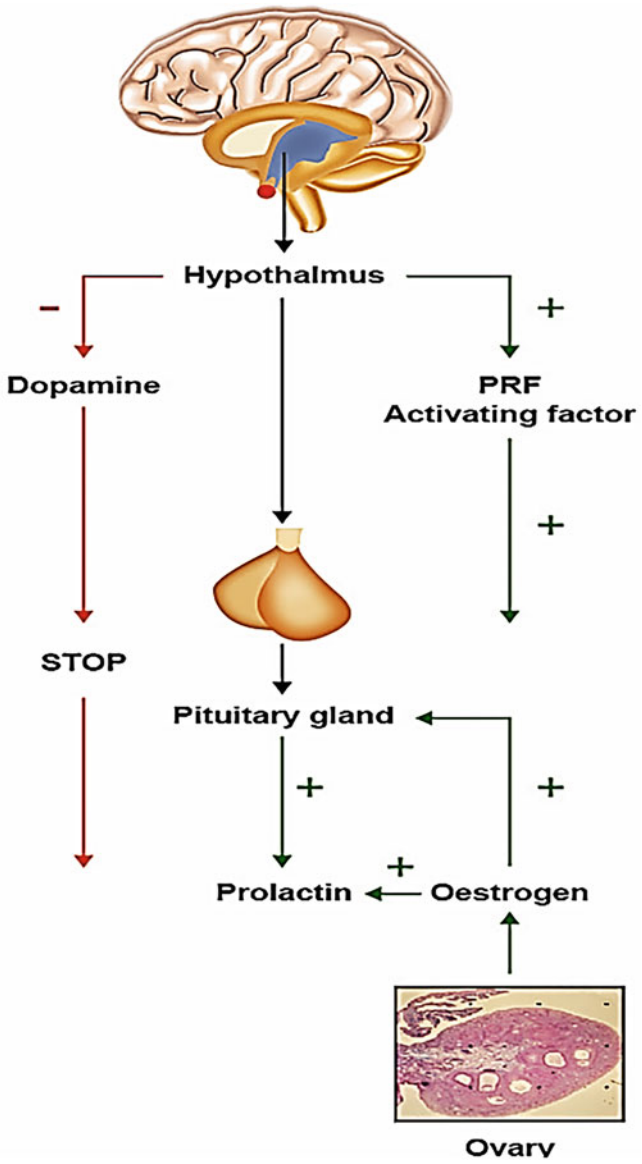

Fig. 4.10 Regulation of prolactin secretion, PRF (TRH), prolactin-releasing factor

4.4.2.2 Regulation of Prolactin Release and Functions

Hypothalamus TRH Thyrotropin-releasing hormone (TRH) actively regulates pituitary PRL synthesis and release, and oestrogen stimulates PRL release (Fig. 4.10) via acting on the D2 receptors of pituitary lactotrophs causing prolactin

release. Oestrogen in pregnancy is an important regulator of PRL production, it stimulates growth of prolactin-producing cells (lactotrophs) and activates PRL production directly, and suppresses dopamine.

Dopamine Regulation: PRL released by the pituitary lactotrophs is significantly suppressed by hypothalamic dopamine to sustain a basal concentration of prolactin. Dopamine antagonists induce PRL production.

Physiological Variations: PRL blood levels undergo several physiological changes; maximum PRL levels are reached at 38 weeks of pregnancy. After birth, it helps ensure lactation continuation for at least 1 month, after which PRL levels start to fall. High PRL levels in women are linked to deficient LH production and absence of ovulation accompanying menstruation. The concentration of prolactin is lower in males, non-pregnant and non-lactating females than corresponding conditions.

Suckling When a new born suckles the breast or udder, this stimulates the release of PRL, which in turn stimulates the mammary cells to produce milk. The suckling stimulus also alerts the pituitary to produce the oxytocin needed to release milk externally. So as long as suckling continues, PRL concentration is kept increased after the pregnancy episodically of feeding which produces peak PRL concentration. If the mother does not continue in lactation for the baby, PRL concentrations decrease to non-pregnant concentrations within 2 weeks.

Sexual Factor PRL levels associate with the sex hormones levels: At maturity**,** the PRL level is higher in females than in males; this is because of its importance in forming the mammary gland, in addition to other effects. It is not affected during the normal menstrual cycle, but after menopause, a reduction in PRL occurs along with a reduction in oestrogen.

Diurnal Rhythm PRL follows diurnal rhythm and ovulatory cycles. Additionally, PRL levels increase in humans 60–90 min after going to sleep and reach a peak level during REM sleep and in the early morning.

PRL levels can raise by stressors, including surgery, exercise, low blood sugar, acute cardiac symptoms (Bullock et al. 1991, 2001; Waugh and Grant 2006; Al-Chalabi et al. 2020).

4.4.2.3 Prolactin in Males

In human male, PRL boosts the action of LH in the production of testosterone and the performance of the male gonads. However, higher than normal PRL levels (hyperprolactinaemia) lead to reduced sexual appetite and decreased testosterone and sperm production (Bullock et al. 1991). Many metabolic disorders, metabolic syndrome are associated with low levels of PRL (hypoprolactinemia) in men with sexual dysfunction. Also, it associates with anxiety or depressive symptoms (Rastrelli et al. 2015). PRL enhances caring behaviour in male and female pigeons,

as it encourages them to feed their young from their lactating crop. PRL also influences male brain during the stress response. Hyperprolactinemia is the most common disorder of the anterior pituitary tumours, called prolactinomas. It may disrupt the hypothalamic-pituitary-gonads axis as PRL inhibits the hypothalamus GnRH which in turn inhibits FSH and LH production from the pituitary, leading to disturbance in ovulatory cycle. Such hormonal disturbances may be represented as amenorrhea and infertility in females and males (Shufelt et al. 2017).

4.4.3 Thyroid-Stimulating Hormone

Thyroid-stimulating hormone (TSH) is one of the critical hormones of the anterior pituitary that act on regulating growth and functions of thyroid gland. The hypothalamus pituitary-thyroid axis controls TSH release. The hypothalamus releases TRH which stimulates pituitary thyrotrophs to stimulate TSH production, which in turn stimulates growth of the thyroid growth and its epithelial cells to release thyroid hormones. TSH regulates also many essential functions in the body as described below.

4.4.3.1 Nature of Thyroid-Stimulating Hormone

It is known as thyrotropin, thyrotropic hormone (TSH or hTSH). It is chemically classified as glycoprotein hormone. TSH is secreted by thyrotrope-like basophils in the anterior pituitary. Structurally, TSH consists of heterodimer two non-covalently linked subunits: α subunit (92 amino acids) and β subunit (118-amino acid) (Wondisford et al. 1988). The α-subunit is similar to those found in the glycoprotein hormones FSH and LH and also to human chorionic gonadotropin (hCG). The β-subunit is unique to TSH and it is the subunit in TSH that has the actual biological impact on the thyroid gland. TSH subunits are animal species specific. In the blood, the TSH β-subunit circulates freely in the blood. Its normal range is 1–10 μU/mL, or 1–2 ng/mL. TSH has a half-life about 30–60 min (Bullock et al. 1991; Ridgway et al. 1974).

4.4.3.2 Physiological Functions of TSH

The α-subunit of TSH has a high ability to bind to its receptors in the thyroid gland.

- TSH activates iodine uptake by the thyroid follicular cells to form thyroid hormones as well as stimulates the gland to break down thyroglobulin and reabsorb it in preparation for secretion of thyroid hormones.
- TSH stimulates the biosynthesis and release of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) (Fig. 4.11) through TSH receptors (TSHR) guanine nucleotide-binding protein-coupled seven-transmembrane-domain, it is a member of the G-protein-coupled receptors which are present mainly on thyroid follicular cells and adipose tissue. TSH binds its receptors activating adenylate cyclase and phospholipase C of the thyroid cells, which in turn increases cellular cAMP level that activates the cell response to TSH (Lado-Abeal and

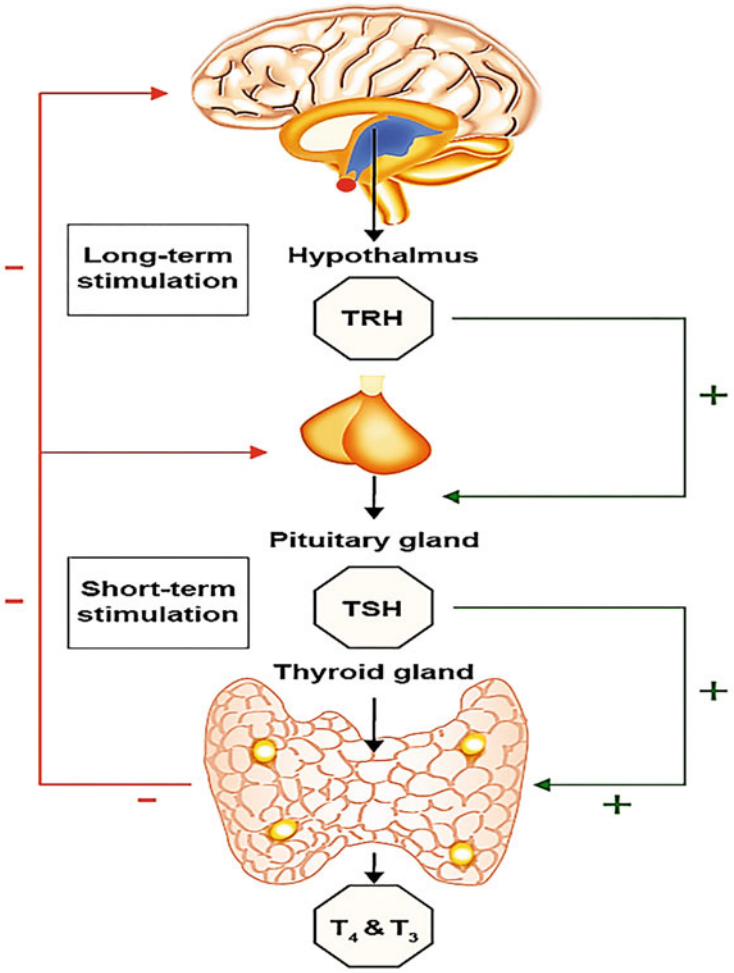

Fig. 4.11 Regulation of thyroid-stimulating hormone (TSH) production. TRH, TSH-releasing hormone, triiodothyronine (T3); thyroxine (T4)

Castro-Piedras 2010). TSHRs are also expressed in placenta and uterus's decidua in human which indicates a functional role of TSH on temporary tissues or pregnancy (Vanes et al. 2012).

- TSH increases the volume of thyroid gland and its vascularization by boosting mRNA. TSH has an effect on the expression of mRNAs of vascular endothelial growth factor (VEGF which is an angiogenesis factor) and its receptor. Stimulation of TSH receptors through the protein kinases paths leads to VEGF synthesis in thyroid follicles. VEGF thereafter activates TSH receptors on the endothelial cells in a paracrine signal, causing cells' proliferation and giving hypervascularity of the thyroid gland, as observed in Graves' disease patients (Sato et al. 1995).

- In human TSH induces cholesterol biosynthesis in adipose tissue. Adipose tissue TSH beta gene (TSH-β) is a paracrine hormone that is modified in corresponding to cholesterol metabolism. TSH-β mRNA is constantly detected in adipose tissue from euthyroid subjects and positively linked with total and LDL cholesterol in serum, and with adipose tissue cholesterol metabolism-related lipids. Cholesterol-decreasing factors such as statins and diet decrease TSH-β mRNA in h-adipose tissue, but additional cholesterol upregulates TSH-β mRNA in h-adipocytes. Moreno-Navarrete et al. (2017) indicate the significance of TSH/TSHR pathway axis on adipose tissue physiological function via the enhancement of mitochondria function (Comas et al. 2019).
- Decreasing serum TSH levels are associated with the lipid and lipoprotein profile in depression (Peng and Li 2017).
- The 24-h secretion of TSH in healthy subjects is constant and robust and does not influence by factors such as sex, age, and body mass index (BMI) (Roelfsema et al. 2013).

4.4.3.3 Regulation of Thyroid-Stimulating Hormone Secretion

As shown in Fig. 4.11, the hypothalamus secretes thyroid-releasing hormone (TRH), which is highly effective even at low levels at adjusting TSH levels in the circulation. TRH activates thyrotrophs of the anterior pituitary to produce TSH which in turn stimulate thyroid hormones T4 and T3. Negative feedback regulates the secretion of TSH via T3 and T4 concentrations in the hypothalamus and pituitary; an increase in T4 signals the hypothalamus to inhibit TRH which in turn inhibits the pituitary, leading to a decrease in TSH. Meanwhile, reduced secretion of T4 stimulates the hypothalamus to secrete TRH, which in turn stimulates the pituitary to release TSH, which activates the thyroid to secrete its hormones (long axis). The pituitary is also affected by changes in T4 levels in the circulation (short axis) (Dietrich et al. 2012; Eghtedari and Correa 2020).

- One of the physiological functions of TSH is the autoregulation, the suppression of TSH by TSH itself through ultra-short feedback path. At the conditions of inter-individual and intra-individual changes to hypothalamo-pituitary function TSH autoregulation decreases change in the TSH deviation. Then, this increases the chance to produce and sustain euthyroid free thyroxine level. TSH autoregulation contributes to the haemostatis of thyroid physiology that provides reasonable clarification for the evolutional choice of this physiological function (Fitzgerald and Bean 2018).
- There is a key role of T3 in rapidly controlling TSH gene expression at posttranscriptional level. Low developmental thyroid hormone concentrations can change thyrotrope number and function, a possible cellular mechanism causes elevated TSH concentrations with either permanent or transient congenital hypothyroidism in neonates (Tonyushkina et al. 2017).
- Somatostatin is the inhibitor which increases the inhibitory effect of the thyroid hormones on the thyrotrophic cells in the pituitary. Somatostatin analogs can be considered as an alternative medicinal tool to surgical intervention in TSHoma

patients. This action is done through the expression of somatostatin receptors such as SSTR5 (Yu et al. 2017).

- TSH and subunit release is activated via adrenergic agonists that act directly on the pituitary through alpha-adrenergic receptor (Klibanski et al. 1983).
- Temperature variation plays a role in TSH release, cold increases TSH secretion as because of the impact of adrenaline. Hence, exposure to cold environment activates the hypothalamo-pituitary-thyroid axis and enhances the hypothalamic-TRH production in animals which had been acclimatized to 30 °C (Rondeel et al. 1991). After birth and immediately, there is a rapid increase in thyroid hormone in serum levels. Since extra-uterus cold environment stimulates TSH secretion; though, the significant secretion of the thyroid hormones is slightly based on moving from foetal to neonatal condition. Summation of factors such as blood dynamic variations, the sympathetic nerve system is acting executively and instantly for TSH function (Slebodziński 1986).
- Other hormones influence TSH; oestrogen regulates TSH gene expression. TSH and TSH mRNA affect T3; also a rise in the number of T3 nuclear receptors was observed in the pituitary after oestrogen administration (Franklyn et al. 1987). There is a negative association between TSH and cortisol (van der Spoel et al. 2020).
- Diurnal rhythm, as the hormone TSH is secreted in a pulsatile manner, with much higher levels in the early morning and lower levels in the afternoon and early evening. The hypothalamic (TRH)-pituitary (TSH)-thyroid axis is regulated by the central circadian clock of the hypothalamic suprachiasmatic nucleus pace-maker. But in some cases of hypo- or hyper-thyroidism, diurnal TSH secretion rhythm is disturbed. Disturbance of circadian rhythms is known as an alarm of the endocrine system and cell cycle progress. Genes expressions of circadian clock are deviant in advanced thyroid cancer but not in a healthy thyroid or the benign nodules. Therefore, the description of the thyroid clock mechanism could advance the diagnosis of thyroid disorders (Ikegami et al. 2019).

4.4.4 Adrenocorticotrophic Hormone (ACTH)

It is known as adrenocorticotropin. ACTH is secreted by the basic cells of the anterior pituitary, the corticotropes that constitute 15–20% of the anterior pituitary cells. The main function of ACTH in the hypothalamus-pituitary-adrenal loop includes regulating the secretion of cortisol from the adrenal gland cortex and other glucocorticoids, mineralocorticoids, and sex steroid hormones from zona reticularis of the adrenal cortex.

4.4.4.1 Adrenocorticotrophic Hormone Nature

It is a peptide hormone synthesized from pre-pro-opiomelanocortin (pre-POMC) by prohormone convertase enzymes PC1 and PC2 process. The cells produce ACTH that are allocated in the median area, laterally and anteriorly as well as posteriorly nearby to the pars nervosa area. These cells are basophil as a result of the high level

of glycoprotein of the N-terminal glycopeptide of pro-opiomelanocortin. Distributed ACTH-expressing cells are also existing in the human homologue of the intermediate lobe of the pituitary. Specific corticotrophs that produce ACTH prolong into the posterior lobe of pituitary, so-termed 'basophilic invasion' as natural physiological episode. ACTH is released in pulsatile manner and undergoes negative feedback regulation. It exhibits a circadian rhythm model. During gene expression process, the basic precursor compound termed pro-opiomelanocortin (POMC) is subjected to a series of enzymatic modification such as phosphorylation (addition of a phosphoryl group) and glycosylation (attach glycan to proteins) before it cleaves by endopeptidases to give rise multiple polypeptide fragments of various physiological activates. ACTH consists of 39 amino acids. Amino acids 1–20 are the active parts of the hormone, while the rest acts as inhibitors once it performs and completes its functions. ACTH can be additionally converted to produce melanocyte-stimulating hormone alpha (α-MSH), melanocyte-stimulating hormone beta (β-MSH), and corticotropin-like intermediate lobe peptide (CLIP). Along with β-LPH that also could generate γ-LPH and β-endorphin. All these compounds are derived from the same precursor molecule (POMC), the 241-amino acid polypeptide which is why its functions may resemble those of one of these compounds. These compounds may constitute a part of its structure. For example, α-MSH that stimulates the production of melanin makes up part of the structure of ACTH; in other words, α-MSH is amino acids 1–13 from the N-terminus of the ACTH molecule and therefore contributes to its role in skin pigmentation (Bullock et al. 1991, 2001; Fan et al. 2001; Lim and Khoo 2000; Benjannet et al. 1991; Tehraninejad et al. 2017).

4.4.4.2 Physiological Release and Levels of Adrenocorticotrophic Hormone

ACTH levels are difficult to estimate as the baseline level is not a true indicator for it in the plasma. In order to interpret its level, adrenal cortex cortisol's levels should be estimated too. Also, ACTH pulsatile secretion and circadian rhythm should be taken in consideration and in parallel with cortisol.

- ACTH short half-life, which is 12–15 min only, and its episodic release into the plasma lead to rapid and large changes in its levels. Low levels of ACTH or of cortisol may be present in normal people at certain times or may indicate a medical condition such as a pituitary deficiency (Bullock et al. 2001; Waugh and Grant 2006).
- Circadian Rhythm: ACTH secretion is pulsatile pattern, which increases its levels over the course of the day, with negligible early morning levels at 9–52 pg/mL. Corresponding to cortisol, ACTH concentrations change in circadian rhythm endogenously, accomplishing the highest peak between 06:00 and 09:00 am, decreasing throughout the day to the lowest level between 11:00 pm and 02:00 am, then starting to increase again at about 02:00–03:00 am. The rise in ACTH accomplishes capacity slightly than frequency is responsibility of the circadian rhythm. This rhythm in glucocorticoids release is a main route for re-entraining

manner to adapt to extrinsic troubles such as sudden stage transmits of light situations which is called model of 'jet lag' (Kiessling et al. 2010).

Pulsatility of ACTH Release Repetition of blood sampling each 10 min stimulates ACTH secretion in pulsatile pattern from the corticotropes with four pulses ±1.5/day; this pulsatile style associates temporally with the pulsatile release of cortisol, permitting a 15-min interval in secretion. Capacity of pulse's concurrence was 47% for ACTH with cortisol, while it was 60% for cortisol with ACTH pulses. Although the pulsatile of ACTH release may result from pulsatile release of hypothalamic CRH, but many human pituitaries release ACTH naturally in a pulsatile style independently (not associated with CRH as in vitro) (Lim and Khoo 2000; Desir et al. 1986; Lim and Khoo 2000; Krishnan et al. 1990; Veldhuis et al. 1990).

4.4.4.3 Physiological Functions of ACTH

ACTH binds its receptors (G-protein-coupled receptor) on the adrenal cortex cells activating adenylate cyclase, which in turn increases cellular cAMP level that activates steroid synthesis and the cell response to ACTH. ACTH stimulates secretion of steroid hormone through both rapid short-term actions that influence within minutes and slower long-term mechanisms that take place for several hours. The rapid actions of ACTH stimulate cholesterol's entry to the mitochondria which contains cytochrome P450 system enzymes. While the long-term actions of ACTH stimulate the transcription process of the genes coding of steroidogenic enzymes (Hanukoglu et al. 1990).

- The principal function of ACTH is to increase blood flow to the adrenal cortex where it binds strongly to its receptors, hence increasing the weight and volume of the adrenal cortex.
- ACTH is responsible for the production and secretion of steroidal hormones from the three layers of the cortex. Glucocorticoids from the zona fasciculata such as corticosterone/cortisol; mineralocorticoids from the zona glomerulosa such as aldosterone, and sex steroid hormones from the zona reticularis oestrogen and progesterone. The cortex hormones are synthesized using cholesterol and ascorbic acid in the cortex cells.
- ACTH stimulates the energy-deriving capacity of the adrenocortical cells (Raikhinstein and Hanukoglu 1993). ACTH is also involved in carbohydrate metabolism and amino acid uptake in cells. As POMC is converted to many peptides including α-MSH, an essential controller of energy homeostasis, it suppresses food intake and activates energy expenditure. While other POMC-derived peptides such as β-endorphin has feeding-stimulating effect, the β-endorphin antagonistic-effect to MSH does not include all β-endorphin types, but this is to maintain the balance between α-MSH and β-endorphin and also the possible function of multiple POMC conversation in controlling energy balance (Dutia et al. 2012). ACTH has a catabolic effect on fats and its effect is to break down fats, leading to the production of acetone.

- Keratinocytes secrete POMC beside with α-MSH and ACTH in low concentration (Yamamoto et al. 2015). Excessive levels lead to skin hyperpigmentation since ACTH contains α-MSH. Other POMC polypeptide fragments like α-MSH and β-MSH induce skin pigmentation as they elevate melanin in melanocytes.
- Opioids are extremely used as active analgesic therapy for intensive pain, these compounds act on the endogenous opioid, that includes four families of peptides (β-endorphin, dynorphins, enkephalins and nociception/orphanin) (Corder et al. 2018). And four G protein-coupled receptors. β-endorphin functions as an endogenous orexigenic opioid.

4.4.4.4 Regulation of ACTH Secretion

- Neural regulation by the hypothalamus. The hypothalamus-pituitary-adrenal axis, hypothalamic CRH is the principal regulator of ACTH and is affected by external and internal factors. The hypothalamus-pituitary-adrenal axis changes with age progress and sex variance.
- Negative feedback control, a decrease in adrenal cortex hormone levels stimulates the short pituitary axis or the long hypothalamus axis to secrete CRH or ACTH consecutively (Fig. 4.12).
- ACTH is regulated by many hormones and factors in the body. Physiological functions such as food intake and stress response influence the release of ACTH, as stressors increase ACTH release, including physical stress, emotional stress, low blood sugar, exposure to cold, pain, surgery, and depression (Lim and Khoo 2000).
- Pulsatile and circadian rhythm: ACTH is secreted in pulsatile pattern as explained earlier. There are also daily variations, ACTH reaches its peak level in the morning and then gradually decreases as night approaches.

4.4.5 Gonadotropins

Gonadotropins are gonadotropic hormones produced by the anterior pituitary and regulated mainly by gonadotropin-releasing hormones (GnRH) by the hypothalamus. Gonadotropins are the main regulators of the reproductive system in both male and female. Gonadotropins is a fundamental group in the endocrine system, it regulates natural development and growth, sexual differentiation in gestation stages, puberty and reproductive functions (Levi Setti et al. 2015).

4.4.5.1 Follicle-Stimulating Hormone and Luteinizing Hormone, Their Nature

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are the main regulating hormones of gonads and reproductive cycle in female while FSH is called gametocyte-stimulating hormone (GSH) in male. LH is called interstitial cell stimulating hormone (ICSH) in men because of the target of their actions.

FSH, LH, and TSH are heterodimeric glycoprotein hormones, each of which consists of two subunits: an identical α-subunit and a unique/distinct β-subunit for

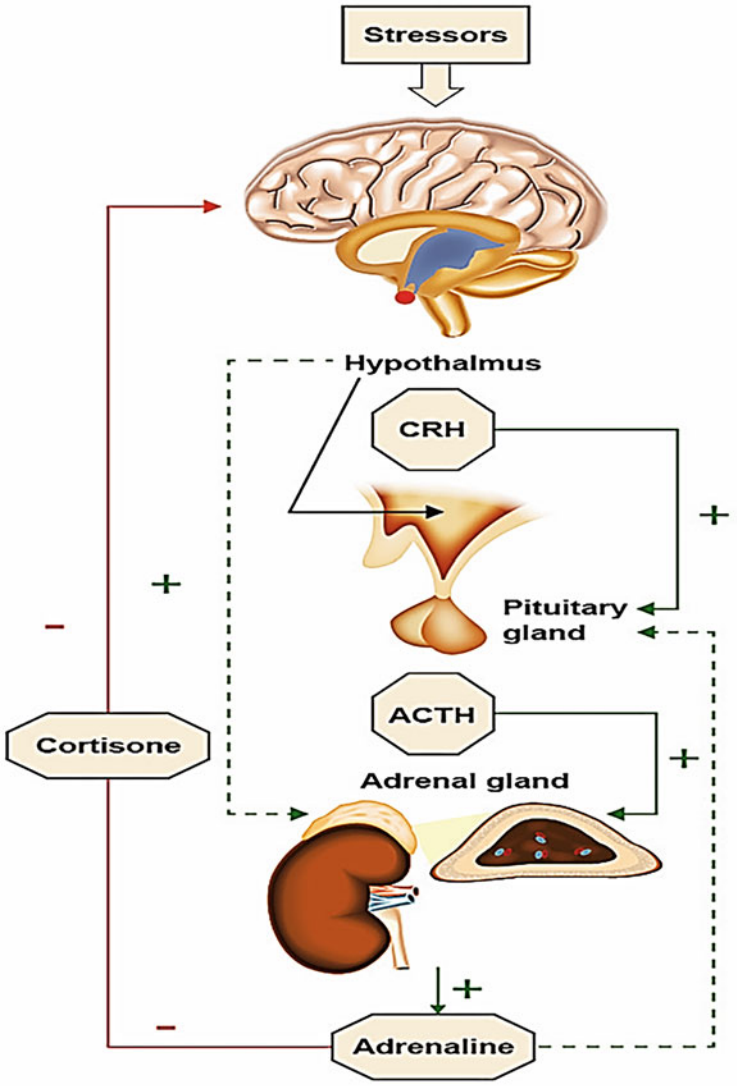

Fig. 4.12 Adrenocorticotropic-stimulating hormone (ACTH) regulatory factors. Corticotropin-releasing hormone (CRH)

each hormone. While the β-subunit gives these hormones their specific activity, as mentioned earlier. FSH and LH are secreted by a type of gonadotroph from the basophil cells in the anterior pituitary. Gonadotropins synthesis and production are regulated by several endocrine, paracrine, and autocrine factors. In addition to the pituitary, there are other sources that produce gonadotropins and can be used medically:

- **Human chorionic gonadotropin** (hCG) is a heterodimeric glycoprotein released from the placenta by the syncytiotrophoblasts which functions as the endocrine tissue part of the human placenta. hCG could be detected in blood few days after implantation, it has a similar structure to LH. It is α-subunit identical to that of pituitary hormones (LH, FSH) and TSH. But β-subunit is a unique to hCG (Bullock et al. 1991; Fournier et al. 2015).
- **Human menopausal gonadotropin** (hMG) is used as a hormonal medication to control ovarian stimulation, as it induces gene expression in cumulus cells and fertility outcome in human. It can be extracted from the urine of menopausal women with activity similar to FSH (Tehraninejad et al. 2017; Cruz et al. 2017).

4.4.5.2 Blood Levels of FSH and LH

The concentration of FSH and LH varies depending on age, sex, and ovarian cycle. LH levels range from 2.1 to 20.8 μg/L, while FSH levels range from 1 to 2.7 μg/L. Evaluation of the activity of these hormones requires measurement of the gonadotropic hormones and that the oestradiol level in women rarely drops below 50 pg/mL. The normal range for testosterone in male serum is 300–1000 ng/dL and a concentration of 10–35 nmol/mL seems to be a sensitive indicator of gonad function (Bullock et al. 1991). Gonadotropins, levels are associated with steroids in both sexes. LH, FSH, and estradiol are elevated; however, testosterone secretion index reduced in male group aged older than 40 years. Serum level of testosterone and its index are decreased in men through the age between 40 and 59 years and so was estradiol in men group through the age between 40 and 54 years. Low concentration of testosterone is strictly linked with dyslipidemia (Chen et al. 2017).

4.4.5.3 Functions of FSH and LH

Gonadotropin hormones endure significant dynamic variations throughout life. They increase through puberty to stimulate steroids secretion from gonads, triggering the secondary sex characteristics and gaining the fertility (Salvi and Pralong 2010). FSH and LH play pivotal roles in reproduction. Generally, IN male or female, FSH and LH are functioning together in different levels according to the phase or the product targeting to be accomplished. FSH and LH target the ovaries and testes via specific receptors and regulate gonadal function to produce:

- Steroidal hormones from the gonads (endocrine functions).
- Gametes production (eggs and sperm) (exocrine functions).

Gonadotropins Functions in Males (Figs. 4.13 and 4.14)

- FSH stimulates, maintains, and regulates testis growth in different ages including prepuberty, puberty, adulthood, and elderly.
- Complete maturation of the sperm requires both LH and FSH.
- LH stimulates the production of androgens (male hormones) from the Leydig cells (called interstitial cells) in the testis. While FSH promotes Sertoli cell functions and then influences spermatogenesis a process supported by this cell (Bullock et al. 1991). Sertoli cells are not sexual, but somatic cells in the testis that

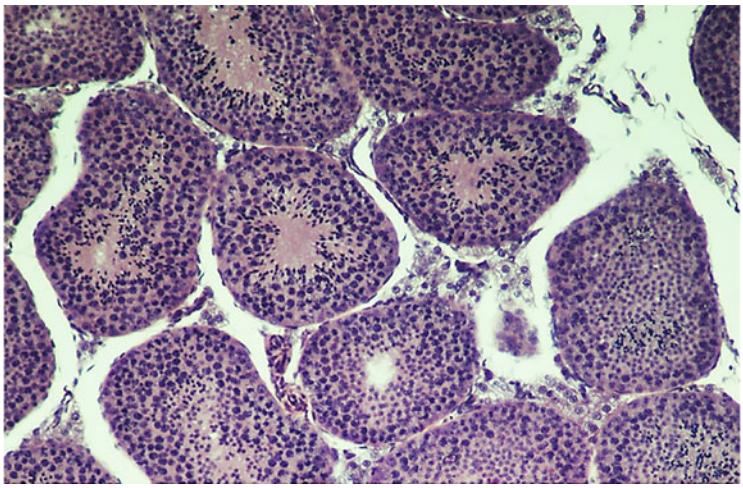

Fig. 4.13 Seminiferous tubules in the testis are affected by follicle-stimulating hormone. H&E magnification 100×

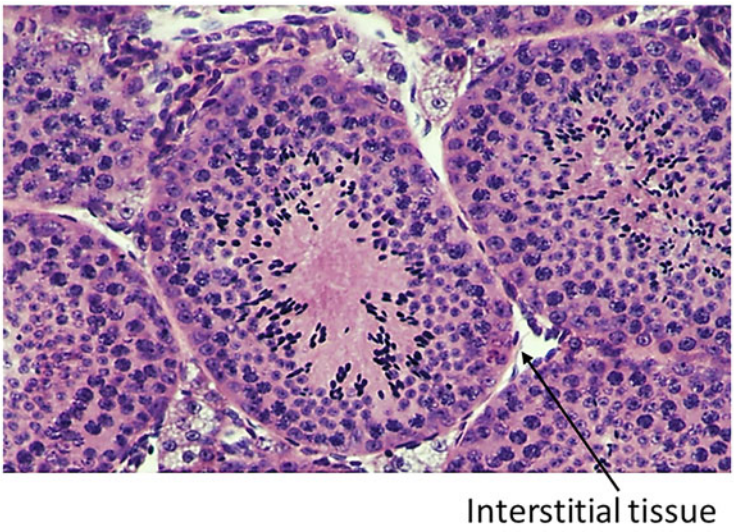

Fig. 4.14 Interstitial tissue includes Leydig cells, the endocrine tissue in the testis which is affected by luteinizing hormone. H&E magnification 400×

are fundamental for testis growth, maintain, and spermatogenesis. Sertoli cells act as facilitator for the development of spermatogonia cells to sperms through direct communication and regulation of the environment in the seminiferous tubules of the testis. FSH and the androgen (testosterone) regulate spermatogenesis process by the action of these two hormones on the Sertoli cells. While the effect of this

androgen is important for spermatogenesis, the effect of FSH slightly supports spermatogenic productivity by rising the Sertoli cell' number (Griswold 1998).

- FSH stimulates the production of androgen-binding proteins from the sertoli cells.
- Gonadotropins are decorated with glycans that control multiple protein functions include folding, heterodimerization, stability, transport, conformational maturation, efficiency of heterodimer secretion, metabolic fate, interaction with their cognate receptor, and selective activation of signalling pathways.
- Clinical uses and applications of gonadotropins in males such as: exogenous gonadotropins have an ability to treat conditions of congenital and acquired abnormalities accompany with deficiency of gonadotropin and hypogonadotropic hypogonadism. Administration of exogenous gonadotropins is a well-recognized therapeutic method in patients with isolated congenital hypogonadotropic hypogonadism. hCG or LH is used in males to stimulate testosterone production by athletes to strengthen muscles but not in female as their effect is not significant. Thus, it is hard to discover unlawful usage of LH. The features and reference standards of hCG and LH estimations utilized in establishing regulation and acknowledged values are required to be defined (Salvi and Pralong 2010; Ulloa-Aguirre and Lira-Albarrán 2016; Stenman et al. 2008).

Gonadotropins Functions in Females (Fig. 4.15)

- FSH and LH in addition to one of the non-pituitary hormones, human chorionic gonadotropin (hCG), and their target receptors play vital functions during the foetal growth, appropriate sexual improvement, oogenesis, puberty, regulation of reproductive cycle, differentiation of female sex organ, secondary characters, and preservation of pregnancy.
- FSH in its high levels and LH in lesser levels have a considerable effect on regulation of the growth of the ovarian follicle in the follicular phase of the ovulation cycle. While a surge in LH concentration with less FSH level halfway through the ovarian cycle is extremely important in stimulating the ovulation process.
- FSH and LH stimulate the production of female hormones (oestrogen and progesterone) from the ovary.
- Continuously increasing LH levels stimulate the corpus luteum in the ovary to release progesterone.
- LH stimulates signalling of protein kinase A in luteal cells, to increase the mitochondrial supply of substrate required for synthesizing progesterone. In the bovine, LH controls the phosphorylation and fixation of the mitochondrial effector dynamin-related protein-1 and steroid synthesis in the corpus luteum.
- The ovarian follicle is comprised of three main cellular layers starting from the inner to outer: the oocyte, granulosa cells, and theca cells. In the ovarian follicular phase, LH enhances theca cells to synthesize androstenedione. In granulosa cells from small antral follicles, FSH enhances the production of aromatase which stimulates the transformation of theca-produced androstenedione to estradiol.

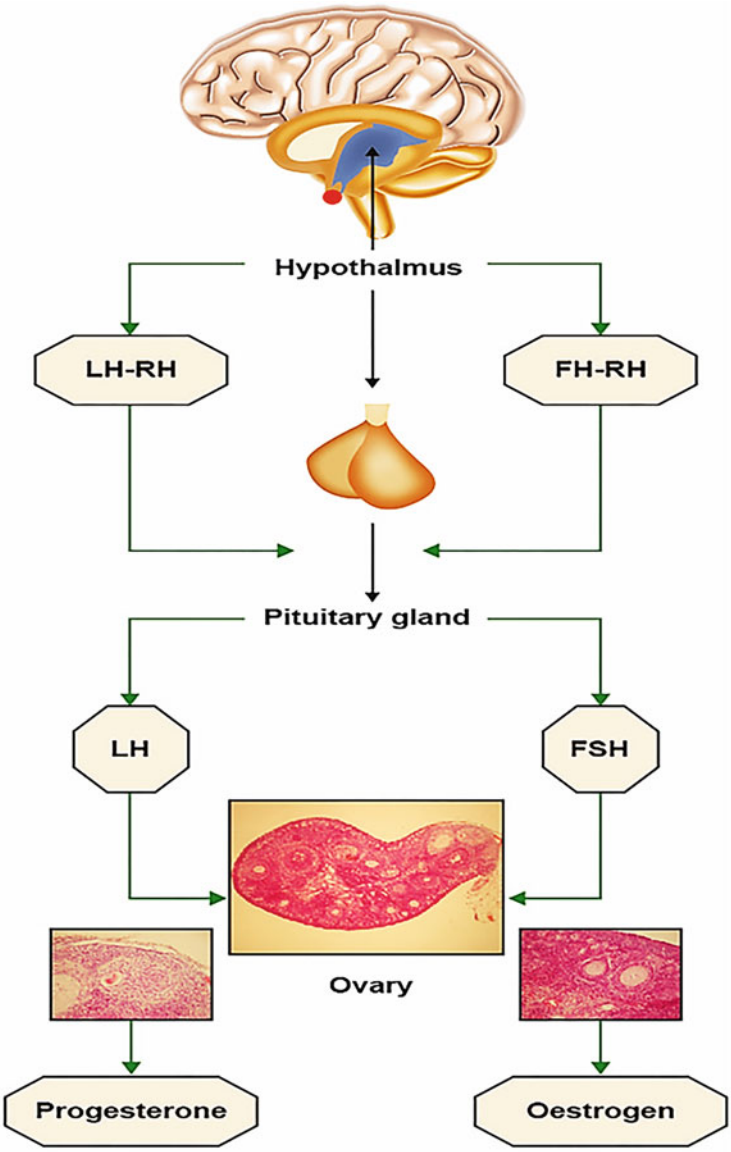

Fig. 4.15 Regulation of the secretion of the gonadotropins and their functions in the ovaries, LH, LHRH, FSH, and FSHRH

- In pregnancy, LH maintains its levels required for maintaining the stability of corpus luteum and to regulate progesterone secretion throughout the three semesters of pregnancy (Bullock et al. 1991; Barbieri 2014; Szymańska et al. 2018; Plewes et al. 2020).

4.4.6 Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a hormone produced mainly by syncytiotrophoblasts of the placenta in pregnancy. It acts as an agonist of LH that stimulates the corpus luteum to produce progesterone. hCG is the primary hormonal message from the placenta to the pregnant.

4.4.6.1 hCG Sources

It is mainly secreted by the placenta. Furthermore, lesser level of hCG is synthesized in the pituitary gland, and in non-endocrine organs such as the colon, and the liver. Pathologically, hCG or hCG-related hormone could be produced by tumours. Also, high serum concentrations of hCG-derived molecules are detected in some tumours (Bullock et al. 1991; Fournier et al. 2015). Recently, hCG is known as a name to define four distinct isoforms, each one is produced by a kind of cell in the body with a different biological activity. These isoforms include production of hCG from cytotrophoblast cells, the anterior pituitary gland, villous syncytiotrophoblasts, multiple primary non-trophoblastic tumours (Ogino and Tadi 2020).

4.4.6.2 hCG Nature

The syncytiotrophoblasts secrete it and is detected into maternal blood during early few (3) days after implantation. hCG reaches its peak at 8–10 weeks of pregnancy. In humans, the placental hormone is a complicated glycoprotein constituted of twin glycosylated subunits: α and β subunits. The α-subunit is same to the α-subunit in the three pituitary gonadotropic hormones (LH, FSH, and TSH), it includes two N-glycosylation locations and is encrypted by a single gene (CGA). Dissimilarity, the β-subunit is different in each of these hormones and presents specific receptor and biological activity. The hCG β-subunit includes two locations of N-glycosylation and four locations of O-glycosylation, it is encrypted by a band of genes (CGB). hCG is present in variable forms in the pregnant serum and urine either in its intact hormone form or in its each of related subunits. While nearly 20% of hCG is emitted in the urine but it is mainly catabolized in the liver. The β-subunit is destroyed in the kidney to be utilized as an essential molecule to be assessed in urine hCG tests (Fournier et al. 2015; Montagnana et al. 2011).

4.4.6.3 Physiological Functions of hCG

- hCG is a luteotropic hormone that supports the endurance and steroidogenic function of corpus luteum through acting via LH receptors that express on theca and granulosa cells layers. The hCG/LH in human luteal granulosa cells activates the pathway termed c-Jun N-terminal kinase, the molecular signalling that plays a key function in upregulating the expression of the steroidogenic enzymes (steroidogenic acute regulatory protein (StAR), 3β-hydroxysteroid dehydrogenase (3β-HSD)) and increases production of progesterone in a dose-dependent approach.

- hCG is the main pregnancy glycoprotein hormone, its maternal level, glycan structure, and functions vary during gestation. Based on its resource, hCG glycol forms show multiple vital biological functions needed for pregnancy completion.
- It behaves as autocrine and paracrine signals, in addition to its function as endocrine hormone.
- hCG produced by villous syncytiotrophoblastic cells acts as a super LH agonist not only to stimulate progesterone synthesized from the corpus luteum in pregnancy, but to maintain progesterone production until the placenta itself releases it and consequent development of cytotrophoblast cells. This is via the effect of hCG that permits a synchronized growth of the embryo and uterus, signalizes the endometrium of related implantation, promotes the formation and differentiation of the umbilical cord, in addition to hCG promoting effects on the growth and the organogenesis of the foetus. hCG acts a key function in quiescence of the myometrium layer of the uterus.
- The average of hCG reduces in spontaneous abortion. An average of fall lower than 21%, 60% at 2, 7 days, respectively, indicates keeping trophoblasts or an ectopic gestation.
- hCG is mostly used in pre-birth assessment and hCG-H acts as a serum biomarker of initial invasion of trophoblast. Additional unusually glycosylated hCG are defined in aneuploidies.
- It has a role in local immune tolerance.
- hCG produced by the anterior pituitary gland is secreted in low concentration during the menstrual cycle, it mimics the functions of the pituitary LH.
- hCG promotes the syncytiotrophoblast growth and angiogenesis via LHCG receptor. In contrast, hCG-H enhances invasion of trophoblast and angiogenesis through linking with the TGFβ receptor 2.
- Hyperglycosylated isoforms of hCG produced by cytotrophoblastic cells support development and invasion of these cells, therefore they contribute to the pathogenesis of choriocarcinoma cells.
- hCG free beta-subunits produced by non-trophoblastic tumours act on the same mechanism. Free β-subunit hCG detection is indicative of malign cancer and poor prognosis. (Bullock et al. 1991; Fournier et al. 2015; Ogino and Tadi 2020; Montagnana et al. 2011; Barnhart et al. 2004; Fournier 2016; Bildik et al. 2020).

4.4.7 Human Menopausal Gonadotropin

Human menopausal gonadotropin (HMG) is a highly purified, urine-derived, human menopausal gonadotropin that contains both FSH and LH physiological activities.

4.4.8 Physiological Activities of HMG

It has an efficient hormone for regulated ovarian stimulation in supported reproductive technology procedures and for ovulation stimulation in anovulatory infertility,

there is still an argument on which gonadotropin therapeutic type must be used, either HMG or human recombinant follicle-stimulating hormone (rFSH). Treatment with rFSH causes a higher oocyte produces/cycle than HMG at similar cost per oocyte (Levi Setti et al. 2015). But in comparison with rFSH, HMG reveals a less marked follicular response and a lesser threat of ovary overstimulation (Deeks 2018).

4.4.9 Hormones of Posterior Pituitary

The hormones oxytocin and vasopressin that is termed antidiuretic hormone (ADH), are neuropeptide hormones made up of nonapeptides (extremely small peptides). They are classified as octapeptides (Bullock et al. 1991) and are secreted by the posterior lobe of the pituitary gland in humans and most mammals.

4.4.9.1 Production of Oxytocin and ADH

The supraoptic nucleus in the hypothalamus is a group of magnocellular neurosecretory cells situated in the anterior hypothalamus. The main function of the supraoptic nucleus is to synthesize two peptide hormones: vasopressin, also termed as antidiuretic hormone (ADH) and oxytocin (Yu and Das 2020). They are produced in the form of a prohormone by the hormone itself and neurophysin carrier protein (Rose et al. 1996; Wu et al. 2008).

Pro-oxytocin = oxytocin + neurophysin carrier

Pro-vasopressin = vasopressin + another neurophysin carrier + a glycoprotein

This takes place in the neurons inside specialized nuclei in the hypothalamus. Peptides are formed in the ribosomes. The prohormone then penetrates the rough endoplasmic reticulum after which the prohormone molecules are formed and filled with secretory granules in the Golgi apparatus. These granules then migrate from the supraoptic nucleus cells through the neuronal axons—in the pituitary stem—until they reach the axon terminations in the posterior lobe of the pituitary. Several additions are made to them as they move through the axons. They are then released as hormone from the axon terminals via a cellular exocytosis process (Figs. 4.1 and 4.5).

Storage The posterior lobe hormones are stored in the anterior lobe of the pituitary until they are released upon stimulus.

4.4.9.2 Functions of Oxytocin

Oxytocin has different functions in the body range from classic functions on certain smooth muscles to metabolic, psychological, and molecular signals.

- Oxytocin has a powerful effect on the smooth muscle cells of the muscle layer of the womb: Oxytocin is released when the reproductive passage is stimulated, for example, during parturition in women, as well as on stimulation in men, oxytocin also causes contraction of the reproductive passage during intercourse to propel the sperm to fertilize the egg in the fallopian tube (Yu and Das 2020).
- The rise in oestrogen levels around the time of parturition increases the action of oxytocin by the oxytocin receptors helping to contract the muscles in the womb. At the end of pregnancy, the oestrogen level increases, which in turn increases the effect of oxytocin during birth. The lower portion expands, leading to further oxytocin release into the bloodstream, which further stimulates pushing of the foetus for longer distances towards the outside of the womb, which in turn leads to further secretion of oxytocin (in other words, there is positive feedback between muscle expansion and oxytocin secretion until the birth process comes to an end).
- Progesterone counters the effects of oxytocin on the womb, especially throughout pregnancy when progesterone levels are elevated.
- The prostaglandins (autocrine hormones) act on degradation of collagenous fibres in the cervix, which leads to it more flexible and wider during parturition.
- Breastfeeding control: Sucking stimulates the nipple receptors, which send nerve signals to the hypothalamus, leading to the oxytocin secretion reflex. The oxytocin released into the bloodstream results in contraction of the epitheliomuscular cells around the follicles, ducts, and cisterns of the mammary glands, leading to the release of milk within 30–60 s, which is called milk let-down or the milk ejection reflex. This feedback is also triggered at usual feeding times or when the mother sees or hears the infant cry. However, it is not at all necessary for nursing in humans (Bullock et al. 1991). Stressors inhibit the milk ejection reflex.
- Oxytocin plays a role in the ovulation in women. In women that show normal levels of LH, progesterone and 17-β-oestradiol in menstrual blood during normal ovulation cycles, it is accompanied with a large increase in oxytocin levels linked to peak of LH levels, which suggests that oxytocin is linked to ovulation in women (Mitchell et al. 1981).
- Oxytocin may be involved with ADH in its water-conserving effect.
- If pregnancy does not occur, oxytocin causes the degradation and disappearance of the corpus luteum until a new oocyte is produced. Prostaglandin is also involved in this process.
- The oxytocin level in plasma is not constant throughout the monthly cycle in normal women if there are no other factors affecting this.
- Oxytocin injection into animals leads to ejection of sperm from the seminiferous tubules.
- Oxytocin is directly associated with different types of sexual behaviour while, at the same time, the mechanisms of different behaviours influence oxytocin levels in men and women and in the marital relationship, which is characterized by high oxytocin levels (Snowdon et al. 2010).

- Oxytocin exerts an effect on social behaviour and family welfare. Oxytocin is an anti-stress hormone and promotes relaxation and well-being in animals. Its calming effect, whether natural or synthetic, is also evident after parturition.
- Oxytocin has multi-functional signalling on improving peripheral insulin sensitivity, pancreatic functions, and homeostasis of lipid which suggest significantly the role for oxytocin system as a therapeutic strategy in metabolic disorder such as obesity and diabetes management. Experimentally, the intranasal administration of oxytocin leads to important weight loss and improvement in sensitivity of insulin and function of pancreatic beta-cell in human subjects (Ding et al. 2019).

4.4.9.3 Functions of Vasopressin/ADH

- A decrease in the body's water level changes blood osmolarity, which in turn affects the hypothalamus receptors and results in increased secretion of ADH, leading to reabsorption of water by the kidney tubules. This restores water balance which increases thirst to make up for water decompensation. In severe cases of water shortage, hormonal regulation is enhanced and vasopressin acts immediately or compulsorily to restore moisture to the body. When ADH levels are below average, the kidney continues to release water without reabsorbing it, which constitutes a non-diabetic urinary condition.
- In camels, ADH levels are very high to preserve water retention under dry conditions in the surrounding environment.
- When blood pressure is low, especially when blood volume falls, for example, due to bleeding for any reason, ADH increases blood pressure to the required level via contraction of the involuntary muscles which line the blood vessels to restore adequate blood circulation.
- Pain and certain medications trigger the release of ADH (Bullock et al. 1991, 2001; Ivell et al. 1983; Yu and Das 2020).

4.4.10 Opioid Categories

The endogenous opioids are categorized as enkephalins like methionine-enkephalin (met-enkephalin), endorphins like (beta-endorphin), and dynorphins. The basic constituent is POMC from which several compounds are derived, including ACTH.

4.4.10.1 Endorphin

The endorphin produced in the anterior pituitary is an endogenous morphine; the term is derived from two words endogenous and morphine, which has been abbreviated to *endorphin*. It is similar to morphine but is produced in the body and is considered an endogenous opioid peptide.

Endorphins Sources The pituitary is the main source of circulating ß-endorphin. It presents in different peripheral tissues. Endorphin has been found in the pancreas, placenta, and semen but is primarily secreted by the hypothalamus, spinal cord, and brain as well as by the intermediate and anterior pituitary lobes, Endorphins are also

synthesized and released by mast cells. The posterior pituitary shows much less opioid activity. Endorphin acts as a neural carrier secreted by the pituitary in the form of ß-endorphin along with ACTH under conditions of stress, physical exercise, pain, eating, and emotional states (Goldstein and Lowery 1975; Simantov and Snyder 1976).

4.4.10.2 Enkephalins

Enkephalins are pentapeptides and are described as endogenous ligands as they are derived endogenously from β-LPH and bind to the endogenous opioid receptors in the body. There are two types of enkephalin: one containing the amino acid leucine and the other containing the amino acid methionine (Marcotte et al. 2004; Noda et al. 1982).

Enkephalins Sources Anterior pituitary gland of human contains high levels of met-enkephalin localized in thyrotrophs (no overlap with POMC) (Roth et al. 1988). Also, high concentration of met-enkephalin is also found in adrenal medulla.

4.4.10.3 Functions of Endorphin and Enkephalin

- In general, endorphin has a tranquilizing effect and brings about feelings of euphoria in situations of pain or danger and other stressful conditions. When the nerve impulse reaches the spinal cord, endorphin is released and prevents the nerve cells from secreting any more pain signals. Endorphin brings about a feeling of well-being.
- Endorphin has a similar analgesic effect to the opiates.
- Endorphin may be necessary for the regulation of food, water, and sex, all of which are associated with the limbic nervous system.
- Endorphin's therapeutic effect is equivalent to that of the corticosteroid hormones.
- The mechanism of endorphin action contributes to the systemic biopsychology of basic emotions. Poisson (2015) found that there are two information sources to refine behavioural responses, leading to homeostasis of the subject. The first source of information is released by the midbrain to the hypothalamus to trigger signals of the peripheral nervous system, which divides into two systems: the sympathetic nervous system, activating motor responses via noradrenaline, and the parasympathetic nervous system, which decreases motor activity via acetylcholine. These two systems act in synchronicity. The second source of information issues from the endocrine system, through three axes: the hypothalamus-pituitary-adrenal axis (for example, cortisol), the hypothalamus-pituitary axis (for example, endorphin and oxytocin), and the hypothalamus-pineal axis (e.g. melatonin). Various emotional behaviours produce from these two sources of information or from an integration of these two sources, then they are managed by the limbic system in connection with the neocortex.
- Human's anterior pituitary gland contains a novel met-enkephalin precursor in thyrotropes which indicates a possible function of met-enkephalin in regulating thyroid functions in human (Roth et al. 1988).

- Met-enkephalin acts as an endogenous mediator of motility of the sperm. The autocrine regulation of the opioid system on sperm function represents a new mechanism for regulating male fertility and a possible target for male contraception (Subirán et al. 2012).
- In human spermatozoa, endogenous opioid peptides such as beta-endorphin and met-enkephalin are found in the follicular fluid with high levels indicating that the opioid system may involve in the molecular mechanism of the acrosome reaction. Also, POMC (the beta-endorphin precursor) is presented and localized in flagellum of spermatozoa and also in the seminiferous tubules of human testis (Urizar-Arenaza et al. 2015).

4.5 Competent Role of Stem and Wave of Progenitor Cells in the Pituitary

Stem cells have topographical localization in the marginal zone around the pituitary cleft. A side population is also found in the postnatal pituitary, which in many other tissues is considered a stem cell-enriched fraction (Vankelecom 2007). As the pituitary gland plays a key role in the endocrine system by controlling all functions in the body, the adult pituitary has resident stem cells, which are highly quiet in homeostatic status. However, the pituitary stem cells show significant marks of activation during the demands of increased gland's cell remodelling such as maturation differentiation at neonatal age, response to physiological requirements, regeneration required for injury, and local tumours growth. It is believed that there are many functions of pituitary stem cells that are still covered. So, the knowledge of the molecular regulators of stem cells in the pituitary will not only provide further essential information in mature pituitary homeostasis and activation, but also help greatly the development of regenerative plans for improving therapies in pituitary deficiency and tumours (Cox et al. 2017; Gancz and Gilboa 2013). Histopathological samples of human embryonic and foetal organs were studied using microscope imaging technique. The morphological analysis showed the distribution of progenitor stem cells in a vast number of ectopic stem cells. Wave group of progenitor stem cells is guided through ectopic stem cells that later independently start to function from migration of germ cells and reach peri-aortal region, in particular to aortal-mesonephric-gonadal. Few progenitor cells diffuse into aorta and then spread through vascular region to become embryonic stem cells at peripheral tissues. Progenitor cells as second wave group are supplied to adrenal. Proliferation of cells occurs inside cortex zona region of adrenal cortex, which then pass through adrenal capsule. After reaching pre-aortal sympathetic plexus, the progenitor cells within plexus ganglia produce the paraganglia. Progenitor chromaffin cells through second path form adrenal medulla that induce sympathetic nerve bundles. Following, initiation of axonal migration occurs, leading to progression of progenitor cells to various peripheral organs (Wartenberg et al. 2018). Differentiation to specificity occurs during axonal migration step. In grown nerve cells, stem cells transfer to

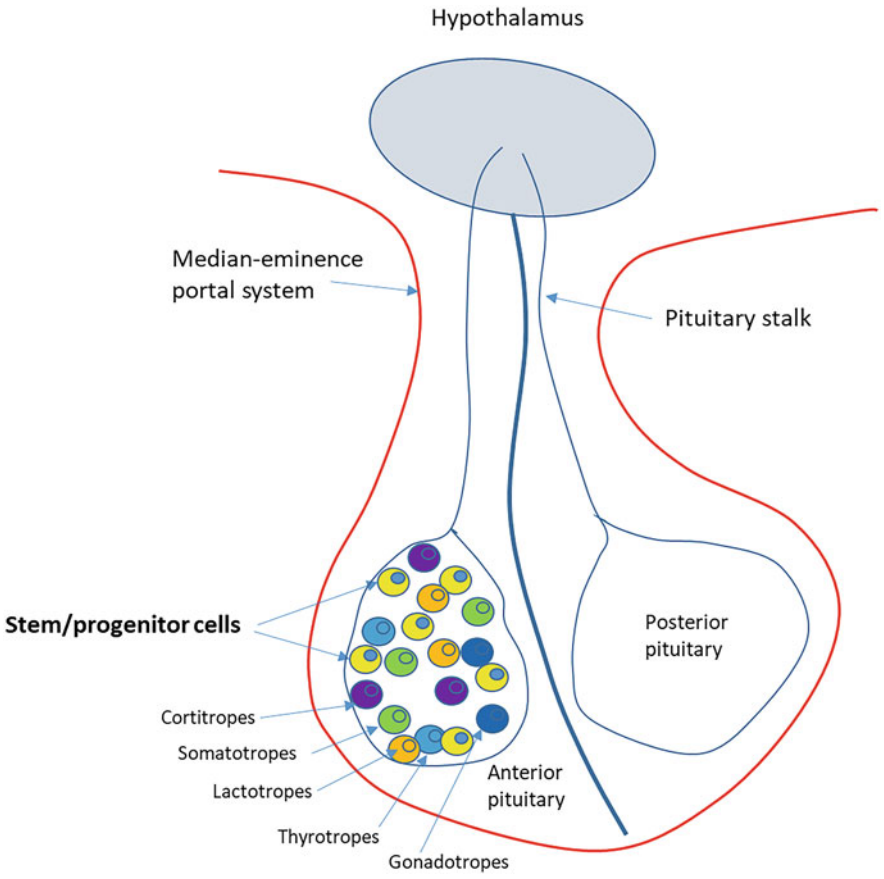

Fig. 4.16 Showing the sites of stem/progenitor cells in the anterior pituitary gland

adrenal's medulla and cortex. Figure 4.16 shows the sites of stem/progenitor cells in the pituitary gland.

Neuroendocrine are defined by the sets of typical cells comprising neurons, glands, and tissues. Transition of mature cells to progenitor cells is irreversible. However, induced pluripotent stem cells (iPS) can be a solution to delivery cells mythologically through forced induction of particular genes. This technique can be eventually used to engineer human cells (regenerative medicine), translational research, and human disease modelling. Several hypothesis driven approaches have been developed based on animal and human ES/iPS cells. For example, stem cells in neuroendocrinology, where neurons are formed by hypothalamic progenitors (vasopressin neurons formed to adenohypophysis). In development of pituitary gland in embryonic stage, Rathke's pouch and pituitary anlage regulate themselves coherently with pituitary gland cells, which have the ability to differentiate simultaneously. Adrenocorticotropic hormones were produced by stimulated adrenal

corticotrophs in response to hypothalamus corticotropin hormone. In animal experimental studies, engrafted corticotrophs cells are stored in hypopituitary as glucocorticoids concentrations systematically. It was considered as that representing the embryogenesis in molecular based surrounding (Suga 2019). The pituitary gland is the master endocrine gland, accommodating stem cells, the phenotype and role are still not fully clear. Organoid model was established by Cox et al. (2001) to study pituitary stem cell biology. The organoids initiated from the pituitary cells expressing the stem cell's marker and expandable, interestingly, these organoids appear with a cystic morphology that looks like the pituitary phenotype; however, the organoids from undamaged gland were mainly dense and regulated in expandability.

The presence of SOX2-positive cells was identified in the pituitary gland of dairy cattle after sexual maturity. SOX2-positive cells were localized in the dairy cattle pituitary gland which was similar to that reported in the marginal cell layer (MCL), dense cell clusters, and single cells scattered in the parenchyma of the anterior lobe of the rodent pituitary gland (Oguchi et al. 2021). In another study, it was reported that stem cells markers such as tetraspanin superfamily CD9 and CD81 were expressed in S100β or SOX2-positive cells of primary and secondary niches in the mice pituitary that exhibit plasticity and multi-potency (Horiguchi et al. 2021a). The stem cells in the adult pituitary are normally present in the quiescent state but these stem cells can be activated due to tissue injuries by activation of the interleukin-6 in the aged pituitary gland (Vennekens et al. 2021). It has been reported that paired-related homeobox 1 (PRRX1) and sex-determining region Y-box 2 (SOX2) double-positive (PRRX1/SOX2-positive) cells were found in the pituitary stem/progenitor cells of the mouse anterior lobe (Shintani and Higuchi 2021). In another report, pituitary stem cells produce paracrine WNT signals to control the expansion of their descendant progenitor cells (Russell et al. 2021). The cluster of differentiation (CD) 9-positive cells was reported in mouse pituitary cells that are adult stem/progenitor cells (Horiguchi et al. 2021b).

4.6 Conclusion

Pituitary gland (hypophysis) is the master endocrine gland situated on hypophyseal fossa of the sphenoid bone in middle cranial fossa of brain. It plays vital role in controlling several body functions and related endocrine glands. Structural and functional relationship with hypothalamus, nature of hormones, functional roles of the pituitary were explained. The three parts of pituitary gland based on their origin and functions were classified as adenohypophysis, neurohypophysis, and stem cells marginal zone. The pituitary is one of the greatest complex endocrine glands from the anatomical, histological, communications and functional concepts. Histology of adenohypophysis explained its three parts: Pars distalis, Pars tuberalis and Pars intermedia. Neurohypophysis cross section was shown for non-medullary neuronal axons situated in secretory supraoptic nuclei and paraventricular nuclei of hypothalamus. Endocrine physiological roles of the gland were detailed involving releasing

factors/hormones for anterior pituitary (thyrotropin, gonadotropin, corticotropin, growth hormone, the multitalented hormone (Prolactin), hCG and MSG are also behaving as analogs of LH and FSH, respectively. The chapter highlighted the physiological functions of oxytocin, antidiuretic hormone (ADH), inhibitory factors of pituitary functions (somatostatin, dopamine, and gonadotropin-inhibitory hormones), as well as other hypothalamic hormones such as appetite-regulating hormone (leptin), hormones that balance water (vasopressin and ADH), neurohormones secretion, and regulation of body temperature and blood born signals. Side population of stem cells was stated. Pituitary hormones and its receptors have high efficiency. For example, deficiency or higher levels of GH or GHR leads to cascades of disturbance such changes in liver physiology and biochemistry. PRL is acting as multipurpose hormone. Endorphin and enkephalin produced by the pituitary have many analgesic and tranquilizing actions.

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Thyroid Glands: Physiology and Structure

5

Ebtesam A. Al-Suhaimi and Firdos Alam Khan

Contents

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Abstract

Thyroid gland is an important endocrine gland. It is essential for life as it represents the main and only source of thyroid hormones. The thyroid gland synthesizes, stores, and releases thyroid hormones that are received by the entire body tissues by specific receptors for its importance in the regulation of energy and metabolism. Thyroid hormones regulate many physiological functions such as thermogenesis, reproduction, female ovarian cycle, and lactation. They are also crucial for regulating appropriate brain growth in infants and metabolic functions in adults, in addition to a broad array of functions on each organ and system. The gland is smaller in females than in males as its development is slower in females. In both sexes, the thyroid's volume increases with increasing age, and with bodyweight which has the clearest effect. The thyroid is made up of large numbers of follicles (Fig. 5.4). The basic functional unit of the thyroid gland is the follicle (acinus) which has a diameter of 15–500 μm. It has a rich blood supply and contains a network of capillaries to support its functions and variable body demands. The follicular epithelium comprises a single layer of cuboidal cells and there are also C cells (parafollicular cells) that communicate with the follicular cells using paracrine signals due to the converged distances between them. The thyroid gland releases important hormones, thyroxine (T4), 3, 5, 3-′-triiodothyronine (T3), and 3, 5, 3′-triiodothyronine (rT3). The thyroid gland secretes 100 nmol of T4 and 5 nmol of T3 daily. Thyroxine is therefore the main hormone that is metabolized and degraded through a deiodination process which converts it to T3. Thyroid gland disorders are the commonest endocrine diseases and one of the very common diseases globally, they are clinically main subgroups deficiency of iodine, thyroid goiter, and thyroid cancer. The thyroid gland possesses side population cells that represent stem/progenitor cells. Mice and human thyroid stem cells were identified in mature thyroids in vivo and in vitro with successful differentiation into thyroid-like cells. This chapter discusses the topics related to physiology and structure of thyroid glands.

Keywords

Thyroid glands · Physiology · Structure · Thyroxine (T4) · 3,5,3′-triiodothyronine (T3) · 3,5,3′-triiodothyronine (rT3)

Abbreviations

AMP	Adenosine monophosphate
APUD	Amine precursor uptake and decarboxylation
DIT	Diiodotyrosine
DNA	Deoxyribonucleic acid
FT4	Free thyroxine
GJC	Gap junction communication.
H&E	Hematoxylin and eosin stain

hiPSC-CM	Human-induced pluripotent stem cell-derived cardiomyocytes
I	Elemental iodine
I^+	Ionic iodine
MIT	Monoiodotyrosine
mRNA	Messenger ribonucleic acid
Na^+/K^+ ATPase	Sodium-potassium adenosine triphosphatase
PRL	Prolactin
T3	Triiodothyronine
T4	Thyroxine
TPO	Thyroid peroxidase
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone

5.1 Introduction

The thyroid is a butterfly-shaped gland located in the front region of the neck (Fig. 5.1). The thyroid gland is an important endocrine gland. It is essential for life as it represents the main and lonely source of thyroid hormones. The principal hormones synthesized by the thyroid gland are thyronines; thyroid takes several steps to synthesize its hormones including: Iodine transport, oxidation, iodination condensation-coupling, thyroglobulin storage, reabsorption and analysis, and the secretion of hormones in the blood circulation. The process is regulated by TSH released by the anterior pituitary. The thyroid gland synthesizes, stores, and releases thyroid hormones that are received by the entire body tissues by specific receptors for their importance in the regulation of energy and metabolism. It also plays a critical role in both male and female reproduction and regulates many essential functions. Thyroid hormones regulate many physiological functions such as thermogenesis, reproduction, female ovarian cycle, and lactation. They are also crucial for regulating appropriate brain growth in infants and metabolic functions in adults, in addition to a broad array of functions on each organ and system. Thyroid hormones employ their metabolic functions also on the heart and bones. Iodine plays an essential intermediator in the thyroid hormone's function. The hormones act synchronously with other hormones and their upstream modifiers to sustain a feedback mechanism loop and homeostasis. The hormones act synchronously with other hormones and their upstream modifiers to sustain a feedback mechanism loop and homeostasis. To support these functions, there is a large content of thyroid prohormones stockpiled in the form of colloidal thyroglobulin released by thyroid follicular cells into its lumen (Figs. 5.2 and 5.3). Once the hormones are needed, the colloidal prohormone colloid converts to mature hormones to be secreted into the bloodstream (Beynon and Pinneri 2016; Sorisky 2016; Núñez et al. 2017; Singh and Sandhu 2019; Shahid et al. 2022). Each cell in the body owns specific receptors for thyroid hormones as they regulate cell energy, metabolism, and cellular

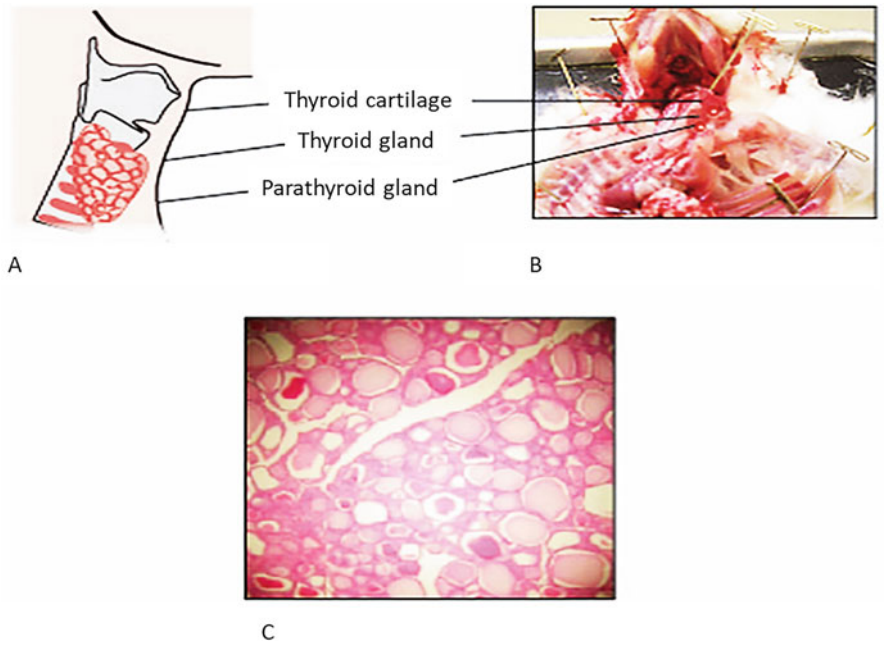

Fig. 5.1 (**a**) Lateral view of the thyroid gland in humans. (**b**) Lateral view of the thyroid gland in rabbits and (**c**) a cross-section of thyroid gland. H&E magnification 40×

mechanisms. Thyroid follicles confine between its cells other neuroendocrine-origin cells termed parafollicular cells or C cells that produce calcitonin; calcium lowering hormone. Many functions have been reported by the C cell, it is a serotonergic cell (Barasch et al. 1987). Both thyrocytes and C cells can act as thyroid gland stem cells (Al-Suhaimi and Aljafary 2019). Thyroid hormones circulate in the blood as bound with proteins or free to meet the body's requirements.

5.2 Functional Structure of the Thyroid Gland

The thyroid gland is a highly vascularized endocrine organ. Its lobes lie laterally to the left and right of the second to the fourth tracheal rings and inferior to the larynx (Fig. 5.1). The thyroid differs in the shape in individuals. The size of each thyroid lobe in human is 4.0–4.8 × 1.8–2.0 × 1.0–1.6 cm, with the two lobes connected by an isthmus, the isthmus may also be absent (Bullock et al. 2001). The adult thyroid gland's weight varies according to age, sex, and physiological status (Pankow et al. 1985). The weight of the thyroid gland ranges from 12 to 25 g. The mean weight of 20–69 years of age is 17.5 g in males while 14 g in females (Bullock et al. 2001). In healthy women, the menstrual cycle appears to relate to cyclic variations in thyroid size, mean variation in thyroid volume reaches approximately 50% between lowest values in day 9 (15.4 ± 3.1 ml) and highest values in day 23 (24.4 ± 4.8 ml)

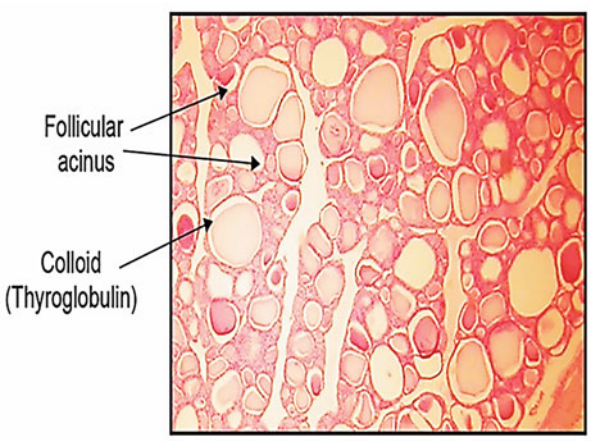

Fig. 5.2 The presence of thyroglobulin within thyroid follicles. H&E magnification 200×

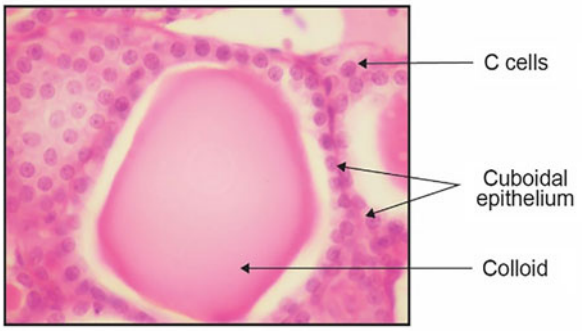

Fig. 5.3 Cross-section showing the thyroid follicles with an epithelium comprised of cuboidal cells with a basal cytoplasm and circular nuclei. It can be seen that the follicular lumen contains a colloidal substance and C cells can be seen at a distance from the cavity H&E magnification 100×

(Hegedüs et al. 1986). The gland is smaller in females than in males as its development is slower in females. In both sexes thyroid's volume increases with increasing age, and with bodyweight which has the clearest effect. Other factors influence gland size (Hegedüs 1990) and weight such as smoking and geographical location. The thyroid is made up of large numbers of follicles (Fig. 5.4). The basic functional unit of the thyroid gland is the follicle (acinus) which has a diameter of 15–500 μm. It has a rich blood supply and contains a network of capillaries to support its functions and variable body demands (Young and Heath 2000). The follicular epithelium comprises a single layer of cuboidal cells (Fig. 5.5). There are also C cells (parafollicular cells) which communicate with the follicular cells using paracrine signals due to the converged distances between them. These C cells are found singly or in small clusters between the follicles. They secrete calcitonin (the hormone which lowers calcium levels in the blood). This occurs at a distance from the margins of the lumen. In human, the parafollicular cells clusters stand as a part of neuroendocrine system and classified as APUD (amine precursor uptake and decarboxylation) cells. The shape of the follicles is adapted to their function. The shape of the follicular epithelial cells varies physiologically according to whether there is activation by

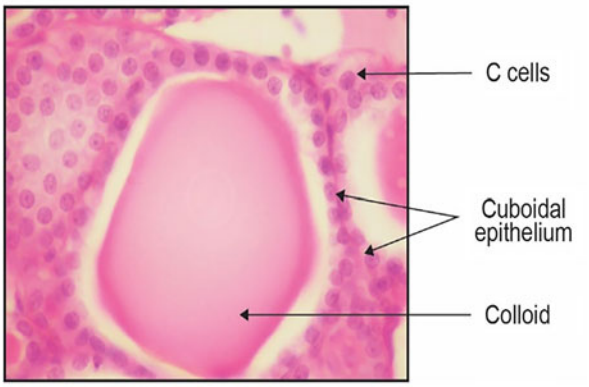

Fig. 5.4 Cross-section showing the thyroid follicles with an epithelium comprised of cuboidal cells with a basal cytoplasm and circular nuclei. It can be seen that the follicular lumen contains a colloidal substance and C cells can be seen at a distance from the cavity H&E magnification 100×. The follicle lumen is filled with a clear amber-colored protein material called colloid or thyroglobulin. This is the main constituent of the contents of the thyroid gland

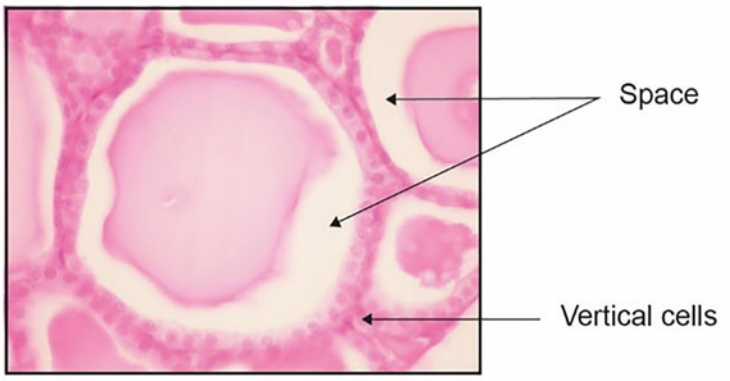

Fig. 5.5 Cross-section showing the structure of the thyroid follicles. The cells which line the follicles have become vertical and there are spaces separating the colloid from the cell layer, pointing to secretary activity of the cells. H&E magnification 100×

thyroid-stimulating hormone (TSH) or inhibition of the thyroid by other hormones or substances. The thyroid epithelial cells vary in the physiological range in form depending on the degree of activation, when under normal conditions they are cuboidal epithelium (Fig. 5.4), whereas activated they become vertical/columnar (Fig. 5.5) and flat on inhibition (Fig. 5.6). All these variations are within the physiological limits.

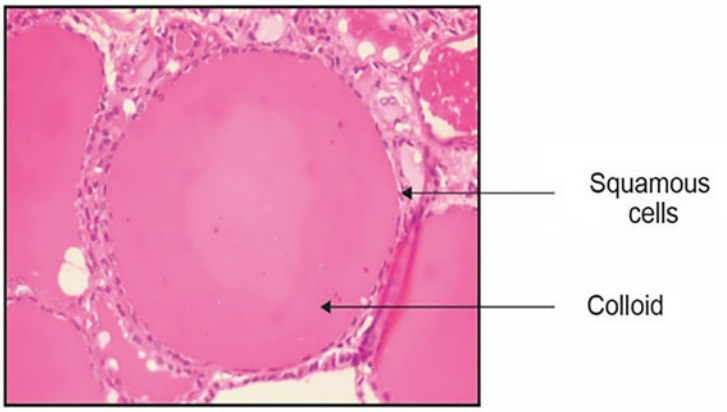

Fig. 5.6 Cross-section of the thyroid follicles. The cells which line the follicles have become simple squamous cells with a flattened shape as a result of pressure from the colloid that has filled the cavity without any spaces, indicating decreased secretory activity. H&E magnification 100×

5.3 Importance of Thyroid Gland

The thyroid gland releases important hormones, thyroxine (T4), 3,5,3-′-triiodothyronine (T3), and 3,5,3′-triiodothyronine (rT3). The thyroid gland has unique properties that distinguish it from other endocrine glands: The thyroid gland synthesizes its prohormone in the lumen, reabsorbs it, and releases it into the circulation depending on the level of stimulation. It is the main source of thyroxine and has a functional structure that allows it to store ample quantities of the hormone in its intermediary form. This is because of the importance of having sufficient reserves of this hormone. Thyroid gland cells have brush border on the apical membrane. Although there is a high iodine concentration in the thyroid gland compared to the concentration plasma, the gland has high ability to attract iodine from the blood due to its participation in thyroid hormone synthesis (Bullock et al. 1991, 2001; Guyton and Hall 2006). Additionally, thyroid contains clusters of parafollicular cells with very important functions in regulating blood calcium and phosphorus ions as well as other significant hormones and functions related to thyroid itself will be discussed in this chapter.

5.4 Physiological Functions of Thyroid Gland

- The thyroid gland produces iodothyronines in the form of the hormones T_3 and T_4. These are derived from the amino acid *tyrosine* and are bound to iodine (Bullock et al. 2001). The thyroid cells produce 80% T4, while the remaining 20% is T3. When T4 is secreted into bloodstream, it could be converted to T3 via

the deiodination process (Eghtedari and Correa 2020). Under normal conditions, the thyroid gland stores sufficient quantities of thyroid hormone as prohormone (thyroglobulin) to maintain stable levels in the thyroid gland (euthyroidism) for several months without having to synthesize more hormone (Bullock et al. 2001). The overall iodine content in the thyroid gland is distributed in the form of 95% in the thyroglobulin and 5% in the follicular cells. Thyroglobulin is found in the follicular lumen in a condensed coupled form, while in the plasma 99.6% of thyroid hormones are bound to the proteins, globulin and albumin. The remaining 0.4% is released in the form of free unbound thyroid hormones (Bullock et al. 2001).

- Thiodine intake properly is very important. In thyrocytes, cell polarization is of critical significance for appropriate functions of thyroid. Several essential mechanisms of self-regulation regulate the main factors required in biosynthesis of thyroid hormone, corporate in top cellular microvilli, to the extent that dangerous enzymatic and biological processes may happen without injuring the cells. In abnormal situations, this enzymatic compound is disordered, the cytoplasm contains certain active components abnormally, leading to more failure in thyroid morphology and functionality. Once iodine intake is improved, out-thyrocytes autoregulatory actions are stimulated. Both thyrocytes and the closed blood capillaries form the angio-follicular components acting like the functional structural components of the thyroid gland. Usually, as a result of iodine deficiency, the microvasculature expands rapidly. Iodide supply is improved in the presence of nutrients and oxygen. These changes happen by triggering the angiogenic signals liberated by thyrocytes through a reactive oxygen species/hypoxia-inducible, factor/vascular endothelial growth factor pathway. At what time these intra- and extra-thyrocyte autoregulation and adaptation fail, other alternates may happen such as euthyroid goiters (Colin et al. 2013).
- In contrast, extreme amounts of I^- for 1 or 2 days prevent the biosynthesis of thyroid hormones, a process termed Wolff–Chaikoff effect. Na^+/I^- symporter facilitates uptake I^- by the thyrocytes, which is considered the first and regulating phase in thyroid hormones biosynthesis. The Na^+/I^- symporter expression and function in thyrocytes are controlled by hypothalamic TSH and by the levels of I^- intracellularly (Arriagada et al. 2015).
- Parafollicular (C) cells may own advanced property to act in the early period of pregnancy to regulate ossification process in the human fetus (Das et al. 2017). Parafollicular cell granules are unlike from other amine-storing granules that contain ATP; therewith, since parafollicular cell vesicles stock 5-HT and possess the same 45 kDa as is present in serotonergic axons terminals. So, parafollicular cell granules may act as analogous to the synaptic vesicles of serotonergic nerve cell (Barasch et al. 1987).

5.5 Phases of the Production and Secretion of the Thyroid Hormones

Thyroid hormones synthesis requires the coordination of regulating signals by hypothalamic TRH, pituitary TSH, and thyroid (Fig. 5.7). TSH is the key regulator for synthesis of thyroid hormones, while it is regulated by TRH. Once TRH signal receives, it binds its receptor (TSH-R) on the basal surface of the thyroid follicular

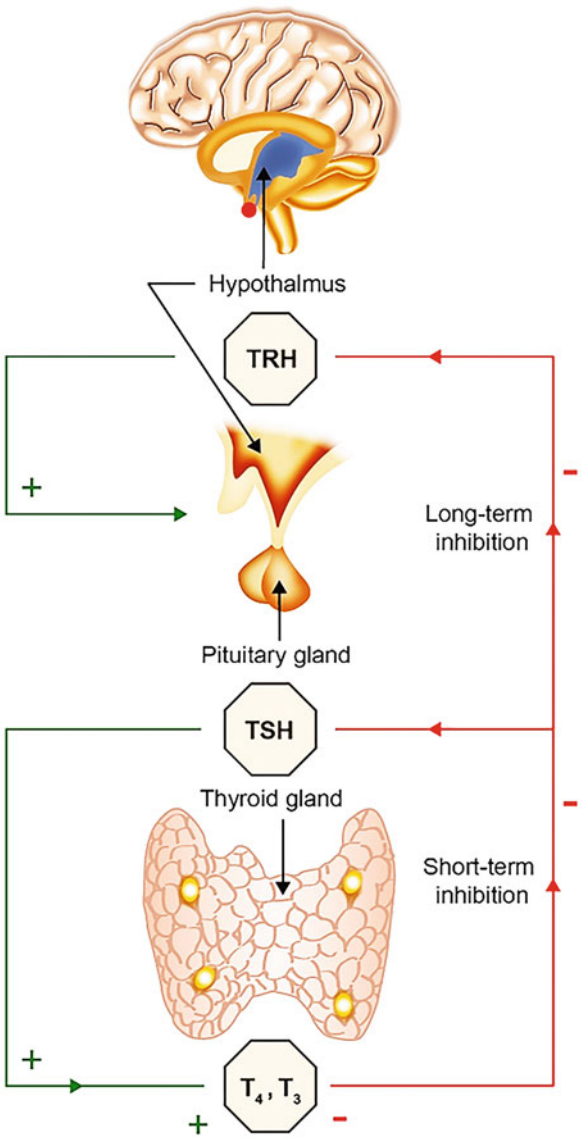

Fig. 5.7 Mechanism of regulation of thyroid hormone secretion

cells activating the receptor leads to activate of the cyclic Adenosine Monophosphate (cAMP) and phosphatidylinositol regulatory cascades that exert responding effects represented by production and release of thyroid hormones and the modification in thyroid hormones–responsive genes (Gaillard and Fredric 2009). Then, the biosynthesis and secretion of the thyroid hormones include three phases each includes some steps either inside or outside the follicular cells. The phases include:

1. **Production** includes the process of capturing the materials needed for hormones synthesis such as tyrosine and iodide, then their making-up.
2. **Storage** of thyroid hormones to meet the body demands in any case for long periods.
3. **Proteolysis and secretion** of T4 and T3 hormones, and
4. **Conversion** of the lesser activity prohormone T4 to the high effective hormone T3. TSH regulates the first three phases. Proteolysis of colloid thyroglobulin is inhibited by iodide, the explanation of these phases is listed below according to Bullock et al. (2001) and Mendoza and Hollenberg 2017. These phases and steps are shown in Fig. 2.3 (Chap. 2).

5.5.1 Phase 1: Hormone Production

Production of thyroid hormones includes these steps: iodide catching, oxidation, iodination of tyrosine residues, and condensation-coupling. All these steps are curial in thyroid hormones synthesis from the amino acid tyrosine and its corporation with the iodide. These processes happen either in the follicular cells or in the lumen of thyroid follicles as following.

5.5.1.1 Iodine Trapping and Transport

The normal iodine level in the human thyroid gland in relation to its level in the plasma is (30–40):1; in other words, the iodine concentration in the thyroid is 30–40 times higher than its concentration in the plasma. After TSH signal receiving, the thyroid gland cell traps iodine by mean of an active transport mechanism which involves an energy that requires Na^{+-}-K^{+} ATPase and leads to the active transport of iodine in the basal layer of the follicular cells from which it diffuses to the apical (brush border) membrane, then a specific protein carries it into the follicular lumen. The thyroid gland has abided not only to capture the iodine element eagerly from food sources but also to store a large amount of the iodinated tyrosines to maintain the release of thyroid hormones during relative iodine deficiency's periods (Fig. 2.3).

5.5.1.2 Oxidation

Iodine is oxidized soon after it enters the cell by means of the enzyme *thyroid peroxidase* (TPO) which converts it into active iodine such as ionic iodine I^{+} at the apex of the cell in the presence of hydrogen peroxide; there are also several other enzymes that are necessary for this process (Fig. 2.3).

5.5.1.3 Iodine Organification (Iodination)

This process requires three enzymes: peroxidase, tautomerase, and transaminase. Iodine binds to tyrosine within seconds, giving rise to monoiodotyrosine (MIT), which consists of a tyrosine molecule and an iodine atom. This is followed by the formation of diiodotyrosine (DIT), the precursor of thyroid hormones which come from iodination of MIT on a meta site of the phenolic ring of tyrosine. MIT and DIT are inactive forms (Fig. 5.8). The concentration of inorganic iodine is not noticeable in the cell because it is converted directly on entering the cell into an organic form after binding to the protein. If the iodine organification process is stopped, its concentration rises to 1–500 times higher.

5.5.1.4 Condensation-Coupling

Tyrosine condensation takes place at the apex of the cell and requires peroxidase. It stimulates all the steps leading to the formation of iodothyronines, but it has not been demonstrated that its absence is responsible for any defects in the condensation process. Any shortcoming in the condensing process leads to a deficiency in the production of thyroid hormones. The thyroxine molecule T_4 binds to four iodine atoms; it is secreted more than T4 which binds to three iodine atoms. The iodotyrosine molecule forms peptide bonds with thyroglobulin which changes it into the active form (iodothyronine T3 and thyroxine T4) as follows:

- Two DIT molecules bind to form T4.
- Two DIT molecules and one MIT molecule bind to form T3, as shown in (Fig. 5.8).

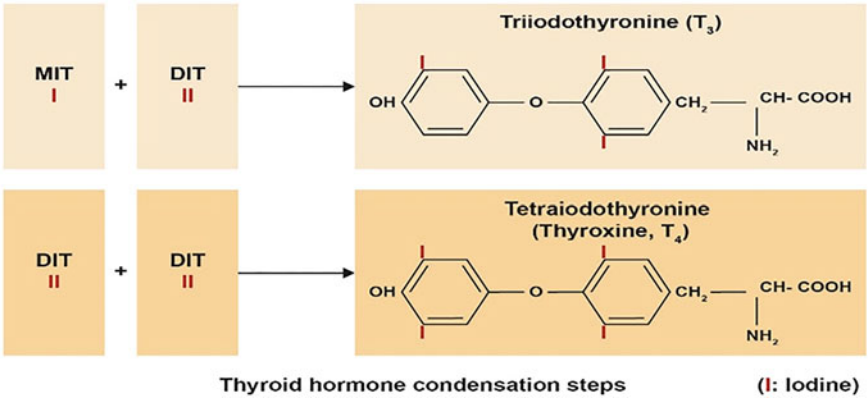

Fig. 5.8 T3 and T4 production. Iodine binds to tyrosine, giving rise to monoiodotyrosine (MIT), which consists of a tyrosine molecule and an iodine atom. This is followed by the formation of diiodotyrosine (DIT), which consists of two tyrosine molecules and two iodine atoms. One molecule of MIT binds to two molecules of DIT to form T3. While two molecules of DIT bind with two molecules of DIT form T4

5.5.2 Phase 2: Storage of Hormones

Storage function of thyroid gland is performed to act as an immediate supplier for the hormone from its prohormone form once required. The thyroid hormones are stored in the form of large molecular weight molecules termed thyroglobulin in the lumen of the thyroid follicles in a structure of a prohormone until they are needed. This colloid material is one of the distinguished properties of thyroid gland functions as it keeps a large stored amount of the inactive hormones for long period up to 3 months to meet the requirements of the body even if the thyroid lacks some of the essential supplies. This unique function is exclusive for thyroid gland only.

5.5.3 Phase 3: Proteolysis of Thyroglobulin and Hormones Secretion

Pseudopods of engulfing thyroglobulin are formulated by thyrocytes, after cellular absorption of the thyroglobulin from the apex, followed by internalization and accumulation of thyroglobulin in the cytoplasmic vesicles, the colloid droplets fuse with lysosomes. Thyroglobulin is degraded by proteolytic enzymes. Thyroglobulin uptake happens mainly by micropinocytosis, because of the two processes: fluid's pinocytosis and receptor-mediated endocytosis. The high concentration of colloidal thyroglobulin enhances its pinocytosis. Low-affinity receptors are appropriate for thyroglobulin uptake to release hormone, while high-affinity receptors act to receive thyroglobulin far from lysosomes by either recycling it inside the colloid or by transcytosis in the blood circulation. There are several apical receptors that promote thyroglobulin uptake and intracellular escaping. A thyroid asialoglycoprotein receptor internalizes and returns immature thyroglobulin's forms back to the colloid, a role also referred to a N-acetylglucosamine receptor. Megalin (a multi-ligand binding receptor presents in the plasma membrane of several absorbent epithelial cells) mediates thyroglobulin uptake under TSH activation, leads to transcytosis of thyroglobulin from the colloid to the circulation, an action that prohibits extreme release of the hormone (Marinò and McCluskey 2000; Botta et al. 2011). T3 and T4 are secreted, along with inactive iodothyronines and free amino acids. Next, T3 and T4 enter the bloodstream by cellular exocytosis or simple diffusion across the cell membrane, while iodine is released from MIT and DIT, a process stimulated by the hormone TSH (Fig. 2.3).

5.5.4 Phase 4: Conversion and Forms of Thyroid Hormones

The bioactivity of each hormone is different. In human, the ratio of T4 to T3 released into the blood is approximately 14:1. T4 converts to the active T3 within the target cell. So, T_3 sources: either it is released by the thyroid cell directly into the blood capillary or by the local conversion of T_4 to T_3 in the peripheral tissues after being stripped of one iodine atom from the former by deiodinase called 5′-iodinase type

2 (Mullur et al. 2014). The proportion of serum has been shown to be constant in healthy adults. In the control group, the FT3/FT4 ratio was $3.03 \pm 0.38\ 10^{-2}$ pg/ng with no age or gender differences according to Oto et al. (2015). The following explains the potency of thyroid hormones:

- The active thyroid hormone is free and not bound. Whenever the body needs it, a small part of it is released called free thyroxine (FT_4).
- T_3 is 4–5 times more biologically active than T_4.
- The turnover of T_3:T_4 is 4:1.
- T_3 has a shorter life span than T_4.
- T_3 constitutes 0.4% as free, while 99.6% in bound form in the circulation.
- T_4 represents 0.04% as free and 99.96% as bound hormone in the circulation. (Guyton and Hall 2006; Pilo et al. 1990; Oto et al. 2015; Mendoza and Hollenberg 2017).

5.6 Thyroid Hormone Metabolism or Deiodination

The thyroid gland secretes 100 nmol of T4 and 5 nmol of T3 daily. Thyroxine is therefore the main hormone that is metabolized and degraded through a deiodination process which converts it to T3. The release of iodine from compounds proceeds gradually by means of the enzyme *deiodinase*. Less than 20% of T3 is secreted by the thyroid, while 80% of it is produced after the iodine atom detaches from the outer ring; in other words, from one of the MIT molecules of T4 to release T3 in the peripheral tissues. The most active thyroid compounds are T_3 and T_4 and although the products derived from them after deiodination are generally less active, but certain products are more biologically active than the original compounds, for example, acetic acid, propionic acid, and pyruvic acid, as well as other compounds derived from decoupling of iodine from T4. Inactive compounds such as returning T3 and T2 metabolites are filtered in the plasma. A gradual decline in thyroid hormone levels takes place through partial consumption by the tissues when they interact with receptors in the target cells. Another part is converted into inactive compounds in the liver, kidneys, and muscles as is the case with the lysis of other hormones. Two-thirds of iodine is excreted in the urine, while a proportion is taken up by the thyroid gland from the bloodstream (Bullock et al. 2001). The enzyme *deiodinase* is important in regulating the hypothalamic and pituitary response to thyroid hormone levels in the blood (Fig. 5.9). Deactivation of thyroid hormones metabolites happens through different mechanisms including deiodination, sulfating, or glucuronidation, to be eliminated through renal or fecas (Köhrle 2018).

5.7 Physiological Functions of the Thyroid Hormones

Subtypes (isoforms) receptors of thyroid hormone are expressed in multiple vital central organs as well as in peripheral tissues in both fetus and adults. This indicates the significance of the thyroid hormones on the functions of these target organs and

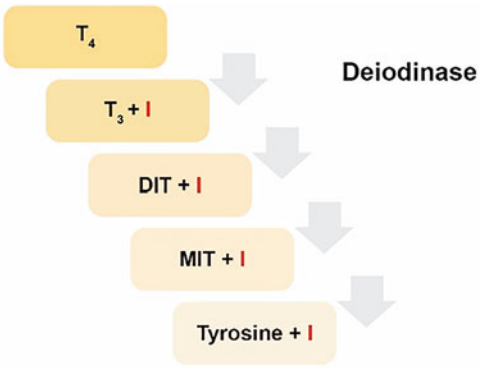

Fig. 5.9 Deiodination process of thyroid hormones

tissues. The subtype receptor alpha (TRα) is mainly expressed in the central nervous system particularly the brain, heart, and skeletal system. While the subtype receptor beta (TRβ1) of thyroid hormone is expressed in other main organs: the kidney, liver, and thyroid gland. The TRβ2 is predominantly in the pituitary, retina, color vision, cerebellum, and cochlea. Mutations in TRα or TRβ can lead to disorders (Mullur et al. 2014; Ortiga-Carvalho et al. 2014; Pirahanchi and Jialal 2020). Once thyroid hormone binds to its receptors, the hormone exerts the following functions according to the target organ.

- **Thermogenesis**: Thyroid hormones have an effect on the lungs. The basal metabolic rate in the euthyroid state is 35–40 kcal/m^2 of body surface area/hour. This is lower in females. Thyroid hormones affect oxygen consumption by increasing the basal metabolic rate, increase the number and size of mitochondria, and stimulate the oxidization by regulating the enzymes leading to thermogenesis (Bullock et al. 2001). T3 boosts Na-dependent breathing associated with an increased action of NaK-ATPase action. Thyroid hormone not only activates Na pump, but also the cell membrane's permeability to sodium and potassium ions. These two actions may grant the thyroid thermogenesis effect (Asano 1978).

  The thyroid gland has a definitive function in the regulation of thermogenesis as described above by managing the metabolism, oxygen consuming, then controls energy release as heat production to meet the body requirements, but the mechanism for adapting is as the following: In the rest, these processes are subtle and subjected to alterations by thyroid function. Thyroid function alongside with the adrenergic system defines the capacity of body to adapt to low temperature as cold weather. This adaptation gives rise to deiodination of T4 the process that increases levels of T3 in humans and animals' circulation. T3 is an inductor of the expression of iodothyronine deiodinase in many organs such as brown fat, kidney, and liver. This enzyme, deiodinase, moves a key role in body adaptability in response to cold through participating in high adrenergic reaction of brown fat. T3 increases expression of separating proteins and separating oxidative phosphorylation and rises heat production (Tsibulnikov et al. 2020).

Thyroid hormones levels change according to the surrounding climate temperature. So, they increase in winter and decrease in summer; all these fluctuations are limited in the normal physiological levels of thyroid hormones in the circulation.

- **Growth and general metabolism**: Thyroid hormone is involved in regulating normal growth and metabolism in the adult. The thyroid hormone receptor isoforms, TRα TRβ, are expressed dissimilarly in organs to perform different functions of thyroid hormone signaling. The functions of thyroid hormone in the regulation of metabolism pathways may serve as novel curative objective for diseases (Mullur et al. 2014). The following is some of mechanisms of the thyroid hormone actions:
  1. Thyroid hormones act on the central nervous system to modulate energy balance and peripheral metabolism. TRβ presents in the ventromedial hypothalamus and plays an important physiological role in regulating appetite, bodyweight (Hameed et al. 2017) and energy balance (Martínez-Sánchez et al. 2017).
  2. Conversion of T4 to the active form T3 locally by the enzyme 5′-deiodinase type 2 is a crucial action of thyroid hormone regulation of metabolism. 5′-deiodinase type 2 is expressed in certain tissues such as the hypothalamus and energy-related tissues; both white and brown adipose tissue as well as skeletal muscle for thermogenesis regulation that could be modulated by nutritional signals such as leptin and peptides controlling appetite. The nutrient situation of the cell gives feedback on the route of thyroid hormone signaling through epigenetic modulating of histones.
  3. Combination of thyroid hormone signaling with the adrenergic nervous system is performed centrally in the hypothalamus and peripheral organs such as liver and fat tissues.
  4. Thyroid hormone regulates the metabolism of cholesterol and carbohydrate by several mechanisms including governing bile acid signaling mechanism, gene expression, signaling nuclear receptors.
  5. Thyroid hormone modifies hepatic-insulin sensitivity which is important to suppress liver gluconeogenesis (Mullur et al. 2014).
- **Bodyweight**: It is well known that thyroid hormone regulates the energy and metabolism, but the most unknown is a new function of thyroid hormones that they regulate bodyweight and they may help determine which individuals are more exceptive to weight loss diets (Li et al. 2017).
- **Carbohydrate Metabolism**: In normal levels, thyroid hormones boost the effect of insulin and reinforce glycogen-store building and glucose consumption. High levels (hyperthyroidism) result in increased blood sugar levels as it leads to the degradation of glycogen, aids the formation of glucose from non-carbohydrate sources (gluconeogenesis) under the effect of TSH. It also increases glucose absorption from the intestines. Hyperthyroidism therefore further aggravates diabetes (Bullock et al. 2001).
- **Protein Metabolism**: Thyroid hormone influences protein turnover: normal levels have an anabolic (a protein-building) effect, whereas induced hyperthyroidism leads to the catabolic effect (breakdown of proteins). However,

hypothyroidism-induced changes in amino acids uptake may lead to skeletal muscle damage (Gołyński et al. 2016).

- **Fat Metabolism**: Normal levels of T3 support hepatic lipogenesis concurrently with stimulating the thermogenic process in brown adipose tissue through the parasympathetic and sympathetic nervous systems, respectively. It also has an impact on all aspects of fat metabolism; hyperthyroidism leads to increased levels of cholesterol and low-density lipoproteins and is accompanied by increased fat metabolization (lipolysis), resulting in increased levels of fatty acids and glycerol in the blood (Bullock et al. 2001).
- **Vitamins Metabolism**: Protective interactions between thyroid hormones and vitamins like vitamin D3. Also, there is an interrelationship between the thyroid hormones and vitamin A. Following stress, such as surgery, there is an interaction between them and binding proteins. Several small molecules such as 1, 25-dihydroxycholecalciferol (Vitamin D) or thyroid hormones act as nuclear receptor ligands. They stimulate signaling in gap junction communication (GJC) to a similar extent as carotenoids or retinoic acid. Interactions between these signals may be involved in GJC regulation. This mechanism could possibly explain the protective role of carotenoids against cancer (Stahl and Sies 1998). T3 is an important hormone in regulating vitamin A and carotene metabolism, with gene expression taking place in the cells of the small intestine (Yamaguchi and Suruga 2008). Hypothyroidism may lead to increased carotene concentrations in the circulation which manifests as pale-yellow skin.
- **Tissue, Cell, and Stem Cell Functions**: Thyroid hormone T3 changes the permeability of the cell membrane, cell organelles, and sodium-potassium pump (Asano 1978). Thyroid hormone is a key factor for tissue functions in vivo. The family of deiodinase regulates the tissue-specific activation/inactivation of intracellular thyroid hormones. The regulation of T3-dependent transcriptional program is required by several cell's systems, particularly the stem cells. There is a strong relationship between thyroid hormones and different signal mechanisms involved in the control of stem cell functions. The deiodinases may take a role in the biology and physiology of stem cell. Stem cells possess an unlimited self-renewal capability and the potency to differentiate into multiple types of mature cells. The deiodinases play a role in the modulation of the thyroid hormone signals in stem cells of adult tissues (muscle and intestine), and how their actions control the accurate balance throughout self-renewal, proliferation, and differentiation. Explanation of the molecular mechanisms managing thyroid hormone effects on stem cells may uncover possible therapy for regenerative disorders and tumor (Salvatore 2018). The thyroid hormone is vital for the appropriate development and differentiation of human cells. Also, T3 has a dose-dependent effect on the differentiation of bone marrow mesenchymal stem cells in female rat (Janssen et al. 2017).
- **Molecular Level Function**: Thyroid hormone also has an effect at the molecular level, for example, the effect of T3 depends on AMP-activated protein kinase-induced regulation of signaling pathways in the ventromedial nucleus of the

hypothalamus. Also, after hypoxia, thyroid hormone (T3)-induced mRNA gene expression takes place (Hameed et al. 2017).

- **Brain Development**: The thyroid hormones play a critical role in brain development in adult and its physiological functions. Fetal development is mostly dependent on thyroid hormone and appropriate placental function, with a vital role in placental mitochondrial DNA and mitochondrial DNA methylation. Maternal thyroid hormone does not cross the placenta in sufficient quantities for this function and therefore these effects are dependent on fetal thyroid secretion mostly (Janssen et al. 2017) in addition to maternal thyroid function (Segni 2019). Iodine is found in the thyroid tissues which appears in the human fetus at an early stage. Thyroid hormone regulates and stimulates mental development as well as nerve tissue growth in the brain and boosts the function of growth hormone because a deficiency in the myelin sheath of the neuronal cells in the brain is found when there is a decrease in thyroid secretion (Janssen et al. 2017).
- **Neuronal Recovery**: Thyroid hormone contributes to neuronal recovery after traumatic brain injury in vitro and in vivo as it supports growth hormone. In the adult spinal cord, oligodendrocyte precursor cells and multipotent neural stem/progenitor cells exist that can differentiate into mature, myelinating oligodendrocytes. In vitro, 3,3′,5-triiodothyronine (T3) promotes oligodendrogenesis and oligodendrocyte maturation (Li et al. 2017; Shultz et al. 2017).
- **Prevention of Mental Retardation and Depression**: As mentioned thyroid hormone has an important function for normal growth of the brain and skeletal system, this function of thyroid hormone is done on key genes for neurodevelopment, the process that must be performed in a specific time period. Since a short time of thyroid hormone deficiency causes irrevocable impairment in the brain. Although thyroid gland of fetus plays its role throughout the first trimester of gestation, fetal brain growth is fully dependent on the sources of thyroid hormone either the maternal (Segni 2019) or the fetal source (Janssen et al. 2017). Congenital hypothyroidism stands as one of the highest avoidable reasons for mental retardation, but it requires early diagnosis in order to avoid permanent brain damage. Currently above than 70% of the children globally are born in regions deprived of a systematic screening program (Segni 2019). In human adolescents, early life upset and adverse were accompanied with decreased T3 circulated level (Machado et al. 2015). Additionally, thyroid hormone contributes to preventing depression. The cellular uptake or outflow of thyroid hormone through transmembranal proteins provides an important key of regulation during neurodevelopment. In humans, deficiency in one of these proteins which is called solute carrier SLC16A2 (MCT8) is accompanied with psychomotor obstruction (Sharlin et al. 2018).
- **Cochlea Function**: Thyroid hormone is required for the auditory system growth; the cochlea is a main target tissue. Activation of T3's receptor β is vital for normal cochlea differentiation, function and morphology (Richter et al. 2011) and anatomy (Sharlin et al. 2018). Comprehensive stimulation of TRβ by T3 by is vital

signal for normal physiological function and morphology of cochlear. Normally, T3 binds to thyroid hormone nuclear receptors TRβ on cochlea. At positive regulated genes with the deficiency of thyroid hormone, nuclear co-repressors bind to TRβ and reduce basal transcription level. Binding with ligand (T-3) leads to the disconnection of co-repressors and employs co-activators to the compound that leads to full transcriptional activation. These mutations were hurtful to the development of tectorial membrane and change significantly cochlear morphology and damage of its function (Richter et al. 2011). The cochlea anatomy requires transport mechanisms to transfer circulating hormone to its target tissues. Mutations in the transporters, Slc16a2 and a related gene Slc16a10 in mice are associated with hearing loss. Insufficiency of these transporters leads to retarded growth of the sensory epithelium like weakness resulted in hypothyroidism, accompanied by an advanced retrogression in hair cells of cochlear and damage of endocochlear capability. Treatment with T3 mostly recovers the growth of the sensory epithelium and function of limited auditory. Thyroid hormone T3 transporters are essential for cochlear growth, development, and functions (Sharlin et al. 2018).

- **Cardiac Output**: Thyroid hormones influence heart rate, myocardial contraction, and cardiac output by controlling the number of adrenaline receptors from the sympathetic nerves in the heart. Also, regulate vasodilation, enhance blood flow to some organs. Changes in thyroid hormones condition influence significantly cardiac contractile and electrical activity. Deng et al. (2017) reported that T3 supports the proliferation of epicardial progenitor cells. A permissive role of combined thyroid gland hormones and glucocorticoids during the cardiac cell's differentiation is sufficient for T-tubule growth, boost Ca release, and further ventricular-like excitation–contraction conjunction. This new hormone maturation way could promote the use of human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) for disease designing and cell-based treatment (Parikh et al. 2017).
- **Sexual Maturation and Reproduction**: Thyroid hormones play an important role in sexual maturation through its effect on the gonads. It is needed prior to sexual maturation to allow the sex glands to develop. It is needed after maturation to produce gametes. Also, it supports gonadal hormones in regulating ovarian cycle. Normal and regular reproductive functions, cycles, and physiology are dependent on essentially normal concentrations of thyroid hormones. Hypothyroidism particularly is usually correlated with infertility cases. Thyroid level changes within the normal physiological range are important in regulating ovulation; high levels within the physiological range lead to luteinizing hormone elevation which boosts ovulation, while low levels below within the physiological range lead to the secretion of follicle stimulating hormone (Bullock et al. 2001). In women, thyroid disorder is mostly the second endocrine case of reproduction stage of age. Thyroid hormones are required in regulating menstrual cycle and in perfect fertility as they impact the functions of FSH and LH on steroid synthesis through specific T3 locations on oocytes; hence, this influences wholly reproduction functions (Medenica et al. 2015). Thyroid hormone is

required in normal lactation, as it helps PRL and promotes the animal production (milk, egg, etc.) in cold environments where thyroid hormones increase in cattle in winter.

5.8 New Functions of Thyroid Hormones

- **Immunity**: Thyroid status and its hormone metabolism are associated with several properties of the immunity. Based on mutual communication and regulation between the neuroendocrine and immune systems, Jara et al. (2017) reported that thyroid hormones and thyrotropin can modulate immunological functions and therefore their therapeutic use might contribute to restoring normal physiological function from pathological statuses. Thyroid hormone metabolism acts an important function in the host immunity against contagion by altering cellular function of innate immunity in inflammation. The mechanism of thyroid hormone on immunity can be explained according to van der Spek et al. (2017) who reported that blood levels of thyroid hormone play a great impact on function of immune cells; macrophage, neutrophil and dendritic cell. Usually, high levels of thyroid hormone increase the pro-inflammatory reaction of these immune cells. This mechanism includes genomic and other effects of extracellular thyroid hormone in addition to the cellular reaction to pro-inflammatory signal depending on intracellular thyroid hormone metabolism. This is explained by the fact that the family of deiodinase enzymes and in certain cells also receptors of thyroid hormone seem to play vital role for appropriate functions of innate immune cell.
- **Hemopoiesis** (Erythropoiesis): Thyroid hormone stimulates the proliferation of erythrocyte precursors directly by hemopoietin stimulating agents. Thyroid dysfunction may result in anemia (Szczepanek-Parulska et al. 2017; Fein and Rivlin 1975; Marinò and McCluskey 2000). Also, in a catfish that lives in freshwater, the pineal gland or melatonin stimulates the level of hemopoiesis; however, the extent of this process depends on gonads, the stage of the yearly reproductive cycle, the time. While thyroid plays a timing-day dependent superfine role (Shedpure and Pati 1996).
- **Kidney**: Human's hypothyroidism is associated with incomplete acidosis in distal renal tubular, as it leads to respond inappropriately to acidity challenge through excreting less acid (Mohebbi et al. 2007). Thyroid hormones T4 and T3 levels are lower significantly in undialyzed patient's chronic kidney disease than healthful controls (Srivastava et al. 2018). Chronic kidney disease is commonly synchronized with dysfunction in thyroid hormone. Decrease in thyroid function does not relate with a weakness in kidney functions. But the association may be clarified by kidney dysfunction leading to changes in thyroid hormone (Meuwese et al. 2019).

5.9 Regulation of Thyroid Hormones

- The hypothalamus regulates the thyroid hormones by secreting thyrotropin-releasing hormone (TRH) which reaches the pituitary via the hypophyseal portal system and stimulates the basophils of the anterior lobe to produce TSH. This, in turn, stimulates the thyroid gland to produce its hormones (Fig. 5.8).
- Negative Feedback Mechanism: Free T_3 and T_4 levels in the bloodstream regulate the secretion of TSH on the short-term axis (pituitary level) or the long-term axis (hypothalamus). They are inhibitors of TSH secretion when their levels in the blood increase and vice versa as shown in the figure below (Fig. 5.8) (Mullur et al. 2014).
- Parafollicular cells (C cells) are mainly involved in the regulation of thyroid follicular cell activities in a paracrine manner. C cells regulate the newborn growth rate by changing thyroid hormone concentrations in the early postnatal period (Irmak and Kirici 2004).
- Cold and hot seasons have multiple physiological effects on thyroid physiology. Low external temperatures stimulate the secretion of TRH from the hypothalamus which in turn signals the pituitary gland to secrete TSH, and this leads to stimulation of the thyroid gland (Bullock et al. 2001).
- Age Factor: In infants and adults: Thyroxine metabolic processes increase and reach a peak in fetuses and children, which aids neuronal, sexualm and mental development. Levels start to decline after maturity then become stable until the age of 60 years, after which thyroid hormone levels start to decrease with age even though hormone function remains normal in the elderly.
- Thyroglobulin has an effect on thyroid cell behavior particularly on the process of follicular heterogeneity as a highly regulated cycle of controlling (increasing and decreasing) colloidal thyroglobulin level that functions to optimize thyroid hormones production by regulating the transcriptional activation or inhibition of specific genes (Akama et al. 2014; Sahin et al. 2017).
- Other factors influence thyroid hormones: T_4 levels increase during pregnancy, also T_3 affects but to a lesser extent. There is an intrinsic control of thyroglobulin on thyroid function as thyroglobulin does not act as a precursor of mature thyroid hormones only, but it also functions as a key signal molecule in the regulation of thyroid hormone biosynthesis (Sellitti and Suzuki 2014). Thyroid volume increases in patients with insulin resistance and polycystic ovary syndrome (Sahin et al. 2017). Estrogens stimulate the secretion of TSH, then it influences thyroid functions and hormones. Somatostatin inhibits TSH secretion and reduces TRH response. Meanwhile, dopamine decreases its basal secretion. Both excessive iodine uptake and a shortage of iodine inhibit the production and secretion of thyroid hormone. Exposure to heavy metals such as cadmium and lead links to decreasing T_4 (Akgöl et al. 2017).

5.10 Goiter and Thyroid Diseases

Thyroid gland disorders are the commonest endocrine diseases and one of the very common diseases globally, they are clinically main subgroups deficiency of iodine, thyroid goiter, and thyroid cancer (Maniakas et al. 2018). Enlargement or increased size of the thyroid gland is called goiter. The substances responsible for this condition prevent the formation of thyroid hormone. Goiter does not define the functional status of the thyroid gland and is generally linked to oversecretion of TSH. Iodine is a mineral that shows a key function in the biosynthesis of thyroid hormones. As described, it is necessary for normal health throughout life. Thus, a deficient in iodine consumption may lead to dysfunction in thyroid with goiter, also it may relate to clinical characters such as undersized development and psychological retardation called iodine deficiency. Deficiency of iodine is still remaining an essential community health issue in several regions in the world. The best strategy for avoiding it is the worldwide salt iodization. Although this strategy improved the situation greatly still there are many areas that suffered from iodine deficit (Giordano et al. 2019). In elderly, thyroid nodules are a common diagnosis. Most patients of thyroid nodules show rare or without symptoms as nodules are non-functioning. While in elderly, toxic multinodular goiter is the common reason for spontaneous hyperthyroidism (Faggiano et al. 2011).

5.11 Stem or Progenitor Cells of the Thyroid Gland: The Promising Alternative Source

Thyroid follicles, thyrocytes, and C cell differentiation are essential for physiological functions of thyroid gland. As it is the only source of thyroid hormones, this has motivated scientists to learn more about the origins, organization, and regeneration of the thyroid gland to help resolve and treat thyroid dysfunctions and diseases. So, there is great interest in studying thyroid stem cell biology (Davies et al. 2011; Augenlicht 2017). Both human embryonic progenitor cells and human-induced pluripotent stem cells can differentiate into any cell population in the human body. The significant step in generating organ progenitor cells is the differentiation into definitive endoderm for many organs including the thyroid (Korostylev et al. 2017). The thyroid gland possesses side population cells that represent stem/progenitor cells (Hoshi et al. 2007). Mice and human thyroid stem cells were identified in mature thyroids in vivo and in vitro *w*ith successful differentiation into thyroid-like cells (Davies et al. 2011). In developing mouse thyroid, epithelial release of angiogenic factor and vascular endothelial growth factor A is required for endothelial cell recruitment and growth. After this, endothelial cells regulate follicular epithelium re-organization, folliculogenesis, and differentiation, as well as thyrocytes and C cell differentiation. Loss of blood supply makes embryonic endothelial progenitor cells recover folliculogenesis by expanding its lumen and activate calcitonin expression in C cells (Hick et al. 2013). Previously, it was known that the thyroid gland is not a regenerative organ, but Ozaki et al. (2012) used partial thyroidectomy to create

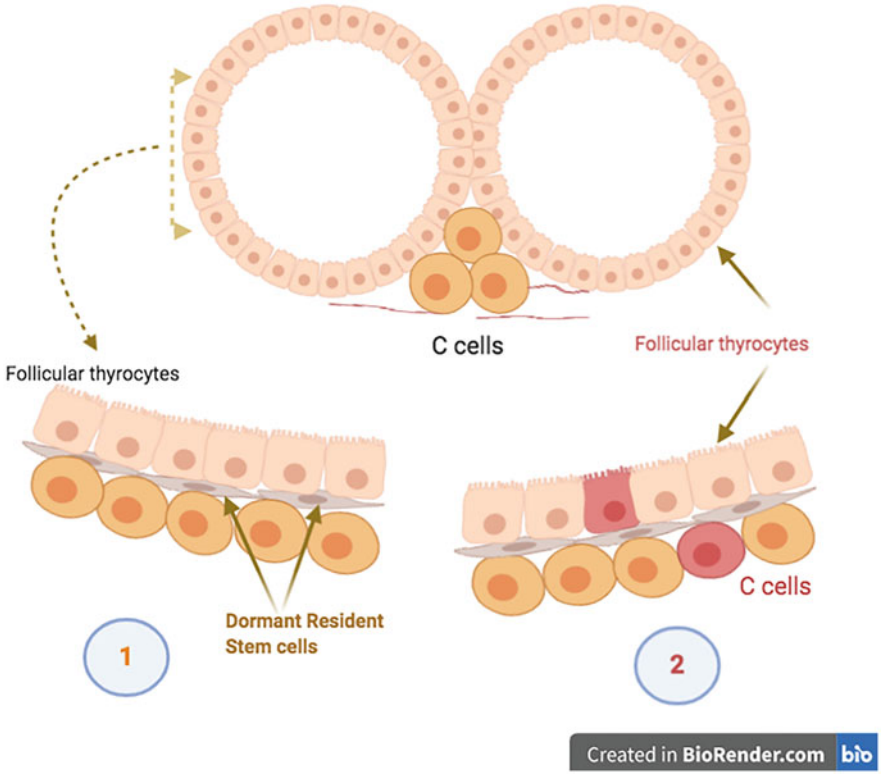

Fig. 5.10 Thyroid gland cells showing positions and models of its stem cells. (1) Indicates dormant resident stem cells that can proliferate and differentiate. (2) Indicates some mature follicular thyrocytes (producing T3 and T4) and some C cells (producing calcitonin) that could be reprogrammed back to immature endoderm cells and act as stem cells

conditions for inducing thyroid regeneration. The centers of both intact thyroid's lobes serve as proliferative central regions where micro-follicles, bromodeoxyuridine-positive, and/or C cells were present. Both C and thyroid follicular cells change by fractional thyroidectomy to serve as immature cells or immature cells-derived from stem/progenitor cells during their passage to differentiate to C cells or follicular cells. The immature clear cells take part in the repair/regeneration process of the thyroid gland's cells. Thyroid gland cells possess dormant resident stem cells that can proliferate and differentiate and also some mature follicular thyrocytes (producing T3 and T4) and some C cells (producing calcitonin) can be reprogrammed back to immature endoderm cells and act as stem cells as shown in Fig. 5.10.

From a clinical view, adult thyroid stem/progenitor cells may have possible mechanisms for thyroid tissue repair and regeneration. Two models have been put forward for thyroid repair: the first for mature cells reprogrammed back to immature endoderm lineage-obliged progenitor cells. The second should be adult-resident

stem cells/progenitors (Kimura 2014). Hypothyroidism is a common disorder. Regenerative medicine methods such as a bioengineered thyroid have been recommended as possible therapeutic procedure for patients with hypothyroidism. Pan et al. suggested a novel method to generate thyroid grafts using decellularized rat thyroid matrix. The recellularized thyroid exhibited successful cellular engraftment and specific function such as synthesis of thyroglobulin and peroxidase. Moreover, the decellularized rat thyroid skeleton could be recellularized with both human-derived thyroid cells and parathyroid cells to restructure a humanized bio-artificially endocrine organ that maintained expression of main genes such as thyroid thyroglobulin, thyroid peroxidase, and parathormone hormone (Pan et al. 2019).

Efforts are being made to regenerate the thyroid function by transplantation of differentiated pluripotent stem cells. It has been reported that thyroid progenitors derived from mouse pluripotent stem cells can be matured into thyroid follicular organoids that provide functional secretion of thyroid hormones. Moreover, normal and disease-specific induced pluripotent stem cells can be generated from the patients with hypothyroidism (Kurmann et al. 2015). In other studies, thyroid tissues were generated from embryonic stem cells in mutant mice (Ran et al. 2020; Wen et al. 2021). In addition, functional thyroid tissues were derived from using 3D-culture of embryonic stem cells (Antonica et al. 2017).

The functional description of the mechanisms of stem cell's differentiation into efficient complete thyroid follicles is needed in cancer development via one type of these cells: prothyrocytes, thyroblasts, or fetal cell. Some factors are responsible for diverse cancers formation; they are (1) mutation in specific gene in the thyroid mature cells or (2) existence of a kind of cancer stem cell. Additionally, many biomarkers of stem cell in thyroid gland either are reviewed including transcriptional factors such as octamer-binding transcription 4, thyroid transcription factor 1, thyroid transcription factor 2, the transcription factor GATA-4, homeobox transcription factor Nanog and nuclear factor such as hepatocyte nuclear factor 4 as well as stem cell antigen 1. Considering the different mechanisms of cancer formation, expression of different biomarkers and factors in health and disorders of thyroid gland is encouraging molecular tool in the area of thyroid regenerative medicine and in the treatment strategy for thyroid cancer (Al-Suhaimi and Al-Khater 2019).

5.12 Conclusion

Thyroid gland is a highly vascularized organ consisting of two lobes connected by isthmus and located in neck. One of the lobes lies at the left and another at the right to fourth tracheal rings and inferior to larynx. The shape of thyroid varies depending on the individuals. Thyroid gland secretes two important hormones: thyroxine (T4) and triiodothyronine (T3). The gland is composed of basic functional unit follicle also known as acinus with size diameter ranging between 15 and 500 μm. Rich blood supply and presence of capillaries around the follicles assist the important hormonal functions. Follicles shape and size variation occurs with thyroid-stimulating

hormone (TSH) activation or inhibition. The main role of thyroid gland is to produce iodothyronines in the form of the hormones T3 and T4. The hormones bioactivity is different, derived from amino acid tyrosine and is bound to iodine. Plasma concentration of free T4/free T3 is 1:2. Sufficient hormones are stored as prohormone (thyroglobulin) under normal conditions (euthyroidism). The chapter describes about the stages in the synthesis and secretion of thyroid hormones, physiological functions of the thyroid hormones, and mechanism of action. Thyroid hormones metabolism or deiodination is demonstrated along with stem/progenitor cells of the thyroid gland, thyroid follicles, thyrocytes, and C cell differentiation.

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Bone Remodeling Physiology: Regulation of Parathyroid Glands, C Cells, Vitamin D, and Bone as an Endocrine Organ

6

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Contents

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Abstract

The chapter also discusses the location, tissue structure of parathyroid glands, and important functions of PTH. PTH performs its functions in coordination with calcitonin and the active forms vitamin D to regulate calcium levels in the circulation. On another hand, bone is commonly known as a passive tissue, it is recently reported as an endocrine organ produces regulators, osteocalcin hormone, sclerostin and lipocalin that integrate with PTH and influences other metabolic functions. Calcium metabolism regulating hormones, PTH, PTHrP-1, and their derivatives roles have been explained through their receptors in the bones, intestines, kidney tissue, placenta, and breasts as well heart. Physiological functions of biologically active forms of vitamin D are discussed with different origin cell types for parathyroid differentiation. PTH has paradoxical and therapeutic effect as anabolic hormone on bone formation. The integration between PTH, calcitonin, and vitamin D active forms is significantly required for the formation and remodeling of the bone and on stem cell and hematopoietic progenitor cells differentiation. Different origins for parathyroid differentiation are established from endoderm, thymus, tonsil, and adipocytes which lead to optimism management of parathyroid diseases and treatment.

Keywords

PTH · Calcitonin · Calcitonin gene-related peptide Vitamin D · 1,25(OH)2D · C cells · PTHR1 · PTHrP · PTHrP-1

Abbreviations

1,25(OH) 2D3	1,25-dihydroxyvitamin D (3)
1,25(OH)2D	25-dihydroxyvitamin D
1-α hydroxylase	1-alpha hydroxylase
20(OH) D3	20-hydroxyvitamin D (3)
24,25(OH)2D	24,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
APUD	Amine precursor uptake decarboxylase
C cell	Parafollicular cell
Ca^2/Ca^{2+}	Calcium ions
CaSR	Calcium-sensing receptor

CGRP	Calcitonin gene-related peptide
ERS	Endoplasmic reticulum stress
H&E	Hematoxylin and eosin
HCO_3^-	Bicarbonate
hPTH	Human parathormone
IL-6	Interleukin-6
IMD	Intermedin
Osteoblast	Bone-forming cell
Osteoclast	Bone-reabsorbing cell
P450	A cytochrome
PTH	Parathormone (also known as parathyroid hormone)
PTHR1	Parathormone receptor 1
PTHrP	Parathyroid hormone-related protein
PTHrP-1	Parathyroid hormone-related protein-1
rhPTH	Recombinant human parathyroid hormone
VDR	Vitamin D receptor

6.1 Introduction and Bone Remodeling

The parathyroid glands are acknowledged as an organ necessary for life (Kalra et al. 2013). The parathyroid glands secrete parathyroid hormone (PTH). PTH, C cell (parafollicular cell) hormones such as calcitonin, sex hormones participate in minerals regulation with other hormones. Their receptors are distributed in specific organs of the body and contribute particularly to the systemic physiological regulation of calcium and phosphorus. This takes place in conjunction with active forms of vitamin D, a secosteroid hormone responsible also for regulation of these minerals in the body. The main function of PTH is physiology and metabolism of calcium. It was believed that hyperparathyroidism leads to severe bone loss, but subsequent studies on PTH in humans led to surprising paradoxical results, it has been evidenced that PTH could be used pharmacologically for bone formation. Hypocalcemia (decreased calcium level in the blood under the minimum physiological limit) is the very common obstacle post thyroidectomy (Verma et al. 2020). This is attributed to hurt or ischemia in parathyroid glands (Chisthi et al. 2017) that is located adjacent to thyroid gland as we will describe in this chapter. Thyroidectomized patients are treated with supplementation with calcium and vitamin D after total thyroidectomy surgery (Verma et al. 2020; Păduraru et al. 2019). Calcitonin regulates calcium and phosphate ions in blood circulation by lowering calcium to its physiological levels. The hypocalcemic effect of calcitonin is reliant on phosphate ions; however, the hypophosphatemic effect is calcium-independent. Calcitonin transfers phosphate ions to osteocytes and its microenvironment leading to collection of electron-dense substance in lining cells and their microenvironment at bone surfaces, in dissimilarity to decrease the transport of calcium ions from bone cell to the circulation

(Talmage et al. 1981). Vitamin D includes two common hormones classified as secosteroids; they are ergocalciferol D_2 as pharmaceutical form and cholecalciferol D_3 synthesized in the skin—with light—such as calcidiol, and calcitriol increases calcium ion levels in the circulation in synergy with PTH. The parathyroid hormones play key functions in the human body and act in unison with calcitonin and calcitriol to achieve their systemic effects on the kidney, intestines, and bones physiologically and pharmaceutically. In this chapter, differentiation of different cell types of stem cell (includes) into parathyroid cells will be clarified and bone will be described as an endocrine organ.

Bone remodeling begins in fetal till maturation targeting epiphysis's closure or completion of longitudinal bones. Bone remodeling is moving of bone from one site and forming it at another sites. Bone skeleton is a very specific and dynamic system that is subject to constant regeneration. For bone's homeostasis in adult, sustaining acquisition of peak bone's mass, shape and mineral homeostasis, bone remodeling is essential and critical process which balances between two stages: bone formation and resorption. Bone regeneration continues as essential requirement after maturity by periodic surrogation of ancient bone with recently formed one in the same bone, named remodeling. This process is also needed for repairing of damaged bones as a result of workaday physical load to avoid aging consequences which prevents osteoporosis. Bone remodeling is extremely regulated through specific osteocytes (Parfitt 1982; Martin et al. 2009; Siddiqui and Partridge 2016). Bone remodeling is regulated by growth and systemic factors. Systematic factors include PTH, PTHrP, vitamin D3, calcitonin, estrogen, androgens, thyroid hormone, glucocorticoids, growth hormone. Growth factors that regulate bone remodeling are bone morphogenetic proteins, transforming growth factor-β, epidermal growth factors and receptor, fibroblast growth factors, insulin-like growth factor-1 and WNT and WNT antagonists (Siddiqui and Partridge 2016). Endogenous PTH signals play a key role in fracture healing (Sun et al. 2020). Bone protein hormones play important roles in bone formation, modeling, remodeling, and in some disease's prediction (Maurizi et al. 2021; Hong et al. 2021).

6.2 Functional Structure of the Parathyroid Glands

The parathyroid and thyroid glands are separated organs, each owns particular functions. But this does not cancel a direct or indirect communication or interaction in the functions between these two organs. It is believed that an insufficiency of the parathyroid gland relates to almost the thyroid function (Tanberg 1916). The parathyroid glands consist of four small, oval-shaped glands usually found in the posterior thyroid tissue, which is why they are called the parathyroid glands. Each gland weighs 40 mg, and around 15% of people have a fifth gland (Figs. 5.1, 5.2, 6.1, and 6.2). The parathyroid glands consist of endocrine tissue interspersed with septa extending from the thin capsule which divides the glandular tissue into lobes. The

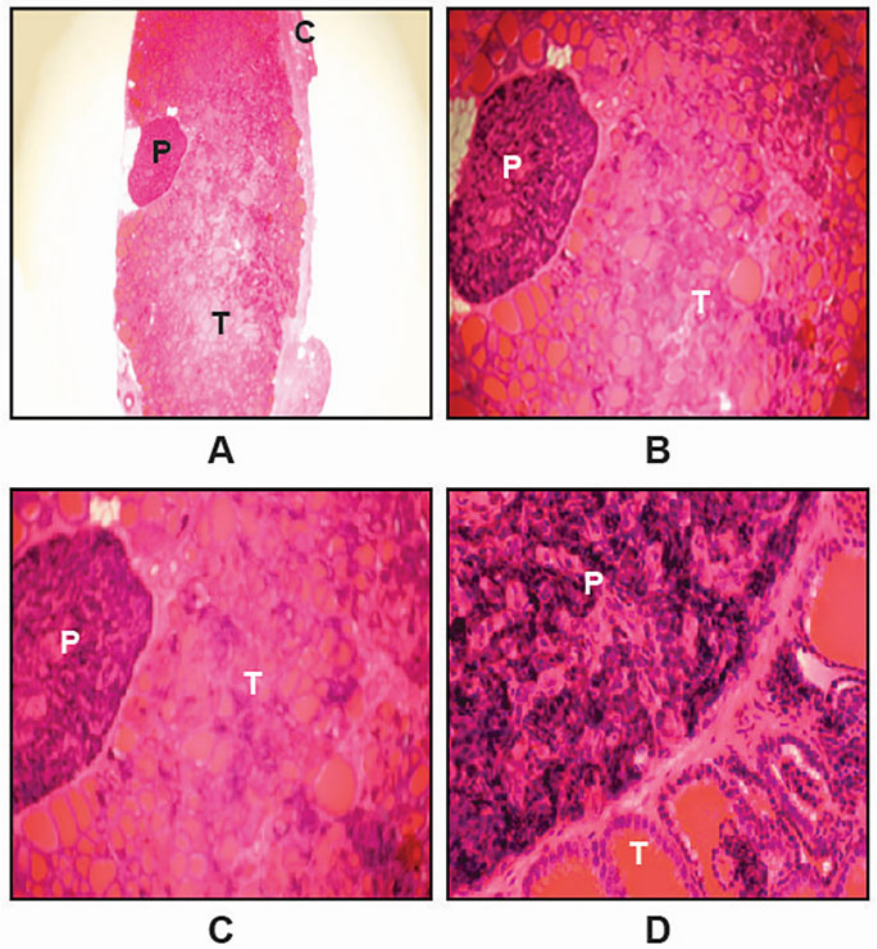

Fig. 6.1 (**a**–**d**) Various magnifications of parathyroid tissue cross-sections (P) adjacent to the thyroid (T) surrounded by a single capsule (C) in humans: (**a**) H&E ×4, (**b** and **c**) H&E ×10, (**d**). H&E magnification 400×

septa have a rich blood supply to support the secretory cells. Parathyroid tissue consists of two types of cells, each containing parathormone (PTH).

- **Chief Cells**: The parathyroid glands are composed foremostly from principal round-shaped cells that secrete parathormone, they are called chief cells. In addition to adipocytes that usually present as a half of the cells of parathyroid gland as stromal fat in the adult (Dekker et al. 1979).
- **Oxyphil Cells**: They are clusters of cells called oxyphil cells distributed throughout the gland tissue. Figures 6.3 and 6.4 show chief cells stained with hematoxylin & eosin (H&E) ×100. Chief cells appear with undefined borders, red

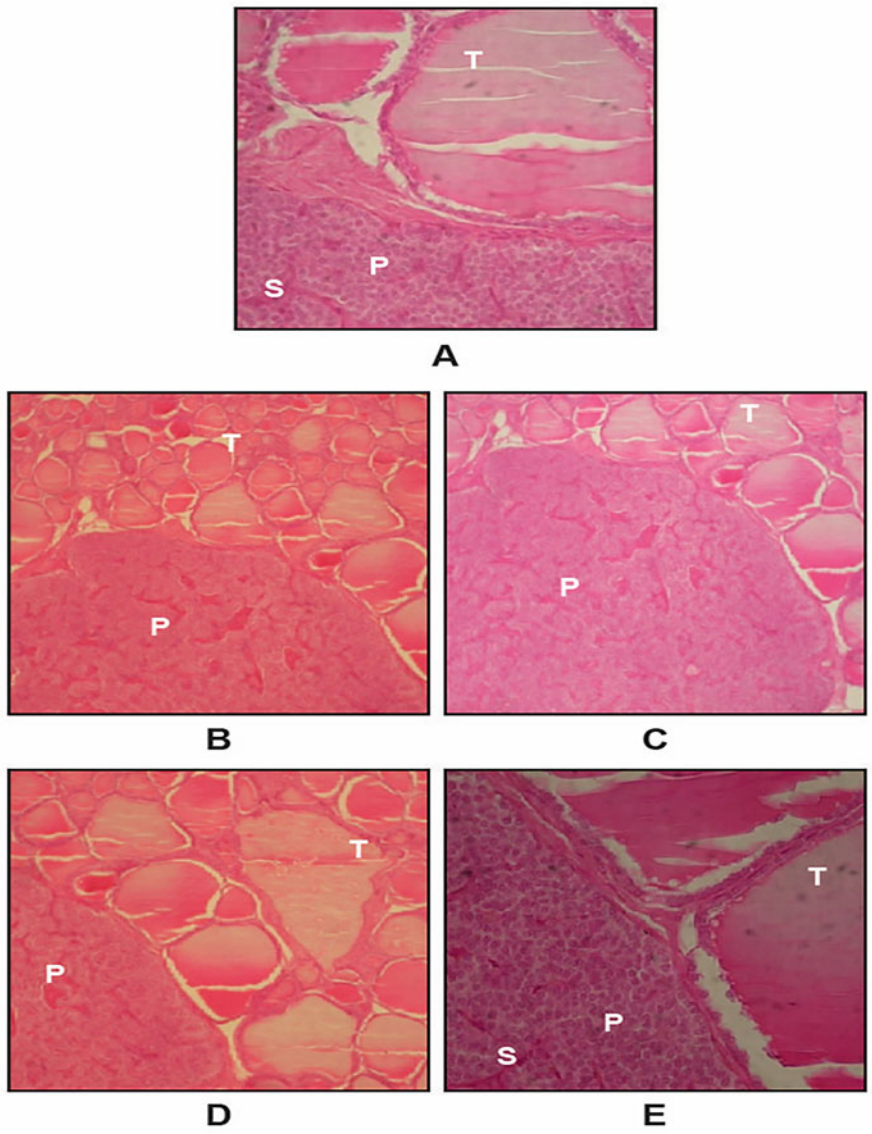

Fig. 6.2 (**a**–**e**) Parathyroid tissue cross-sections (P) adjacent to the thyroid (T) and septa (S) in mammals. (**a** and **b**) H&E ×4, (**c**) H&E ×10, (**d** and **e**). H&E magnification 400×

cytoplasm, with big rounded nucleus. Under light microscopy, oxyphil cell is larger with eosinophilic cytoplasm, small nucleus, and seen fewer repeatedly and more than chief cells (Baloch and LiVolsi 2013). At physiological calcium levels, oxyphil cells produce about 50% more PTH than chief cells. The number of oxyphil cells increases in parathyroid glands in some diseases like chronic kidney

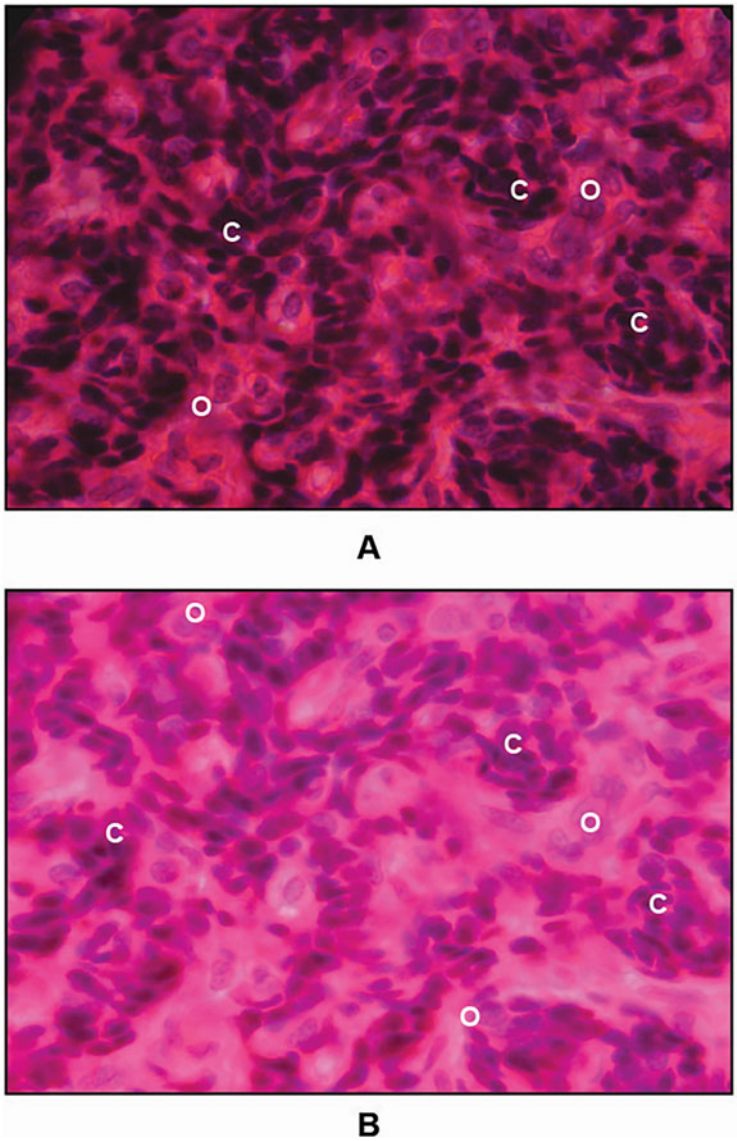

Fig. 6.3 (**a**, **b**) Cross-sections of parathyroid tissue (P) in human showing chief cells (C) and oxyphil cells (O). H&E magnification 400×

disease (Young and Heath 2000; Ritter et al. 2012; and Mini and Manju 2017). Under normal conditions, both cell types associate differentially with age, while oxyphil cells show a positive correlation in its number and diameter with age in human.

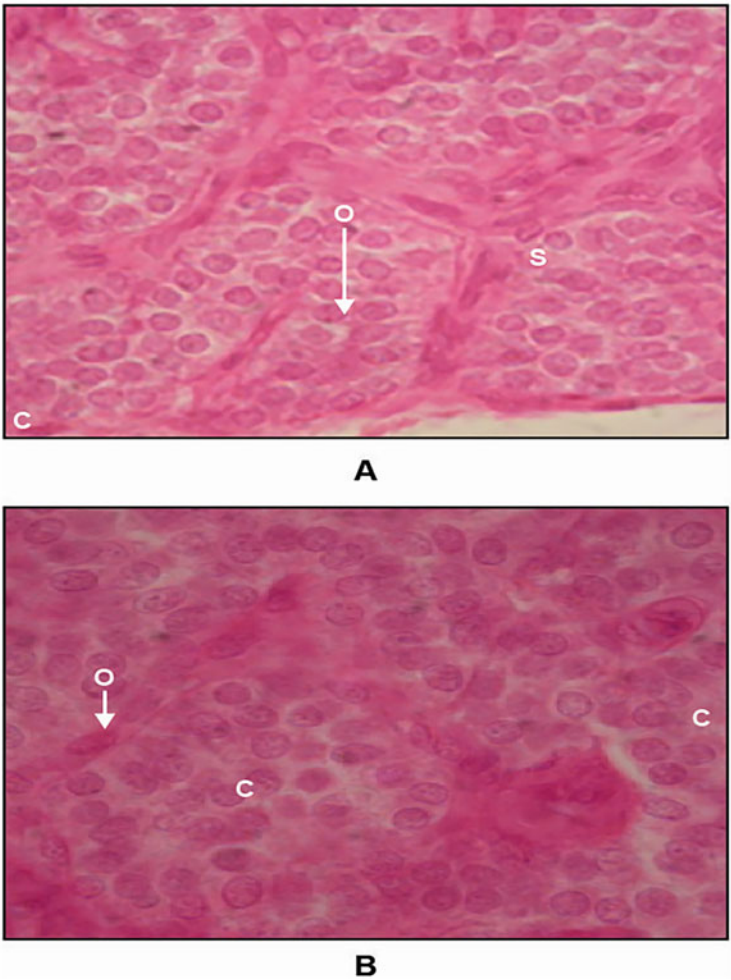

Fig. 6.4 (**a**, **b**) Cross-sections of parathyroid tissue in mammals showing the septa (S) extending from the capsule into the tissues which divides the tissue into small lobes with a rich blood supply to the chief cells (C) and the oxyphil cells (O). H&E magnification 100×

6.3 Importance and Function of Parathyroid Glands

It was previously thought that the parathyroid glands secrete a single hormone called PTH. However, research on PTH has undergone multiple phases, starting before the twentieth century. The roles of the parathyroid glands were established in 1925. Understanding the functions of PTH led to the identification of its role in calcium physiology, clarifying that hyperparathyroidism (hormone excess) leads to severe bone loss, while PTH deficiency leads to hypocalcemia; this concept continued over

the subsequent years. The structure of PTH and its key receptor (PTHrP receptor [PTHR1]) have been recognized. In 2005, Potts mentioned that experiments on purified hormonal peptide in humans led to the surprising paradoxical results that PTH could be used pharmacologically for bone formation, exhibiting a large therapeutic effect for osteoporosis. This encouraged and raised many questions on the role of PTH on calcium and bone metabolism and potential directions in therapy (Potts 2005). In the presence of active vitamin D, parathormone induces an increase in calcium levels in the blood, along with calcitonin (secreted by C cells in the thyroid gland), which lowers calcium levels in the blood. These hormones work in synchronicity to regulate the level of extracellular calcium in the blood, particularly ionized calcium and phosphorus, within a narrow physiological range and at a constant ratio of 2:1, the ratio needed for homeostasis in humans.

Also, the PTH (1–34) called teriparatide (therapeutic) is only used by injection and for short duration. PTHrP-1 is the active peptide that could improve cell proliferation and osteogenic differentiation (Wang et al. 2017).

6.4 New Ectopic Parathyroid Hormone Synthesis in Adipose Tissues

Adipose-derived stem cells in both rat model (Zhang et al. 2020) and in mice model (Cui et al. 2020) and stromal vascular fractions in mice model (Cui et al. 2020) have been successfully differentiated into parathyroid gland-like cells and improved their survival. They showed that ADSCs and SVFs get better survival of transplantation of parathyroid through supporting angiogenesis via EYA1-regulating angiogenetic factors either in in vitro or in vivo. Also, in cases with secondary hyperparathyroidism, ectopic PTH is produced by parenchymal cells of parathyroids that have been squeezed out from the glands with progenitor cells of adipocyte during cell's growth of nodular hyperplastic parenchyma and that these cells proliferate in these cases, to form colonies of PTH-producing cells in a very complicated manner with adipose cells (Kakuta et al. 2020). They showed that this finding flattens novel and promising strategy for managing hypoparathyroidism for patients with hypoparathyroidism where their parathyroids devascularized injured or parathyroidectomized.

6.5 Extracellular Calcium-Sensing Receptor (CaSR)

Of the many receptors, the extracellular calcium-sensing receptor (CaSR). Ca^{2+} is its physiological agonist. It is significantly expressed in all tissue's cells required in mineral metabolism and regulation, like the parathyroid glands, bone, kidney, intestine, breast, vasculature, and lungs. CaSR works as a chemo-sensor by incorporating signals from nutritional materials, salinity, acidification. CaSR is the key controller of extracellular Ca^{2+} levels. Understanding CaSR physiology and its signaling may help in understanding of disease states (Lopez-Fernandez et al. 2015).

Extracellular calcium is regulated carefully given how important it is for major biological processes in the body such as breathing, heart and skeletal muscle contraction, nerve synapses, blood clotting, exocytosis of hormones, absorption, and bone growth balance. *Intracellular calcium* is also sensibly regulated such that its concentration is thousands of times lower than that of extracellular calcium because of its importance in cellular function as a secondary messenger as well as for other functions. Any defect in the calcium level disrupts the gland's function; therefore, this gland is very important for life and its removal disrupts this balance within hours leading to respiratory difficulty, tetany and death if not adequately compensated. It has been shown that in therapeutic doses, it could build bone and treat osteoporosis. It was thought in the past that abnormal increases in PTH secretion cause a sharp increase in the levels of ionized calcium, leading to osteoporosis and increased urination to eliminate excess salts in the blood and resulting in thirst and dehydration. This difference may be the result of the different effects it has during abnormal increases when secreted in the body.

6.6 Calcium Distribution

Calcium is the greatest plentiful mineral in the human, whereas utmost of the calcium in the body is impounded in the skeletal system. The free calcium is the hydrated cation in solution, it is a crucial physiological mediator in the regulatory processes and metabolic functions. The free cation levels in the extracellular fluid, called *ionized calcium* (Baird 2011).

In the skeleton: Over 99% of the total ionized calcium (Ca^2) and 80% of total phosphorus in the body are stored in the skeleton. The skeleton of a person weighing 70 kg contains about 1 kg of Ca^{2+}.

In Plasma: The total calcium concentration in plasma is 8.5–10.5 mg/dl, while ionized calcium represents half the total proportion (4.4–5.2 mg/dl). The normal phosphorus concentration is 6–8 mg/100 ml of blood.

In the Cell: The normal ionized calcium concentration in the cell is 10^{-7} mol/l, while the extracellular concentration is lower, it is 10^{-3} mol/l. In other words, there is a ratio of 1: 10,000 which allows calcium to enter the cell easily. There are three forms of calcium: (1) Free form Ca^{2+} at a proportion of 50%. (2) Complex-bound calcium (calcium citrate or phosphate) in a proportion of 10%, keeping in mind that variations in complex-bound calcium impact the ionized form. (3) Calcium bound to the protein albumin, at a proportion of 40% (Bullock et al. 1991, 2001).

6.7 Regulating Hormones of Ionized Calcium's Metabolism

As mentioned, at least three hormones are necessary for regulation of non-protein bound ionized calcium: PTH, calcitonin, activated vitamin D, and other substance. They act principally on the following tissues: bones, intestinal mucosa, kidneys, and other tissues (Figs. 6.5 and 6.6). Vitamin D has a regulatory effect. All of these hormones act on both calcium and phosphate homeostasis and to maintain blood concentrations within tight limits. The pituitary gland does not play a direct regulation on cells which secrete the three hormones.

6.8 Bone Functions and Cells

The skeleton is one of the biggest systems in the body; it forms for approximately 15% of total weight. The skeleton is well known as dynamic connective tissue, vital mechanical support for architecture and movement. It protects vital organs and stores minerals (Ca, P, Mg) and collagen fibers. It acts also as amorphous matrix and hematopoietic niche. The skeleton is also responsible on continuous remodeling of its structure and constitutes during lifetime. Skeleton remodeling as mentioned above requires two distinguished phases: osteoclasts strip damaged bone and then osteoblasts subsequently replace it with new bone and osteoblasts encompass of 5% of all bone cells, which are obliged for type I collagen's formation and the precipitation of mineralized matrix to promote synthesis of bone. Moreover, osteoblasts lead to differentiated osteocytes, which are plenteous and form most of bone cells in the bone matrix. This immobilized type (osteocytes) controls bone synthesis via translation of mechanical stress into biochemical signals to enhance the remodeling process (Sugiyama et al. 2010; Crockett et al. 2011; Feng and McDonald 2011; Florencio-Silva et al. 2015; Zoch et al. 2016; Mizokami et al. 2017; Suchacki et al. 2017; Han et al. 2018).

6.9 Bone as an Endocrine and Paracrine Organ

It had been known that the skeleton system is a target of hormones such as parathormone, calcitonin, vitamin D, and steroids. But bone is not a passive tissue for that just functions under external regulation. Skeleton does not only behave as a scaffold but also act as an endocrine organ, which regulates several metabolic processes. It is vibrant that bone acts as an endocrine organ that dynamically produces regulators for systemic metabolism through the hormones (Guntur and Rosen 2012; Shao et al. 2015; Nakamura et al. 2020). Skeleton synthesizes protein hormones called osteokines released by different cells of bone. Osteoblasts produce different molecules to regulate osteoclastogenesis. Osteoblasts also release VEGFA enhancing osteoblastogenesis and angiogenesis. While the main bone cells (osteocytes) synthesize sclerostin that acts on both inhibition of osteoblast differentiation and stimulation of osteoclast differentiation. In turn, osteoclasts form some

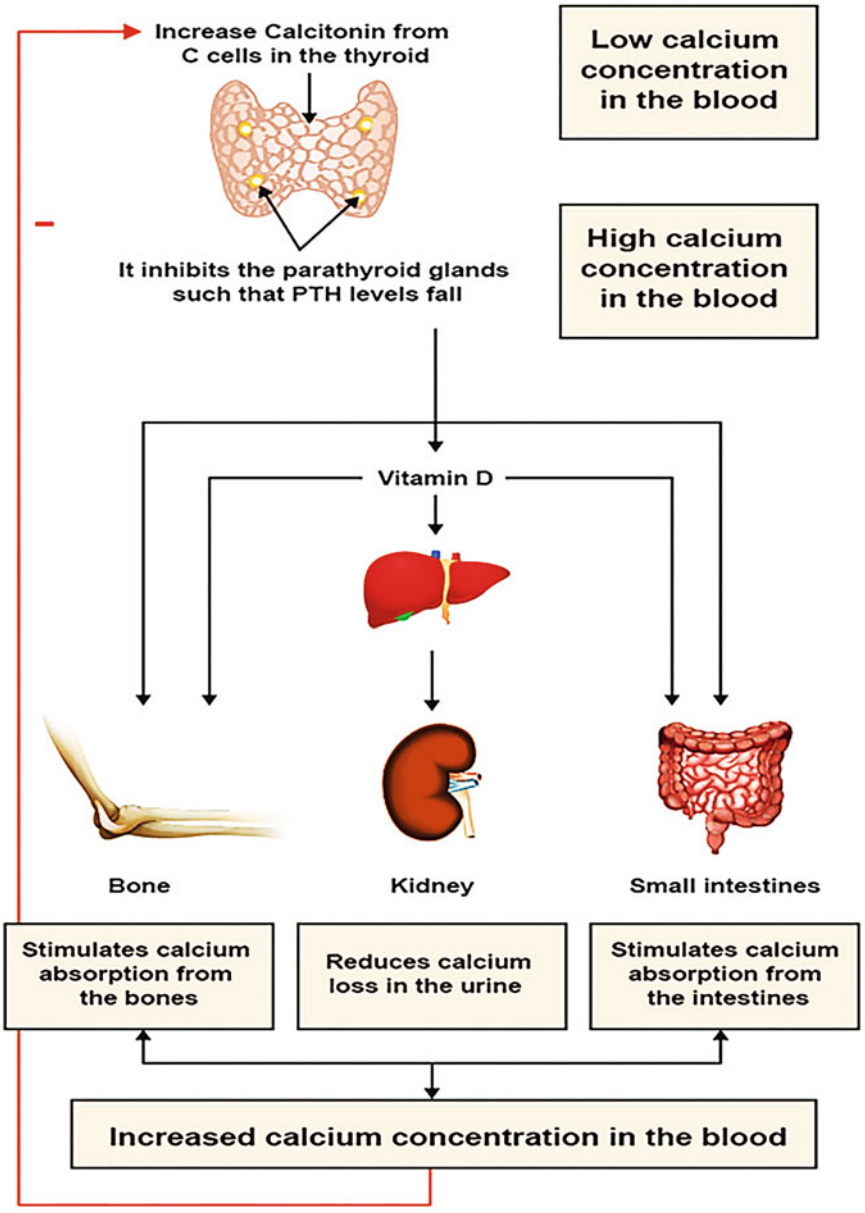

Fig. 6.5 Mechanism of regulation of calcium levels in the blood

osteokines that influence Osteoblasts and osteocytes, herewith influence osteogenesis. Osteoblastogenesis is also promoted by osteoclast precursors that form the angiogenic factor to form type H vessels. The skeleton hormones can act as

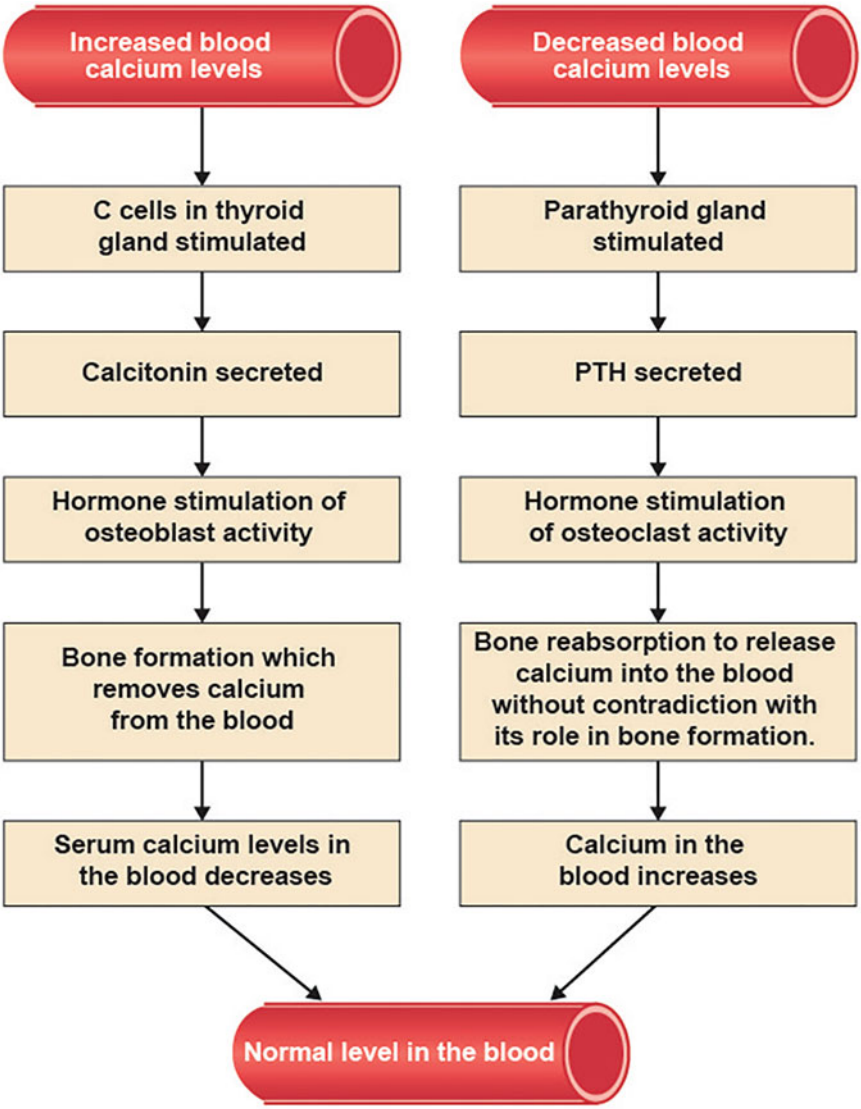

Fig. 6.6 Effect of increase and decrease in blood calcium levels on the secretion of PTH and calcitonin

endocrine, paracrine, and autocrine signals to perform its functions. In addition to osteokines that act as endocrine signals, also, secretion of osteocytes, osteoblasts, and osteoclasts acts as paracrine. These secretions uncovered the connections between the bone and other organs which became promising in management of related diseases (Han et al. 2018). These regulators such as Osteoprotegerin and Dickopf (Shao et al. 2015) and the regulator Sclerostin (Shao et al. 2015; Fayed et al.

2020) have important roles in bone formation, modeling, remodeling, and homeostasis. Bone can also secret hormones, such as osteocalcin, which promotes proliferation of β cells, insulin secretion, and insulin sensitivity (Shao et al. 2015; Nakamura et al. 2020). More details are below on bone hormones.

6.9.1 Osteocalcin

It is a vitamin K-dependent-protein and bone-derived hormone plays crucial roles in energy expenditure (Al-Suhaimi and Al-Jafary 2020) and affects metabolism (Karsenty 2014; Shao et al. 2015; Moser and van der Eerden 2019; Nakamura et al. 2020). It regulates blood glucose, energy metabolism, reproduction, as well as awareness (Han et al. 2018). But Manolagas (2020) reported that osteocalcin promotes bone mineralization, but it is not a hormone. Osteocalcin is a particular product by osteoblasts in bone, it is stimulated by the deficiency of the factors linked to progress of osteoporosis. But it was well acknowledged as the one hormone produced by the osteoblasts as above references indicated.

Functions of Osteocalcin

- Osteocalcin has many actions on glucose, energy metabolism, gonads endocrine, and reproduction in male (Ajit and Munoz 2004; Shao et al. 2015).
- There is a strong relationship between blood vitamin k and dependent-osteocalcin levels with risks of type 2 diabetes and obesity. Osteocalcin improves insulin resistance, lipid and glucose levels, and arbitrate vitamin K helpful effects. Insulin and CNS influence osteocalcin, then it regulates mineralization of the bone (Al-Suhaimi and Al-Jafary 2020). By this role, osteocalcin integrates with PTH and calcitonin on the bone.
- As osteocalcin is vitamin K-dependent-protein, therefore, regular carboxylation of vitamin K-dependent hormone is an important process for inhibiting apoptosis and calcification process in vascular endothelial cells (Al-Suhaimi and Al-Jafary 2020).
- While undercarboxylated osteocalcin acts as a biomarker of glucose instabilities and cardiovascular threat. Inclusion of undercarboxylated osteocalcin with the usual type 2 diabetes risk factors gives rise to better performance profile. Therefore, the measurement of blood undercarboxylated osteocalcin may be beneficial tool to recognize the level of type 2 diabetes and cardiovascular risks in particular patients (Riquelme-Gallego et al. 2020).
- The reduction in osteocalcin production bone is dependable on the fall in mental function accompanying with aging. Additionally, exercise involvement for healthy old age is known to be effective for preventing of dementia. The improvement of bone health with aging could provide valuable effects on cognition (Nakamura et al. 2020).

6.9.2 Sclerostin

Sclerostin is a glycoprotein, soluble antagonist of Wnt/β-catenin signaling released by osteocytes. It acts via reducing the canonical Wnt route required for osteoblastic action leading to reduce bone formation (Fayed et al. 2020). The pathway of Wnt/β-catenin mechanism plays key biological function for osteoblast. Sclerostin acts as a local paracrine regulator for bone metabolism instead of an endocrine hormone. However, human blood concentration of sclerostin frequently reveals alterations in the bone's microenvironment, as a response to hormonal signals through many of either physiological or pathophysiological status. Intermittently or continuously administration of PTH reduces sclerostin concentration. Also, estrogen has a suppressive effect on sclerostin concentration. Mechanosensory effort leads to consistently rise in sclerostin levels with skeletal unloading. On the contrary, sclerostin decreases with promotion of skeletal loading. Sclerostin is synthesized by osteocytes and prevents bone formation, as it acts as local/paracrine hormone for bone metabolism rather than being endocrine hormone (Drake and Khosla 2017).

6.9.3 Lipocalin

Lipocalin-2 is produced by osteoblasts (Han et al. 2018) and it is also an adipokines produced by adipose tissue (Recinella et al. 2020). Tt affects energy metabolism through inhibition of appetite center in the brain (Han et al. 2018). Lipocalin-2 is known as neutrophil gelatinase-associated lipocalin (NGAL) and acts as a regulator of bone homeostasis. Upregulation of lipocalin-2 experimentally diminishes osteoblast differentiation and enhances the NF-kB pathway for osteoclastogenesis. High serum concentration of lipocalin-2 is associated with increased exposure to fracture risk in elderly women. In patients with primary hyperparathyroidism (PHPT), lipocalin-2 helps in prediction of bone recovery and mineral density after parathyroidectomy in PHPT (Hong et al. 2021). In cirrhosis, urinary neutrophil gelatinase-associated lipocalin (u-NGAL) detects the exact type of acute kidney injuries, it also improves mortality's prognosis. Thence it is a potential plan for acute kidney injuries in cirrhosis (Allegretti et al. 2021). In early stage of COVID-19, determination of u-NGAL among other assessment is deserved to be incorporated with other measurements to help in identifying patients with a bad prediction (He et al. 2021). In healthy individuals but not in postmenopausal osteoporotic women, Lipocalin 2 serum concentrations connect with biomarkers of bone turnover and age. Serum lipocalin 2 is not higher in osteoporotic or osteoarthritic patients, but it correlates with age and other assays in healthy individuals (Maurizi et al. 2021).

6.10 Functions of Parathormone (PTH) and PTHrP-1

A polypeptide hormone consists of 84 amino acids secreted by the chief cells. Additionally, the oxyphil cells of the parathyroid glands contain parathormone (Figs. 6.3 and 6.4). PTH (1–34) is a part of the PTH molecule and consists of a 34-amino acid peptide from the 1–34 region of the PTH molecule. It has multiple names such as teriparatide and parathyroid hormone-related protein (PTHrP-1) and multiple fragments such as rhPTH (1–34) (Zhang et al. 2012a) and bPTH(1–34) and hPTH(28–48) (Klaus et al. 1994). PTHrP-1 performs most of the physiological functions of PTH, particularly the osteogenic ability after injection (Wang et al. 2017). PTH is a hypercalcemic hormone in the body as a result of its effect on the bones, intestinal mucosa, and kidneys. There is a negative feedback relationship in the serum between ionized calcium and PTH (linear then sigmoidal relationship). This is responsible for the regulation and stability of the hormone and calcium levels; in other words, there is an inverse relationship between Ca^{2+} concentration in the plasma and the secretion of PTH. When there is an increase in extracellular calcium levels, its receptors in the parathyroid cells are triggered and decrease PTH secretion. When Ca^{2+} levels decrease, PTH secretion increases (Bullock et al. 1991, 2001; Burkitt et al. 1996; Guyton 1986; Guyton and Hall 2006, 2016; Morley et al. 2001). PTH and PTHrP-1 and their derivatives have in the bones, intestines, kidney tissue, placenta, and breasts.

6.10.1 Bone Cells and Formation: Balance, Remodeling, and Repair

To achieve physiological remodeling of skeleton, the balance between bone formation and bone resorption involves direct signals between different bone cells, hormones, and growth factors. Bone tissue contains three types of bone cells they are: *(1)* ***Osteocyte*** *is* a bone-forming cell that has become entrapped within the bone matrix. *(2)* ***Osteoblasts*** *is* a bone-building cells. In the bone marrow, osteoblasts are differentiated from mesenchymal stem cells stroma to be committed for producing bone matrix and its mineralization. *(3)* ***Osteoclasts*** is a bone-reabsorbing cells which reabsorb bone. Osteoclasts are multinucleated and giant cells produced from the incorporation of mononuclear cells; macrophage, monocytes, or monocyte progenitor cells in order to accomplish the procedure of osteoclastogenesis. Imaging of live cells has showed a grand standard of heterogeneity in osteoclast multinucleation because of the different models of the differentiations, mobility of the fusion precursors, in addition to the style of fusion in comparison with variable nuclei's numbers. Osteoclasts with their precursor cells are arrayed in specific cellular groups known as bone multicellular units. These unites are to support natural balance of physiological remodeling of skeleton (Courpron et al. 1975; Anderson 2000; Siddiqui and Partridge 2016; Takito and Nakamura 2020).

The multiple activities of the osteocytes and other bone cells are regulated by hormonal concentrations like (PTH, calcitonin, Vitamin D) and factors like

movement, mechanical stresses on the bone, and the levels of calcium and phosphorus in the circulation. Osteocytes functions under regulating hormones as the following:

- In bone marrow, parathormone-related peptide (PTHrP) stimulates differentiation of osteoclasts by enhancing osteoclast's progenitors via the PTH/PTHrP receptor (Nakashima et al. 2003). PTH also has an effect on osteoclast fusion (Li et al. 2018). Multinucleation process of osteoclast is critical to like these environmental signals which boost the reorganization of cytoskeleton's actin. Additionally, osteoclast multinucleation that is achieved with macrophage fusion led to production of multinucleated giant macrophages (Takito and Nakamura 2020).
- **Strength and Health of the Bone's Matrix**: Osteocyte is the most abundant bone cell type as it comprises about 95% of bone' cells in adults. It is a mature osteoblast and trapped individually in bone matrix it produced, osteocyte continues to form bone to a level which is necessary for maintaining the strength and health of the bone's matrix. So, it has the longest life (decades) among bone cells. In fact, osteocyte has physiological functions for extend away from the maintenance only. Although every osteocyte is physically separated within the matrix, it has a good communicated network with osteocytes, osteoblasts, osteoclasts, and also distant cells, tissues, and organs through its dendrites which extend into its canaliculi that infiltrate the surrounding bone maintaining direct communication with its neighbors (Chen et al. 2015). The role of matrix-embedded osteocytes in regulating bone homeostasis has gained attention. Proteins such as sclerostin (a Wnt inhibitor) inhibit osteogenesis. Receptor activator of nuclear factor-kappa B ligand (RANKL) is a cytokine secreted by the osteocyte and involved for osteoclast formation. A systematic balancing action of antibodies between the proteins (sclerostin and RANKL) is used for osteoporosis therapeutic purpose. Also, osteocytes regulate the hematopoiesis, hematopoietic stem, and progenitor cells (HSPC) physiological function (Pajevic and Krause 2019). These activities are regulated by parathyroid hormone (PTH) receptor 1 (PTHR1). Targeted downregulation of PTHR1 inhibited osteocyte remodeling and upregulation of osteoclast expression. This process could be recovered by restoration of PTHrP, indicating the key role of PTHrP signaling via the osteocyte PTHR1 which in turn induces RANKL production (Xiong et al. 2011). In case of fracture healing, hypoparathyroidism influences osteoclast function through decreasing expression of RANKL in osteoblasts (Sun et al. 2020).
- **Influence on Bone Remodeling**: The human skeleton in adult is a multifunctional system that undergoes regular remodeling via the countering activities of the bone-resorbing osteoclasts and the bone-forming osteoblasts. The balance between these two processes is responsible for skeleton homeostasis in healthy adults. Such balance may disrupt in diabetes as glucose metabolism is uncontrolled, leading to increased bone osteoporotic fractures. This sheds the light on metabolic key functions of glucose metabolism during osteoclast and osteoblast differentiation (Karner and Long 2018). Bone remodeling is a process regulated

by the interaction between bone cells and several hormones and molecules like PTH. The hormone promotes higher level of bone resorption when administered in lower dose. PTH receptors present in osteoblasts to regulate directly its lineage differentiation and function and indirectly osteoclastogenesis. Furthermore, receptors' functional presence confirmed in osteocytes to participate in the co-ordination of bone remodeling. The mechanism may be explained by PTH regulation. Under PTH control for bone cells, osteocytes undergo to a negative feedback mechanism and activity's self-regulation by releasing substances through its dendrites to activate or inhibit osteoclasts and osteoblasts to manage the remodeling of the bone (Ginani et al. 2017; Yavropoulou et al. 2017).

- **PTH effect on Sclerostin**: As discussed, it released by osteocytes, the primary source of sclerostin. It regulates bone metabolism as it acts as a bone formation's inhibitor. Osteocytes combine bone's response to mechanical and hormonal stimulant, increased level of sclerostin inhibits osteoblast and stimulates osteoclast activities which decrease the formation of new bone. While downregulation of sclerostin stimulates osteoblast activity (bone anabolism), hence allows the formation of additional bone in bone areas subjected to load or mechanical stress. Conversely, PTH-induced bone formation does not require downregulation of sclerostin—as shown earlier—to be required for bone gain induced by mechanical loading (Delgado-Calle et al. 2017). Estrogen has a suppressive effect on sclerostin circulating levels (Drake and Khosla 2017).
- Osteocyte under PTH regulation secretes special **growth factors** that stimulate osteoblast activity in the injured area. Osteocyte senses and detects the daily wear-and-tear that occurs in a healthy skeleton, releases the required substances, and communicates with osteoblasts and osteoclasts leading to continuous bone repairs, as the unaddressed "microdamage" would result in fractured bones which carry the body weight (Chen et al. 2015).
- **Regulation of Mineral Balance**: Parathyroid hormone receptors are found in different bone cells and play a key role in the maintenance of skeletal bones integrity, bone homeostasis, and mineral regulation particularly calcium and phosphate metabolism. Bone osteocytes release chemical messengers, which enter the circulation to regulate the excretion of excess minerals through kidneys. In case of calcium demand like the cases of lactation or calcium deficiency meals, osteocytes sense the decreased calcium blood concentration and reabsorb calcium from bone from the inner walls of their lacunae, this in turn releases more calcium into the circulation (Chen et al. 2015; Yavropoulou et al. 2017).

6.10.2 Effect of PTH and rhPTH at Aging

Serum PTH increases with age, which may contribute to bone disturbance in postmenopausal that is related to reduction in functions such as kidney function, calcium absorption, and serum [25(OH)D] (Need et al. 2004). Although, at aging, osteocytes' activity decreases with age, lifespan shortens, loses ability to sense microdamage, then reduces capacity to manage the proper repair responses (Chen

et al. 2015). But injection of intermittently of rhPTH (1–34) reveals an osteoanabolic effect described with direct functions on bone growth, rises skeletal density, and decreases fracture threat. Clinically, for postmenopausal women suffer from osteoporosis, rhPTH (1–34) influences positively on bone construction than elcatonin. rhPTH (1–34) was safe with well tolerance (Kroll 2000).

6.10.3 Paradoxical and a Glance on Therapeutic Functions of PTH

- PTHrP is an exclusive multifunctional protein that has many biological domains and isoforms came from its posttranslation, so it has variable effects on tumor cell behavior. In its early phases of tumor, PTHrP prevents its growth. While in advanced tumor, PTHrP behaves in the inverse model and supports tumor development and metastasis particularly in the bone, as a usual organ for metastasis, in which PTHrP's effect on osteolysis is important for tumor growth. Additionally, there is main role for PTHrP to change tumor's state from a dormant state to emergence tumor. PTHrP has a unique biological effects and domains that drive its different signals: endocrine, paracrine, autocrine, and intracrine which could be a promising strategy for developing antitumor therapeutics (Edwards and Johnson 2021).
- Although it is well-known that PTH acts in unison with calcitriol to increase the absorption of Ca^{2+} and phosphate from the bones, which increases their levels in the blood, and stimulation of its activity leads to an increase in osteoclasts activity, but PTH could be used pharmacologically for bone formation exhibiting a large therapeutic effect on osteoporosis. These different/paradoxical functions may be attributed to different physiological PTH concentrations, secretion pattern, pharmaceutical doses, use, and administration. PTH paradoxically leads to net loss of bone through resorption when given in a continuous model, while net formation of bone forms through deposition when given intermittently according to the differential actions of PTH on the bone osteoblastic and osteoclastic cells clusters.
- Both precursors of preosteoblastic and preosteoblasts possess receptors for PTH. The hormone stimulates differentiation of the precursors to preosteoblasts which in turn form the osteoblasts. The osteoblasts release cytokines (interleukins) like IL-6 which stimulates the differentiation of preosteoclasts into osteoclasts.
- Intermittent PTH administration has effects on bone formation and fracture prevention. Bone marrow adipocytes show a unique responsiveness to PTH in addition to osteogenic and adipogenic properties. This led to an important mechanism for the therapeutic effects of PTH through its ability to direct the fate of mesenchymal cells (Fan et al. 2017). Interrupted PTH 1–34 administration enhances osteogenesis, bone marrow and circulating mesenchymal stem cell (MSC) density postmenopausal osteoporosis in women and stimulates in vitro osteogenic differentiation (Tang et al. 2019).
- Sclerostin levels are inhibited by parathyroid hormone either intermittently or continuously, also by mechanical loading and cytokines.

- While calcitonin hormone increases sclerostin and its expression in osteocytes (Gooi et al. 2010).
- Teriparatide recombinant human PTH [rhPTH (1–34)] is recommended as an effective therapy for osteonecrosis of the femoral head induced by glucocorticoids. PTH enhances self-activation of autophagy mechanism to protect osteocytes survival from apoptosis and damage induced by dexamethasone (Zhu et al. 2017).
- There is a potential therapeutic effect of combined pharmacological PTHrP and mechanical stimulant to promote bone mass, maintenance, and restore skeletal deterioration induced in diabetic patients (Maycas et al. 2017).
- Although PTH is traditionally known to be a skeletal catabolic hormone. But when provided in humans and animals intermittently at lower dosages PTH effectively activates the growth of trabecular and cortical bone. The natural hPTH-(1–84) and its osteogenic fragment (hPTH-(1–34)) had been already applied as advanced clinical trials phases. The new PTH osteogenic- effect analogues are promising for curing osteoporosis as they have similar effect of hPTH-(1–84) and hPTH-(1–34), with less effect on inducing hypercalcemia, the main issue side effect of PTH treatment. In addition to treating osteoporosis, PTHs also may support fracture curative, after treating with extreme glucocorticoid, rebuild bone losing in powerless patients, or following long air flight, and as psoriasis therapy (Morley et al. 2001). Interrupted PTH 1–34 administration enhances osteogenesis, bone marrow, and circulating mesenchymal stem cell (MSC) density postmenopausal osteoporosis in women and stimulates in vitro osteogenic differentiation (Tang et al. 2019).

6.10.4 PTH Functions on Intestines

- The absorption of calcium and phosphorus from the intestines is affected by parathyroid activity. Hypoparathyroidism is accompanied by reduced absorption, while hyperparathyroidism is accompanied by increased calcium absorption.
- PTH also acts indirectly and increases Ca^{2+} absorption from the intestines results from the vitamin D metabolite called Calcitriol $1.25(OH)_2D$. PTH converts vitamin D in the kidneys from its inactive form to its active form to absorb calcium and to a lesser extent, phosphate from the intestines. Parathyroid hormones disturbances may lead to distinct effects on the gut such as steatorrhea in hypoparathyroidism, and constipation, peptic ulcer, and pancreatitis in hyperparathyroidism (Ebert 2010).

6.10.5 PTH Effects on Kidney

- While calcium is basically reabsorbed along with sodium from nephron proximal convoluted tubule, **PTH acts directly and noticeably** to increase calcium reabsorption via distal convoluted tubule.

- PTH inhibits the absorption of phosphate-sodium from proximal convoluted tubule which means that the excretion of phosphate, sodium, potassium, and HCO^{3-} in the urine is increased.
- Increased PTH secretion stimulates the enzyme 1-α hydroxylase which, as mentioned before, converts vitamin D in the kidneys into its active form. This boosts parathormone activity in the intestines to absorb calcium from food (Bullock et al. 1991).

6.10.6 PTH Effects on Placenta

There is a special physiological regulation of normal placental calcium metabolism in infants through gene targeting model, which helps in developing novel therapy for osteoporosis and related bone diseases (Kovacs 2000). In pregnancy, calcium and phosphorus in embryonic circulation are maintained to a high concentration to provide a chance to growing skeletal system to fuse sufficient amount of required minerals content through its actively transportation by placenta. In maternal period, calcitriol's partial regulation happens to elevate calcium absorption from intestine to meet calcium needs in fetal, while mineral regulation is mainly conditional on PTH and PTHrP regulation, which their production is—in turn—regulated by CaSR. If there is insufficient in calcium delivery by placenta or any other reason, the maternal bones will suffer resorption by PTHrP (Salles 2016).

6.10.7 Hematopoietic, Repairing, and Proliferation Prompting Effect of PTH

Both amino-terminal and mid-regional fragments of PTH increase synthesis of DNA, proliferation, and colonization in chondrocyte cultures via cAMP analogs in a calcium-dependent manner. Both fragments bPTH(1–34) and hPTH(28–48) upregulate expression of vitamin D ((1,25-(OH)2D3) receptors but it is not cAMP-dependent manner, while in a PKC-dependent way that requires transcription and translation steps. Both PTH fragments influence—in similar way—the proliferation of chondrocyte and the upregulation expression of vitamin D receptors, but each fragment differently stimulates cAMP production (Klaus et al. 1994). Also, hPTH has a positive effect on stem cell proliferation. hPTH influences hematopoietic progenitor cells in specific mice and mesenchymal stem cells. Also, there is a synergistic action of hPTH and mesenchymal stem cells on a proportion of hematopoietic progenitor cells in a xenotransplantation model (Lim et al. 2013). PTH treatment activates the notch pathway as well as save hematopoietic disorder in Bmi1-null mice, also. Hematopoietic disorder is not only because of decreased self-renewal of hematopoietic stem cells but also a result of weakened microenvironment of bone marrow (Lu et al. 2014). PTH is also effective in modulating and expanding the stem cell niche's activity and bone marrow-derived stem cell as long as hematopoietic stem cells are able of both self-renewal and differentiation. PTHs

intermittent administration enhances bone formation in mice and human. So, PTH administration was approved for treating osteoporosis. Since PTH is known to stimulate migration of the bone marrow stem/progenitor cells into blood stream. PTH can enhance the migration of long-term repopulating hematopoietic stem cells (LT-HSCs) (Huber et al. 2014; Even et al. 2021).

The novel concept that PTH mobilizes endogenous stem cells/progenitor cells from the bone marrow helps in discovering recovering functions of PTH. Pos ischemic stroke, PTH is feasible regenerative therapy. In ischemic stroke in adult mice, it was proven that PTH therapy indicatively boosts many functions in the brain such as the expression of trophic and regenerative factors in the brain and raises the newly formed neurons in the peri-infarct cortex, increases angiogenesis since Glut-1 and BrdU vessels, have been remarkably grown, and improved migration of neuroblast from the subventricular zone. Also, PTH-treated mice group displayed significant improvement in sensorimotor functional recovery in comparison with untreated ischemic stroke mice group (Wang et al. 2014a). Therefore, PTH offers novel therapeutic plans in bone marrow, ischemia, stroke, hematological disorders, and stem cell harvest and transplantation.

6.10.8 PTHs Effect on Breast and Lactation

CaSR which is expressed in those organs and tissues is also expressed in breast epithelial cells and stimulates a nuclear signal of PTHrP action which activates cells proliferation and inhibits their death and helps cancer cells adapt to higher extracellular calcium levels. Studying of CaSR may provide findings on physiology of lactation, progression of breast cancer, and osteolytic bone metastases (Kim and Wysolmerski 2016). Serum PTH is an important parameter, in addition to bone-resorbing serum markers that alter after delivery partum, as their level is significantly higher in mothers' group who were breastfeeding their infants in comparison to group who were non-breast-feeding or mixing both of formula and breastfeeding. Increased resorption of bone happens in the breastfeeding mother's group only. Bone metabolism considerably alters throughout the duration from gestation and post-delivery lactation. Lower density of minerals in skeletal may be observed in small cases of breastfeeding only (Miyamoto et al. 2019). Physiological bone resorption in reproduction period is usually not long term-effect and does not lead to insistent osteoporosis or fracture (Salles 2016).

6.10.9 PTH Effect on Heart

PTH can recover heart function in rats with adriamycin–induced cardiomyopathy (ADR-CM) proposing a potential therapeutic management for PTH in non-ischemic CM (Wu et al. 2018).

The end result of the effect of PTH on the bones, intestines, kidneys, and breasts is to maintain the calcium level in the plasma at 10–14 mg/100 ml and the phosphate

level in the plasma at 6–8 mg/100 ml which in turn leads to balancing in bone metabolism.

6.11 Calcitonin and Calcitonin Gene-Related Peptide

A polypeptide is comprised of 32 amino acids. It is secreted by the parafollicular cells which are neuroendocrine cells called C cells. They constitute 1% of the thyroid gland (Fig. 6.5). Thyroid C (parafollicular) cells affiliate to the APUD of neuroendocrine cells. The main function is to activate thyroid cells, although it has an osteogenic effect on bone, but it is not its main function as was earlier believed. It inhibits the osteoclasts which intervene in bone reabsorption; in other words, it is a hypocalcemia hormone in the blood. Its biological effect takes place on the bone, intestinal mucosa, and kidneys whose cells carry calcitonin receptors. The hormone regulates ionized calcium Ca^{2+} levels according to a linear positive feedback mechanism: when Ca^{2+} increases in the plasma or outside the cells, the C cells are induced and release more calcitonin, whereas calcitonin secretion stops when calcium levels are low (Bullock et al. 1991, 2001; Pondel 2000).

Calcitonin Gene-Related Peptide (CGRP) CGRP is a neurotransmitter that consists of 37-amino acid, released centrally and peripherally. It is a member of the calcitonin peptide family but should be differentiated from calcitonin. There are two main forms α and β CGRP. It affiliates to a family of peptides that wholly acts on infrequent receptors family, as CGRP is mainly produced from sensory cranial nerves; therefore, it is involved in pains routes (Russell et al. 2014). Trigeminal neuralgia (TN), the fifth cranial nerve, which is responsible for face sensibility and motive functions; TN is one of the most popular neuropath pains. CGRP is a one of nociceptive neurotransmitters that its nociceptors—work to feel any pain—are expressed in the trigeminal ganglions, it has a key role in transferring pain. Inhibiting the expression of CGRP and its nociceptors can treat the pain in trigeminal ganglion (He et al. 2020).

6.11.1 Functions of Calcitonin and Calcitonin Gene-Related Peptide

- **Effects on Thyroid Gland Follicles**: Although there is a lot of evidences that calcitonin plays a key role in increasing bone formation and reducing fracture risk, the presence of parafollicular cells (calcitonin-secreting cells) in the thyroid follicles led to the reevaluation of the main function and therapeutic use of calcitonin. C cells are paracrine cells that regulate the function of follicular cells in the thyroid gland (Irmak and Kirici 2004). C cells regulate the growth rate in newborns via changes in thyroid hormone concentrations in the early postnatal period. C cells promote the physiological functions of thyroid glands and play a role in their adaptation to various environmental factors, thus improving its

performance and provide the difference of thyroid functions in variable populations.

- **Effect of CGRP on Respiratory System**: CGRP is known in COVID-19 infected patients, there is lower concentrations of CGRP that weaken physiological functions of the respiratory system as a result of vasoconstriction, inappropriate angiogenesis, weakness in repairment of epithelium, and improper immune reaction. This indicates that recovering circulating CGRP concentrations in these patients may lead to a novel management for COVID-19's therapy (Ochoa-Callejero et al. 2021).
- **Effect on Male Reproduction**: Beyond its classic role in bone, calcitonin has physiological functions on embryonic/fetal development and sperm (Pondel 2000). Calcitonin affects Leydig's cell line and rat Leydig's cell cultures (Nakhla et al. 1989). The inguinoscrotal stage during 25–35 week of fetal age needs the immigration of the gubernaculum from the groin of thigh to the scrotum; the process is regulated by the genitofemoral nerve that produces calcitonin gene-related peptide regulating by the androgen (Hutson and Hasthorpe 2005). A bloc of 20 neurons differentiate throughout metamorphosis to innervate the sperm ducts and male reproductive accessory glands. These neurons express four precursors of neuropeptide one of them is calcitonin-like diuretic hormone (CDH) and allatotropin, in addition to, allatostatin C, allatotropin-like peptides and myoinhibitory peptide (MIP). Spontaneous contraction of the seminal vesicle and accessory glands could be stimulated in a dose-dependent effect by CDH and allatotropin, while allatostatin C and MIP provoked dose-dependent inhibitory effect. Receptors of these neuropeptides are expression in organs innervated with that bloc of neurons. Furthermore, these neuropeptides have a regulating role in movements of the semen during copulation (Čižmár et al. 2019).
- **Effect on Female Reproduction**: Calcitonin gene-related peptide is present in nerves innervating ovaries in the rat (Calka et al. 1988). This function has been utilized in a calcitonin-dependent cAMP assay as there is an endogenous action for calcitonin receptors in the ovary cells of Chinese hamster. Calcitonin stimulates G (s)-coupled GPCR receptors which causes stimulation of adenylyl cyclase and elevates cAMP in the ovary cells (Wang et al. 2011). There is a debate about contributing CGRP in some pathophysiological cases such as polycystic ovary syndrome (PCOS). While Fenkci et al. (2013) reported on abdominally obese PCOS women that serum concentration of CGRP was not correlated with insulin resistance, lipid disorders, and ovarian hyperandrogenism which reveals that CGRP is not having an essential function in PCOS pathogenesis. But other researchers' groups concluded the opposite, they reported that in women with PCOS, the plasma CGRP level is significantly higher than normal females. In PCOS, there is a robust positive correlation between the plasma level of CGRP with gonadotropins (LH/FSH) ratio and plasma level of testosterone, in addition to the same correlation with some hormonal and metabolic parameters such as insulin resistance, insulin, and glucose. Exogenous CGRP increases the release of testosterone and estradiol from the human granulosa cells as CGRP receptors are expressed in these cells (Zhang et al. 2012a, b). Additionally, in

PCOS women, PTH and calcitonin hormones are troubled among many hormones include cortisol GnRH, insulin, LH/FSH, estrogens, androgens, and growth hormones (Krishnan and Muthusami 2017).

- **Bone Formation:** Calcitonin inhibits calcium withdrawal from the bones and reduces the lytic effect of osteoclasts through its receptors in the bone. After calcitonin binds to the receptor, the shape of the cell's changes, and they quickly contract and their effect on the bones starts to diminish within minutes, leading to inhibition of calcium reabsorption from the bone. This could not be its main function as bone could be built in calcitonin-deficient mice. Furthermore, CGRP is a key neurotransmitter that acts as a paracrine signal to support osteogenesis in mature osteoblasts. Zhang et al. (2017) found many mineral nodules and high concentration of Ca^{2+} in CGRP treated groups than the control group, CGRP supports the proliferation and osteogenic differentiation and osteogenesis process in rat bone mesenchymal stem cells. In addition to its bone promoting effect, Malfait and Miller (2016) found that CGRP receptors/pathways and other mediators like bradykinin are promising therapeutic strategies for the management of osteoarthritis.
  Conversely, calcitonin gene-related peptide activates some processes such as proliferation as well as osteogenic differentiation of osteoporotic rat-derived bone mesenchymal stem cells (Liang et al. 2015).
- **Intestinal Mucosa**: In the gastrointestinal tract, CGRP with other substances and peptides participates in regulating neuro-immune function through transient receptor potential ion channels and sensory neuropeptides (Lai et al. 2017). Unlike PTH, calcitonin inhibits the absorption of calcium and phosphate from the intestines. Calcitonin inhibits intestinal digestion and reduces the secretion of gastrin from the stomach but stimulates intestinal secretion.
- **Kidney**: Calcitonin has receptors in the proximal convoluted tubule and therefore calcitonin inhibits the reabsorption of phosphate which increases its excretion with calcium and sodium in the urine (Bullock et al. 2001). Intermedin (IMD) is a member of calcitonin's peptide family and calcitonin gene-related peptide. It protects kidney against renal ischemia/reperfusion through inhibiting endoplasmic reticulum stress ERS and ERS-related apoptosis (Wang et al. 2015). Calcitonin inhibits the action of the enzyme 1-α hydroxylase which leads to a deficiency in active vitamin D synthesis.
- **Cardiac Function**: CGRP has a protective effect on cardiac myocytes which points to a new promising therapeutic strategy for some cardiac conditions. Also, IMD prevents myocardial ischemia-reperfusion injury in hyperlipidemic rats (Yang et al. 2014) and has beneficial improvement in cardiac functions (Zhu et al. 2016).
- **Participation of CGRP in Pain**: Intra-ganglionic CGRP in rats induces distinctive migraine-similar reactions in male and female (Araya et al. 2020). But CGRP antagonists have an ability to relieve migraine and it is considered in developing related drug. Selective blockage of the acknowledged CGRP receptor with erenumab prevents migraine with a vascular safety effect in comparison to control group for 3 months, but for long-term safety of erenumab for migraine subjects, it

needs more studies (Kudrow et al. 2020). Although CGRP is a key peptide in human and mammalian biology, but there are premature results to consider this peptide as new therapy for diseases including skin disorders, arthritis, metabolic disorders such as obesity and diabetes (Russell et al. 2014).

6.12 The Vitamin D3 Endocrine System (Cholecalciferol)

Vitamin D3 is classified as a secosteroid hormone, it has 27 carbon atoms which make it one of the main steroid hormones. Vitamin D can present in several forms but only has a biological effect when it is present in its active forms. There are local steroidogenic and secosteroidogenic systems present in skin. Vitamin D can act in its an autocrine and paracrine signal. Naturally, this steroid is converted into vitamin after the skin is exposed to ultraviolet rays for 15–20 min. It is formed from plant-based foods and is added to milk and dairy products. It plays a key role in some mineral ion homeostasis such as calcium and phosphorus (Bullock et al. 2001; Al-Hashimi and Abraham 2020; Litwack 2019). Classical and novel vitamin D analogs exhibit prodifferentiation, anti-proliferative and anticancer properties (Slominski et al. 2014). Physiological concentrations of vitamin D in the serum are as follows: 25(OH)D: 26.5 ng/ml, $1,25(OH)_2D$: 34.1 pg/ml, while $24,25(OH)_2D$: 1.3 ng/ml (Gardner and Shoback 2007).

6.12.1 Th Most Important Active Metabolites of Vitamin D

Vitamin D (calciferol) includes two hormones categorized as secosteroids; ergocalciferol D_2 available in a pharmaceutical form. Cholecalciferol D_3 produced in the skin after exposure to light includes: (1) Calcidiol (25-hydroxyvitamin D_3) that is found in the blood and has the most potent anti-rickets effect. (2) Calcitriol (1,25-dihydroxyvitamin D_3) that increases Ca^{2+} levels in the blood in synergy with PTH; it is more active than the other form. Although the synthetic molecules of vitamin D, analogs and drugs have vitamin D like effects, they have specific traits and are not functioning similarity in respect of pharmacological activities and their side effects (Bullock et al. 2001; Mazzaferro et al. 2014). Metabolites of vitamin D are transported in the circulation bound to vitamin D binding protein (DBP) and albumin. The liver makes these protein transporters (DBP and albumin) that are reduced in liver disorders or may be missing as in intestine and nephrotic diseases which lead to losing of proteins causing lowering concentrations of vitamin D metabolites although free levels of vitamin D are normal. Small amount of vitamin D metabolites is kept free boundless metabolite in the blood as it is needed by many tissues to easily arrives and enters the cell; nevertheless, the bound vitamin D metabolites enter cells of the kidney and parathyroid gland over a specific mechanism (Bikle 2017).

6.12.2 Conversion of Vitamin D To active Forms

- **In the skin**, after ingestion from plant-based foods, it is converted by means of natural light into its form in the body. The skin is the main site of vitamin D3 activation through two pathways: (1) The classic pathway involves producing an active 1,25-dihydroxyvitamin D (3) (1,25(OH) 2D3). (2) While the novel pathway is by cytochromes P^{450} that is involved in producing 20(OH) D3 androgens, the same cytochromes are involved in producing estrogens, glucocorticoids, and mineral corticosteroids from cholesterol. Slominski et al. (2014) continued their work on cytochromes and have detected novel cytochromes P^{450}-derived secosteroids in other organs including skin, serum, and adrenal gland, they are acting as hormones in vivo based on their concentrations and biological activities.
- **In the liver**, vitamin D3 is converted into active forms such as calcidiol by the enzyme 25-hydroxylase (Bullock et al. 2001).
- **In the kidney**, the mitochondria of proximal convoluted tubules cells are the main site of production of blood 1,25-dihydroxyvitamin D (3). PTH stimulates, while 1,25-dihydroxyvitamin D (3) itself inhibits the enzyme 1-α hydroxylase to convert calcidiol into the other active form which is 1,25-dihydroxyvitamin D3 calcitriol and 24,25(OH)2D. Several vitamin D metabolites are produced but these do not have specific functions. Vitamin D receptor (VDR) is present in the top of brush border cells of the proximal convoluted tubule, it acts as a "sensor" to the circulating level of 1,25-dihydroxyvitamin D (3) and adjusts the efficiency of the 1α-hydroxylase and the 24-hydroxylase accordingly. VDR is not found neither in distal convoluted tubule cells of the kidney nor in other epithelial cell, such as intestinal mucosa cells (Wang et al. 2014b, 2015). Numerous enzymes possess 25-hydroxylase function, while CYP2R1 is the best. In the kidney, 25OHD is additionally converted and metabolized to $1,25(OH)_2D$ mainly by the enzyme 25 hydroxyvitamin D-1α hydroxylase (CYP27B1), despite additional tissues have this enzyme function such as epithelial cells, immune cells, and the parathyroid. In additional tissues, skin, breast, and prostate, 1,25(OH)2D is synthesized and works as a paracrine and autocrine hormonal signal. $1,25(OH)_2D$ is the main form of vitamin D hormone that plays most of the biologic functions. The kidney's synthesis of $1,25(OH)_2D$ is strictly regulated by PTH and suppressed by the minerals, calcium and phosphate, and FGF23 as they regulate the renal 1-hydroxylase but not extra renal 1-hydroxylase that requires cytokines. 24-hydroxylase is the chief enzyme that catabolizes 25(OH)D and 1,25(OH)2D (Bikle 2017).

6.12.3 Physiological Functions of Active Vitamin D

- The receptor of $1,25(OH)_2D$ (VDRs) is a transcriptional factor that binds to additional transcriptional factors such as retinoid X receptor to regulate genes transcription either positively or negatively conditional on other cofactors that it binds. Then the regulated genes immediate the biologic functions of the vitamin.

VDRs are member of nuclear hormone receptors family. VDRs intermediate 1,25 (OH)2D functions but not the whole. VDRs are members of nuclear receptors family. They are not limited in the main target organs (skeletal, intestine, kidney) but they are generally expressed in other cells that require vitamin D for their physiological activities. In experimental animals, vitamin D owns useful effects on many diseases such as hypertension, cardiac diseases, immunologic disturbance. Analogs of 1,25(OH)2D are under development to serve in for non-skeletal target (Bikle 2017).

6.13 PTH-Dihydroxyvitamin D3 System

Vitamin D in the form of calcitriol acts in concert with PTH to increase Ca^{2+} levels. This hormonal vitamin acts directly on the bone, small intestines, and kidneys and on other tissues.

- **Reproduction**: PTH-dihydroxyvitamin D3 system performs the same functions in human placenta, it leads to more absorption of calcium through fetal gut during pregnancy. Also, seminal vesicles contain the same PTH-dihydroxyvitamin D3 system that acts in a paracrine signal to allow high levels of calcium to pass to the ejaculate (Brotherton 1991). In pregnant women, the biomarkers placental of vitamin D metabolism are associated with blood metabolites of vitamin D. 25 Hydroxyvitamin D-1α hydroxylase (CYP27B1) genes are related to increased level of 1,25(OH)2D3. Trophoblast can synthesize and release vitamin D metabolites, particularly 25(OH)D3. Thus, the placenta plays an effective function in the modification of vitamin D metabolite performance in blood in pregnant human (Park et al. 2017).
- **Regulation of Bone Minerals**: Calcitriol acts with PTH to absorb Ca^{2+} and phosphate from the bone. As for 25-hydroxyvitamin D_3, this has a powerful anti-rickets effect by maintaining bone-building contrary to calcitriol 1,25-Dihydroxyvitamin D (Mini and Manju 2017).
- **Effect on Intestinal Mucosa**: The perfect Ca^{2+} absorption in intestine is important for mineral balancing in bone and protecting from osteoporosis. Vitamin D is a pleiotropic and essential hormone for intestinal stem cells functions through vitamin D's receptor signals (Augenlicht 2017). Calcitriol stimulates increased Ca^{2+} absorption in the luminal part of the intestines where it triggers the binding of calmodulin (the protein bound to calcium needed for calcium transport) in the brush border of the intestinal epithelium. Ca^{2+} absorption can be achieved through two pathways: saturable and a non-saturable. Low consumption of calcium upregulates saturable transport, a pathway facilitated by increased synthesis of 1,25(OH)2 D by kidney. While low vitamin D level or any genetic disturbance such as mutation or deletion in vitamin D receptor or CYP27B1 genes decreases calcium absorption through failing in the saturable pathway. In the ileum, the nonsaturable pathway is also controlled by vitamin D level. Other hormones also regulate Ca absorption indirectly as they intermediated through the

regulation of vitamin D metabolism, PTH, thyroid hormone, and testosterone, while estrogen and IGF-1 regulate Ca absorption directly as happen in the absence of vitamin D (Fleet and Schoch 2010). Calcitriol also changes the structure of plasma membrane phospholipids leading to increased calcium flow across it. Vitamin D has an impact on PTH, and the inverse is true via negative feedback mechanism. They work together with calcitonin to regulate calcium absorption in the intestines. While calcitriol has less an effect on phosphate absorption in the intestines than PTH.

- **Effects of Vitamin D on Kidneys**: 25(OH)D is more active than other substances in reabsorbing Ca^{2+} and phosphate in the kidney tubules. PTH and the metabolites of vitamin D have different effects in the kidneys, but it seems that PTH has a more power on calcium and phosphate regulation via the kidneys (Bullock et al. 2001).
- **Effects of Vitamin D Cardiovascular System**: Both vitamin D and PTH hormone act physiologically on the endothelium, heart, and other vascular structures. Khundmiri et al. (2016) reported that hyperparathyroidism and vitamin D deficiency are involved in multiple cardiovascular disorders and complications including hypertension, vascular calcification, atherosclerosis, and kidney disorders. Vitamin D3 influences immunological components and has a key immunoregulator role of cytokines involved in many inflammations (Mohammed et al. 2017).
- **Other Tissues**: In addition to its classical physiological effects, 1,25-dihydroxyvitamin D (3) exhibits pleiotropic functions in multiple target tissues and cell mostly in an autocrine/paracrine signal. For its biological activity, it has been applied as a potential therapeutic agent for the treatment of hyperproliferative disorders like cancer and psoriasis, immune dysfunction (autoimmune diseases), and endocrine disorders such as hyperparathyroidism. But it should be taken in consideration that therapeutic doses required can produce substantial hypercalcemia (Brown and Slatopolsky 2008). Vitamin D has effect on the pituitary and many endocrine glands, blood, muscles, and brain.

It could be concluded *that the factors regulating calcium and phosphorus levels in the blood are PTH, PTHrP-1, calcitonin, calcitonin-gene-related peptide, vitamin D metabolites, sex hormones: Testosterone in males and estrogen in females influence calcium levels in the circulation. Calcium deposits in the bones and fusion of their edges at maturity due to the presence of sex hormones. Delayed fracture healing in the elderly and how easily bones fracture due to low levels of sex hormones.*

6.14 Progenitor/Stem Cell of Parathyroid Glands: Thymus Generates Precursor Cells for the Parathyroid Cells

Endocrinology as usual is an interesting and surprising science, there are different origin cell types for parathyroid origin/differentiation. At the same time, the following facts are not strange if we know that the pharyngeal system is a temporary construction, contains multiple cells came from each of three germ layers that participate in the end to a several tissues in adult. Pharyngeal endoderm forms many types of cells such as thymus, thyroid, parathyroid, ultimobranchial bodies, palatine tonsils, and the inner ear (Magaletta et al. 2020).

The anterior foregut endoderm was described to lead to therapeutically related cell kinds in glands like parathyroid, thyroid, thymus, salivary glands, and organs such as esophagus and lung. A directed differentiation protocol could be used to generate the anterior foregut endoderm from human pluripotent stem cells (Kearns et al. 2013; Korostylev et al. 2017). Researchers in 2009 modified and expanded the established plans to differentiate mouse embryonic stem cell into definitive endoderm in order to highly optimize the expression of specific markers of parathyroid growth. The best method was to use activin A at (100 ng/ml) with BG01 cells to obtain differentiated cell cultures that expressed markers for three phases; median endoderm markers and parathyroid growth markers as well as also markers of obliged parathyroid precursors or developed parathyroid glands such as glial cell missing-2, CCL21 [CaSR], and PTH (Bingham et al. 2009).

The thymus gland participates in generating precursor cells for the parathyroid gland cells. Prothymocytes home the parathyroid lineage rather than the thymic lineage (Bleul and Boehm 2000). The Bingham Protocol uses programmed exposure to Activin A and Sonic hedgehog has been modified by Woods Ignatoski et al. (2011) to improve the thymus cells differentiation into parathyroid-like cells. In the modified protocol, cells treated with same Activin A (but used 50 ng/ml) and Sonic hedgehog (100 ng/ml) for 91 days. The differentiated cells have shown expression of multiple markers and receptors include PTH markers, CaSR, chemokine receptor type-4, and chorian-specific transcription factor. Additionally, these differentiated cells were able to release PTH, which could be inhibited as a negative feedback to high Ca^{+} level in the media. Interestingly, the differentiated parathyroid-like cells did not initiate tumors in immunocompromised mice group. This in vitro method is a promising step at a strategy to recover normal parathyroid physiology using autologous cells (taken from the same individual) and guided to differentiate without genetic manipulation. While from genetics view, Caprio et al. (2021) found that Ezh2 gene is involved for parathyroid and thymic growth via differentiation of the third pharyngeal endoderm' pouch. This finding provides a new explanation for the result of Ezh2 enhancing mutations in parathyroid disorders.

Park et al. (2016) reported that they grew a scaffold-free spheroidal parathyroids tissue via differentiation of tonsil-derived mesenchymal stem cells to retrieve cellular functions of parathyroid gland in vivo. The diagrammatic representation of differentiation of tonsil-derived mesenchymal stem cells into different body cells and tissues is shown in Fig. 6.7.

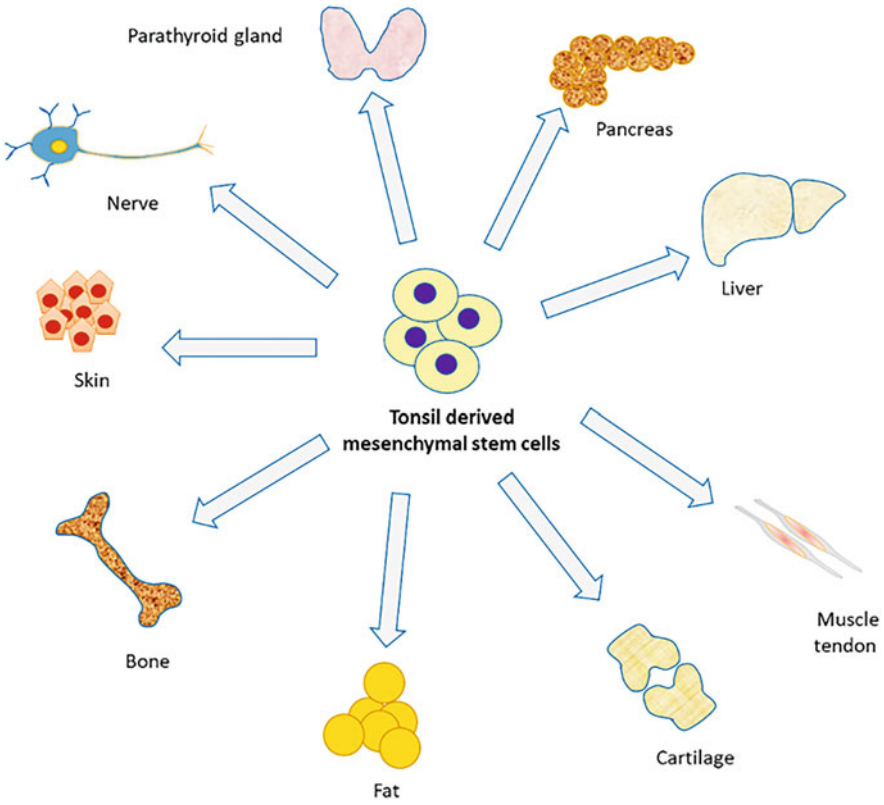

Fig. 6.7 Differentiation of tonsil-derived mesenchymal stem cells into different body cells and tissues (parathyroid gland, pancreas, nerve, bone, liver, muscle tendon, fat, skin, cartilage)

Lawton et al. (2020) reported first protocol to found differentiated PTH-expressing cells from human pluripotent stem cells and show a first step to develop functional parathyroid.

Adipose-derived stem cells in both rat model (Zhang et al. 2020) and in mice model (Cui et al. 2020) have been successfully differentiated into parathyroid gland-like cells and improved their survival.

These different origins of parathyroid-like cells may pave to a novel method for treating hypoparathyroidism, parathyroid disorders, and calcium homeostasis such as osteoporosis.

6.15 Conclusion

The parathyroid glands are renowned as being necessary for life. Parathyroid hormone (PTH) and calcitonin hormone in collaboration with other hormones such as PTHrP-1, calcitonin-gene-related peptide, vitamin D metabolites, and sex

hormones are main regulators for free calcium and phosphorus concentrations in the blood, bone formation and remodeling through targeting three main organs; bones, kidney, small intestines and other tissues. Parathyroid glands consist of small sized four oval-shaped glands located at the posterior surface of thyroid tissue. The gland consists of endocrine tissue interspersed with septa extending from the thin capsule which divides the glandular tissue into lobes. In addition to PTH functions in many physiological functions on mineral's regulation, PTH also has important effects in combination with secosteroid, the active form of vitamin D. PTH has been reported to involve in many vital functions on placenta and heart. It has proliferation and hemopoietic prompting effect, supports lactation. Although hyperparathyroidism was known to lead to severe bone loss (osteoporosis), but recently, it has been evidenced that PTH has pharmacological beneficial effect and could be a potential therapeutic utilization for bone formation in case of osteoporosis. Now, PTH gland and hormones can be differentiated and expressed successfully from different origins such as endoderm, thymus, tonsils as well as adipose tissue, which is promising for feasible regenerative therapy.

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7 Adrenal Glands, Pineal Gland, and the Circadian Rhythm: Structure and Physiology

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Abstract

The adrenal glands are located at the top of each kidney towards the front and weighs around 5 g. Each gland measures 4 cm, weighs 4–5 g, and has a thickness of 3 cm. The adrenal glands are highly vascularized and divided anatomically and physiologically into two different areas in terms of blood supply, innervation, and functions. Each gland consists of three different structures regarding origin, anatomy, histology, physiology, and regulation. The adrenal cortex comprises three zones: the glomerulosa, the fasciculata, and the reticularis, they produce mineralocorticoids, glucocorticoids, and adrenal sex hormones, respectively. A novel zone has been identified between the glomerulosa and the fasciculata zones and this zone was titled as undifferentiated cell zone, where cells can proliferate and migrate bidirectionally to zona glomerulosa and to zona fasciculata centripetally. The pineal gland is called pineal body that is attached to the posterior aspect of the third ventricle by means of a short stem containing sympathetic neural axes penetrating the gland tissue which is connected to the hypothalamus. It contains many cells such as pinealocytes, neuroglial cells, interstitial cells, perivascular phagocytes. Pineal gland produces hormones such as melatonin, serotonin, many polypeptides and indoles. The pineal gland adjusts the function of many endocrine glands. The main physiological function of melatonin is to transfer information of the daily cycle of day and night to body systems to organize the functions that respond to photoperiod alteration which includes the cyclic rhythms. Daily melatonin is secreted as a night signal to organize, stabilize, and support combination circadian rhythms such as core temperature, sleep-wake rhythms. This organization for other physiological functions like antioxidant, immunity, glucose, and homeostasis depends on the melatonin signal. This chapter discusses the topics related to adrenal glands, pineal gland, and circadian rhythm.

Keywords

Adrenal glands · Pineal gland · Circadian rhythm · Structure and physiology

Abbreviations

11 beta-HSD	11-Beta hydroxysteroid dehydrogenase
ACTH	Adrenocorticotropic hormone
AM	Adrenomedullin
ATF5	Activating transcription factor 5
CBG	Corticosteroid-binding globulin

CNS	Central nervous system
CO_2	Carbon dioxide
CRH	Corticotropin-releasing hormone
Cu	Elemental copper
GnRH	Gonadotropin-releasing hormone
GSH	Glutathione
GSSG	Reduced glutathione
H&E	Haematoxylin and eosin stain
HFD	High-fat diet
LH	Luteinizing hormone
Na^+/K^+ ATPase	Sodium-potassium adenosine triphosphatase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
REM	Rapid eye movement
RNA	Ribonucleic acid
T3	Triiodothyronine
T4	Thyroxine
WBC	White blood cells
Zn	Elemental zinc

7.1 Introduction: An Admirable Role of the Adrenal and Pineal Glands in Circadian Rhythm

Circadian rhythms are natural changes in mental, behavioural, and physical physiological activities during 24-h daily cycle in response to light and dark succession. The typical pattern of Circadian cycle is shown in teen. Chronobiology is the science of circadian rhythms, its regulators, and patterns. Recent findings have evidenced marvellous coordination between both glands, in addition to hypothalamic-pituitary-adrenal axis regulation. Some of their physiological functions involve acting synergistically with the brain to control pacemaker activity. Also, the pineal and adrenal glands can act antagonistically to enable melatonin from the pineal gland to protect against heat. Any disturbance in circadian rhythm (diurnal cycle of the hormone) may lead to functional disorders, which draws the attention of the scientists to consider circadian rhythm disturbance in general as a basis for disease diagnosis and treatment plan. Also, da Silveira Cruz-Machado et al. (2017) reported that pineal melatonin and adrenal glucocorticoids are key hormones in defining daily rhythmicity and modulating defence responses. In nightly animals, corticosterone peak happens at light-dark transition, while melatonin peak occurs at the midnight in both types of animals. In inflammatory condition, the crosstalk between adrenal and pineal glands shows that corticosterone promotes nocturnal melatonin production by decreasing the activity of transcription factor (NFκB), as it modulates the expression of an essential enzyme in melatonin synthesis. It is dramatically decreased at the entrance of night in the pineal gland of rat (Fernandes et al. 2016). The understanding of the crosstalk between these two glands is settled in physiological conditions,

indicating that the corticosterone rhythm modulates pineal's phenotype. Besides being regulated by the central clock placed in the hypothalamus, it is also affected by glucocorticoids via the regulation of NFκB gene transcriptional program. Glucocorticoid plays an emerging function of chronopharmacology, centring on disorders that happen by high and insufficiency level of glucocorticoids. However, acting on glucocorticoid concentration is not the only route to return clock-related tasks. But both of (1) the action of the glucocorticoid's receptor that required for signal transduction and (2) melatonin and/or metabolically effective medications and foods, all can be useful for fixing the broken clock system in adrenal gland diseases (Minnetti et al. 2020). Structurally, the adrenal gland classically consists of three zones in its cortex in addition to its central medulla but in 1994 a new functional zone has been identified as stem cells that play important roles in adrenal function in rat under normal condition (Mitani 2014) and under stress (Steenblock et al. 2017). In addition to the adrenal classic metabolic functions for regulating carbohydrates, minerals, and medullary adrenaline, in human, the adrenal is a master regulator gland during response to stress. It participates in responding to stressors. Furthermore, there is a synchronized action of stress-inducible stem (adrenomedullary stress-dependent progenitors) that leads to tissue remodelling and adaptation of cells and functions to stress (Steenblock et al. 2017). On the other hand, severe stress in mice gives rises greyish colour of the hair because of the reduction of melanocyte's stem cells. It could be said that survival of many somatic stem cells is affected directly by the body physiology status exclusively (Zhang et al. 2020). In addition to the pineal gland, both cortex layers and chromaffin cell clock in medulla of adrenal gland are playing key roles in regulating circadian rhythm and stress adaptation.

7.2 Suprachiasmatic Nucleus in the Hypothalamus

The suprachiasmatic nucleus (SCN) is a remarkable construction in the front of the hypothalamus. It represents our focal pacemaker of the circadian clock and controls circadian rhythms, daily cycles of physiological and behaviour functions in human and mammals' body, and drags to the light/dark cycle. The SCN is a network comprised of various kinds of gamma-amino butyric acid (GABA)-ergic neurons in addition to glial cells. Despite each single neuron of SCN owning intracellular molecular mechanism of circadian clock and the capability to pulsate as a cell-autonomous circadian clock with singular particular periodicity, inter-neuronal communications between SCN neurons (cellular oscillators) are fundamental for circadian of the SCN (Mieda 2020) and crucial for the comprehensible rhythm appearance and orchestration of the peripheral organ's "clocks" by the SCN as consonant clocks. The SCN begins to act progressively, as a centric clock during postnatal development. The SCN shows circadian rhythms in clock gene expression from the embryonic phase until postnatal lifetime and the phenotypes continue basically unvaried. While the loss of symmetric circadian rhythms in cryptochrome-deficient SCN uncovered alterations in the SCN communications network that happens in weeks 2–3 postnatal phase. The SCN communications

network comprises various clusters of cellular circadian rhythms that are distinctly incorporated by effect of signalling of both vasoactive intestinal polypeptide and arginine vasopressin based on the duration of postnatal growth (Honma 2020). Fantastic and technical advances, including intersectional genetics, multi-dimension images, and notion of network are starting to clarify the circuit-level pathways and techniques and new features distinguishing the SCN as a unique precise and firm clock (Hastings et al. 2018). Various afferent neuronal tracts extend to the SCN. Its main piece is the retinohypothalamic arising from the retina particularly from photosensitive neuro-ganglion. Efferent protuberances from the SCN provide nerve supply to the pineal gland that secretes melatonin through the night for sleep inducement. Disarray in the SCN's circadian system correlates with different troubles in mood and sleep (Ma and Morrison 2020). SCN system faces severe challenging factors, such as travels across time zones, that leads to in re-concurrence to local ecological time signals, but this re-concurrence is oftentimes joined by reverse short-term effects. When these challenging factors are exposed chronically by individual, cope may not be obtained, such as the rotary of night-shift employees. The temporal and chronic trouble of the circadian system is extremely named as "circadian disruption". Without doubt that the circadian system participates in health and illness which made it a very important system to be further investigated (Vetter 2020).

7.3 Structure of Adrenal Glands

The adrenal glands are located at the top of each kidney towards the front. Each gland is covered with a membrane as shown in Fig. 7.1 and weighs around 5 g. Each gland measures 4 cm, weighs 4–5 g, and has a thickness of 3 cm. The adrenal glands are highly vascularized and divided anatomically and physiologically into two

Fig. 7.1 Mammals' adrenal glands. (Separated from the kidney)

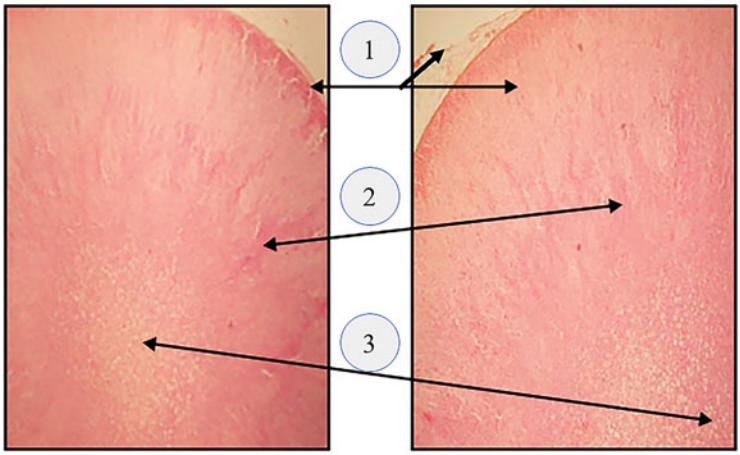


Fig. 7.2 Cross-section in the adrenal gland showing (1) capsule, (2) cortex, and (3) medulla (H&E ×4 and ×10)

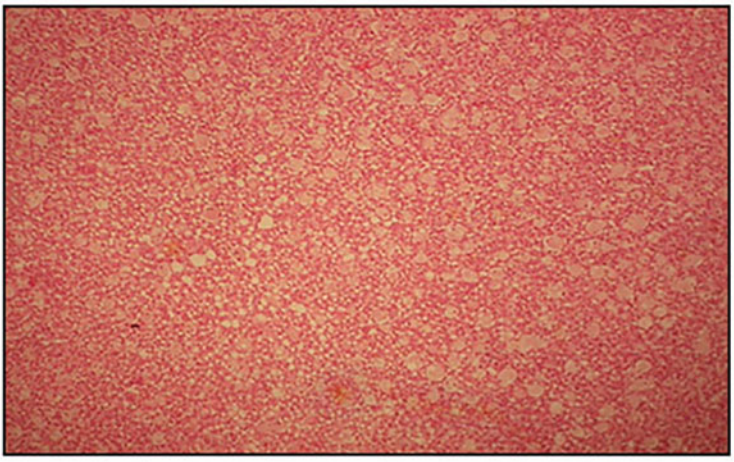


Fig. 7.3 Cross-section of the medulla area of the adrenal gland (H&E ×40) showing the catecholamine-secreting chromaffin cells

different areas in terms of blood supply, innervation, and functions. Each gland consists of three different structures regarding origin, anatomy, histology, physiology, and regulation. They are enveloped in a fibrous capsule as shown in Fig. 7.1. Although the three parts regions of the gland are different, they participate in the same physiological functions including circadian rhythm and glucose homeostasis. They are: (1) Adrenocortical stem/progenitor cells. (2) Adrenal medulla: a neural gland originating from ectoderm; it is not vital to life, Figs. 7.2 and 7.3. (3) Adrenal cortex that originates from the mesoderm and is vital to life, Fig. 7.2.

7.3.1 Adrenocortical Stem/Progenitor Cells

The adrenal cortex comprises three zones: the glomerulosa, the fasciculata, and the reticularis, they produce mineralocorticoids, glucocorticoids, and adrenal sex hormones, respectively. A novel zone has been identified between the glomerulosa and the fasciculata zones. The new zone was not characterized by endocrine functions; hence, it was titled (undifferentiated cell zone) which its cells can proliferate and migrate bidirectionally to zona glomerulosa and to zona fasciculata centripetally. This zone is a group of stem/progenitor cells as found in the rat adrenal cortex to maintain the effective zonation (Mitani 2014). In addition to its localization between the zona glomerulosa and the zona fasciculata, stem cells are also localized in the adrenal capsule, subcapsular region, juxtamedullary region as indicated in Fig. 7.10. Cortex cells produce from the population of stem cells present in the gland's capsule or outer cortex, and emigrate, change their phenotype as they proceed during the cortical zones (Mitani et al. 2003). During expansion, recruitment of the stem cells is activated via signals from the zona glomerulosa. Local regulators in the cortex include catecholamines, cytokines and renin-angiotensin system adjust and revise the influence of the systemic trophic factors (ACTH), Fig. 7.10. So, the functions of the adrenal gland must be considered as an integrated gland more than the summation of its zones' activity (Vinson 2016). Since the adrenal glands are highly plastic organs. The adrenal can adapt the body's homeostasis to multiple physiological requirements. The progenitor cells facilitate the adrenal gland's constant self-renewal, remodelling, cortical zone's reversible expansion, the transformation of cells between zones and the change in biochemical profile responding to physiological/extreme needs of steroids. The cortex zones reversibly extend, retract, or change their biochemical profiles to adjust needs. Therefore, these types of adrenocortical cells play a key role in the physiology and maintenance of the adrenal cortex. Autocrine and paracrine signals are used by the progenitor cells for replacement and differentiation processes. Adrenocorticotropic hormone (ACTH), angiotensin, extracellular matrix, and molecular signals are key determinant factors that interact with cell surface receptors, then cells fate (Kim et al. 2009; Lerario et al. 2017).

In addition to adrenocortical progenitor stem cells Steenblock et al. (2018) identified in mice a pool of glia-like multipotent nestin-expressing progenitor cells. They are located in the adrenal subcapsular area and scattered throughout the cortex and present also between the zona glomerulosa and the zona fasciculata. These cells participate in the plasticity of the medulla of the adrenal gland. The nestin progenitors become active in response to stress, through giving rise to chromaffin cells.

7.3.2 The Adrenal Medulla

Tissue Structure It consists of a large sympathetic ganglion that is modified and specialized; in other words, a neuroendocrine gland containing neural bodies without

axons. The medulla is surrounded by the adrenal cortex and originates from autonomic sympathetic nerve tissue in the embryo. In addition, the nerve signals it receives trigger the secretion of neuroendocrine hormones from it. The adrenal medulla contains chromaffin cells, which do not have axons, but which are well-innervated and categorized as APUD cells (Whitwam 1977). The main hormones of the adrenal medulla are the catecholamines. The adrenal medulla also produces adrenomedullin. Additionally, the granules of the chromaffin cells contain the enzyme dopamine-β-hydroxylase which is necessary for the conversion of dopamine to epinephrine (adrenaline).

7.3.2.1 The Catecholamines

The adrenal medullary cells synthesize neurohormones (the catecholamines) derived from monoamine amino acids such as tyrosine. The catecholamines are synthesized and stored as adrenaline (epinephrine) in a proportion of 80% and as noradrenaline (norepinephrine) in a proportion of 20% in the form of chromaffin granules. The adrenal medulla is mainly responsible for the release of circulating adrenaline. The catecholamines hormones are also produced from other sources such as the central and sympathetic nervous system. For example, large amounts of adrenaline are produced by the chromaffin cells in the adrenal medulla, while small amounts are produced in the brain; noradrenaline is also abundantly available in the adrenal medulla and as a neurotransmitter in the tissues of the central and peripheral nervous system. It is more abundant in the hypothalamus and the peripheral sympathetic nerves (Bullock et al. 1991; Matsuo et al. 2016).

Synthesis of the catecholamine has been previously discussed in Chap. 2 and illustrated in Fig. 2.2. The catecholamines are secreted into the bloodstream and have a high binding affinity for albumin or the closest high linking energy-protein to them. The half-life of adrenal hormones is 10 s.

7.3.2.2 Regulation of Catecholamine Secretion

- Catecholamine secretion increases in emergency situations as a response to stress and this is known as the fight-or-flight response. The pool of glia-like multipotent nestin-expressing progenitor cells responses to stress and gives rise to chromaffin cells.
- Secretion increases in situations of acute stress in preparation for aggression, anger, shock, fear, and anxiety. Three forms of adrenergic responses act synergistically in preparation for the aggression status for the potential fight: (1) endocrine/hormonal adrenaline and norepinephrine appear to be required in the metabolic preparations; (2) a sympathetic system stimulates the required cardiovascular response; (3) CNS prepares an individual for a potential fight. Also, indirect CNS effects include: olfactory stimulation (an essential source of information in rodents), reduced pain sensibility, and memory enhancement.
- Various other stress factors and strenuous exercise. Urinary concentrations of some minerals such as Zn, Cu, and adrenaline and noradrenaline increase with excessive stress, but adrenaline responds to both physical and mental exercises.

- Adrenaline responds to lack of oxygen and suffocation, ether-based anaesthetics, surgery, atmospheric pressure, pH, and also to hypoglycaemia (Kikukawa and Kobayashi 2002).
- Hormones such as insulin administration. The adrenal gland and some CNS catecholaminergic areas respond to insulin administration, and central catecholamines may be triggers for physiological defence roles against insulin-induced hypoglycaemia.
- Myocardial infarction, haemorrhage influence catecholamine release.
- Temperature change: hypothermia-induced stress stimulates catecholamine production.
- Neurotransmitters such as the secretion of acetylcholine from the nerve endings influence catecholamine release.
- Cortisol and ACTH which means the medulla is indirectly dependent on the pituitary which secretes ACTH and the hypothalamus which secretes corticotropin-releasing hormone (CRH).
- Caffeine increases adrenaline and noradrenaline levels, leading to increased blood pressure and heart rate (Han et al. 2011).

7.3.2.3 Concentration of Adrenaline

According to Bullock et al. (1991), the concentration of adrenaline varies as a function of physiological and pathological conditions; baseline level is 25–50 pg/ml, but in hypoglycaemia it reaches 230 pg/ml and in case of ketone body diabetes to 500 pg/ml. While in severe hypoglycaemia reaches up to 500 pg/ml.

7.3.2.4 Receptors of Catecholamines

Catecholamine activity is dependent on the presence of two types of receptors in the central nervous system and peripheral organs: **alpha receptors** and **beta receptors**. In general, noradrenaline stimulates alpha receptors more than adrenaline while adrenaline has more of an effect than noradrenaline on the activation of beta receptors:

Alpha (α) adrenergic receptors: There are a number of secondary receptors (α_{1A}, α_{1B}, α_{1C}, α_{2A}, α_{2B}, α_{2C}). These are the receptors for adrenaline and noradrenaline and are responsible for all stimulation functions in the body; they only have one inhibitory effect (on the intestine).

Beta (β) adrenergic receptors: There are several secondary receptors (β_1, β_2, β_3, β_4). They are not receptors for noradrenaline and are responsible for all inhibitory functions in the body and only have one stimulatory effect (activation of the myocardium) (Bullock et al. 1991). Adrenergic receptors (ARs) are directly or indirectly concerned in regulating wide spectrum of physiological functions and also act as targets of drugs for treating many illnesses such as congestive heart failure, bronchial asthma, etc. The genotyping of human with varied ethnicity explored that the genes encoding α1A-, α1B-, α2A-, α2B-, α2C-, β1-, β2-, and β3-adrenergic receptors are polymorphic in the coding, in regulatory domains and non-coding region regions. Therefore, the functional outcome of these genetic

differences includes alterations in expression level at either transcription or translation, modification of coupling to heterotrimeric G-proteins leading to gain or a lack in the role, and changes in GRK-intermediated the phosphorylation/desensitization of receptors or of agonist-enhanced downregulation (Schaak et al. 2007). Although catecholamines are used as a drug for circulatory chock, but, separately from their hemodynamic actions, that depend on the properties of different receptors such as affinity, density, and the relative effectiveness of the distinctive molecule, catecholamines have other side effects (Hartmann et al. 2017).

7.3.2.5 Catecholamine Physiological Functions

Adrenaline and noradrenaline are released from the medulla following activation of the sympathetic nervous system. They have a similar structure which explains the similarity of their effects; their activity may vary according to the receptor in question.

- **Adrenal hormones participate in the circadian rhythm.**
  In 2003, Terazono et al. (2003) found that sympathetic nerve activation (through noradrenaline and/or adrenaline release) is a controlling factor for the peripheral clock in mice. Also, Lemos et al. (2007) found that rhesus monkeys' chromaffin cells perform other physiological roles like cell survival and cell differentiation through activating transcription factor 5 (Atf5), a factor implicated in apoptosis and neurons differentiation. There is also evidence for circadian regulation of Atf5 by the chromaffin cell clock.
- **Norepinephrine acts on fatal heart** via β-adrenergic receptor to sustain fatal heart rate throughout the transitory phase of hypoxia that may happen in pregnancy. The catecholamine-deficient foetuses die since they cannot tolerate hypoxia-induced bradycardia (Portbury et al. 2003).
- **Effect of catecholamines on the cardiovascular system.**
  The catecholamines increase the rate and strength of the heartbeat and excitation of the myocardium on activation of beta receptors. The catecholamines lead to contraction of the peripheral blood vessels which increase blood pressure. This situation may be reversed when the parasympathetic Vigus nerve is stimulated as this slows down heart rate and reduces cardiac output. The role of epinephrine differs from that of norepinephrine depending on receptor type and smooth muscle condition (Bullock et al. 1991; Zipes 2008; Triposkiadis et al. 2009). Certain smooth muscles in a blood vessel may not be affected by the hormone, while the same muscle in other vessels may be affected; this helps maintain a balance depending on conditions in the body. The catecholamines increase the number of red corpuscles in the blood and blood coagulation, especially in cases of blood loss and haemorrhage, thus, the levels of catecholamines increase with haemorrhage. In physiological conditions, there is also complementarity and coordination between these two hormones and the central nervous system (Vinson 2016). Also, in pathophysiological status such as heart failure, there is complex interaction of multiple neurohormonal mechanisms that become

stimulated in the disorder in order to recover and maintain cardiac output to meet decompensating task. Heart failure progresses when a cardiac hurt or insult worsens the capacity of the heart for pumping the blood and sustaining tissue pressure. So, the most clear among these neurohormonal mechanisms is the adrenergic (sympathetic) nervous system whose action and outflow are extremely increased in heart failure. If the heart works appropriately, this stimulation of the adrenergic nervous system will rapidly restore heart function (Lymperopoulos et al. 2013). In circulatory shock, the use of catecholamines is the first drug recommendation, but away from their hemodynamic actions, different catecholamines have several non-hemodynamic side effects, either in physiological or pathophysiological statuses. In energy metabolism and mitochondrial function, long exposure to catecholamines drives to uncoupling of mitochondria and worsen oxidative stress leading to dysfunction of mitochondria, immunosuppressing effect, and other side effects in the gastrointestinal canal (Hartmann et al. 2017). Catecholamines are the mainstay of the treatment of acute cardiovascular disorders. But the receptors of the catecholamines adrenergic receptors subject to fast desensitization and downregulation when it is exposed to long period of adrenergic stimulation. Furthermore, prolonged exposure to high concentrations of catecholamines in the blood is correlated with multiple effects on several organ suit. Regrettably, in critically disorder patients, adrenergic downregulation interprets into cumulative decrease in cardiovascular response to external administrated catecholamine, driving to refractory attack (Belletti et al. 2020).

- **The mechanism that catecholamines induce endoplasmic reticulum stress** is through α and β adrenergic receptors. Norepinephrine stimulates endoplasmic reticulum stress in vitro in both HepG2 and 3T3L1 adipocytes cell lines. Prazosin, the α-1 blocker and propranolol, the β-blocker suppress endoplasmic reticulum stress enhanced by norepinephrine. The influence of catecholamines to induce endoplasmic reticulum stress is cell type-dependent, as norepinephrine therapy is unsuccessful to induce similar stress in other human cells like fibroblasts. The pathway used by catecholamines to exert changes in metabolism is to supress the receptors to be occupied by these mediators. The mechanism may be investigated as a potential strategy for the management of endoplasmic reticulum stress-induced diseases (Abdikarim et al. 2020).
- **Effect of catecholamines on immune system**: All lymphatic organs either primary or secondary are innervated widely by noradrenergic sympathetic nerves and immune cells have effective adrenoreceptors. Norepinephrine is a neurotransmitter that can target the immune system (Madden et al. 1995). It is known that components of the native immunity contribute in the usual fight/flight response to acute psychological anxiety in human influences blood lymphocyte because of catecholamine-inducing lympho- and leucocytosis effect which happens in two stages after catecholamine administration: a fast (less than 30 min) mobilization of lymphocytes, tracked by a rise in number of granulocytes with a reduction in lymphocyte. Catecholamines mainly influence natural killer cell and granulocyte circulation, while T- and B-lymphocytes counts stay quite unchanged. The

adrenergic receptors play a role in these numbers, as change in lymphocyte count is mainly refereed to β_2-adrenoceptors activation, while granulocyte rise requires **α**-adrenoceptor activation. Also, psychologically acute stress or exercise promotes the immune parameters changes achieved by exposing to catecholamine administration (Benschop et al. 1996). The stimulation of the sympathetic nervous system through an immune reaction is to localize the inflammatory reaction by inducting neutrophil gathering and producing specific humoral immune responses; however, on the systemic aspect, it might inhibit t-helper1 responses, the events protect the body from the injurious of proinflammatory effect of cytokines and immune productions by activated macrophage (Elenkov 2008) as in conditions described by high catecholamine concentration, catecholamines stimulate prolonged-lasting proinflammatory alterations in monocytes pointing to trained immunity that underlies the high cardiovascular case rate in specific patients (van der Heijden et al. 2020).

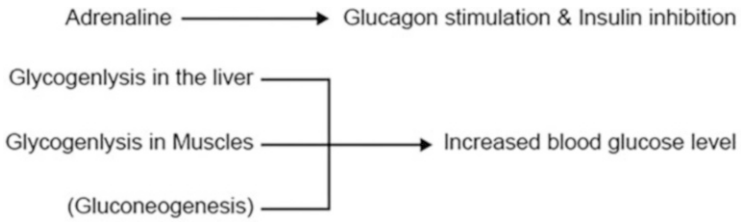
- **Effect of catecholamines on smooth muscle tissue**: The catecholamines act on smooth muscle tissues other than those in blood vessels. They help relax the smooth muscles of the bronchioles via β receptors. So, it could be used as a bronchodilator for the alleviation of asthma. Catecholamines increase pupil dilation via α receptors. They lead to relaxation of the bladder and contraction of the sphincter via β receptors. They also lead to contraction of the bladder via α receptors. They lead to relaxation of the intestinal muscles and decrease digestive juices as well as slow elimination also via β receptors. Under the effect of progesterone, the uterus muscles (myometrium) contract using α receptors in the presence of oestrogen; following binding to β receptors, the muscles relax. These mechanisms interact with childbirth. Relaxation of the smooth muscles enveloping the mammary sacs and ducts stops the excretion of milk (Bullock et al. 1991, 2001).
- **Skeletal muscles**: Catecholamines increase the ability to activate the skeletal muscles beyond their normal activity range in an emergency.
- Noradrenaline plays a role in olfactory information processing and memory in animals.
- Catecholamines can activate the secretion of certain hormones such as glucagon, aldosterone, thyroxine, calcitonin, and parathormone and inhibit insulin. They also stimulate ACTH and therefore lead to an increase in cortisol levels.
- **Effect on metabolites and energy via the β receptors:**
  Catecholamine involvement in the secretion and inhibition of the previously mentioned hormones leads to the following processes and results:

  They increase the production of energy and heat in the body due to increased oxygen consumption and increased rate metabolism. Adrenaline secretion can be accounted for the ventilatory hypercapnia observed during hypoglycaemia by promoting carotid body and sensitivity of body ventilatory CO_2 (Thompson et al. 2016). Adrenaline acts as a counter-regulatory hormone in restoring glucose homeostasis in response to hypoglycaemia through the neurocircuitry that connects the brain glucose neurosensors and adrenal sympathetic outflow to the chromaffin cells through glutamatergic transmission (Sabetghadam et al. 2017).

Adrenaline has a more powerful inhibitory effect than noradrenaline on glucose, which alerts beta cells and leads to reduced insulin secretion.

They also stimulate α cells in the pancreas, leading to increased glucagon release, resulting in: Inhibition of the entry of glucose into the cells which raises its levels in the blood. Local glycogen breakdown in the liver, heart, and muscle cells to increase free glucose availability in the blood. The catecholamines, along with glucagon trigger the synthesis of glucose from non-carbohydrate sources (gluconeogenesis process). They lead to activation of triglyceride lipase which leads to fat lysis and increases free fatty acids in the blood by using β receptors, enabling their use in energy production, but with the formation of ketone bodies. Also, understanding the neural regulation of hypoglycaemia-induced catecholamine release is helpful in identifying new therapeutic strategies for treating hypoglycaemia, a life-threatening condition (Verberne et al. 2016).

The outcome of all this is an increase in blood glucose and free fatty acid levels, making them available for use. The effect on carbohydrates can be summarized as follows:



7.3.2.6 Adrenomedullin (AM)

Adrenomedullin was initially isolated from a tumour of the adrenal medulla. It is a 52-amino acid peptide hormone. Adrenomedullin has physiological functions:

- Adrenomedullin has a potent vasodilatory action and multiple physiological effects leading to homeostatic responses. It is mostly found in the adrenal glands, gut, lung, kidney, and cardiovascular system. Its action is directly mediated by specific receptors (calcitonin-receptor-like receptor).
- AM is considered a new biomarker in multiple diseases.
- It has very useful functions against survival, such as antiapoptotic, antifibrotic, antiproliferative properties and its level increases in renal disease as a protective action. Administration or infusion of AM improved glomerular sclerosis, interstitial fibrosis, and renal arteriosclerosis significantly in multiple models of malignant hypertension.
- Administration of AM modulates blood pressure. It is a therapeutic option for patients with chronic renal failure (Nishikimi 2007; Martínez-Herrero and Martínez 2016).

7.3.3 The Adrenal Cortex

The next area after the capsule is the cortex which surrounds the adrenal's medulla. It contains an embryonic zone that continues until birth. After birth, the adrenals start to decrease in weight due to the disappearance of this zone. The cortex consists of three principal zones and one additional area, the stem cell area, from which progenitor cells originate to form the cells of the cortex. The adrenal cortex plays important role in steroidogenesis, since it produces mineralocorticoids, glucocorticoids and synthesizes precursors of androgen (DHEA with some androstenedione). The cortex has three distinctive histological and functional zones (Burford et al. 2017; Dutt et al. 2020), these zones represent two separate functional areas: the outer one is the zona glomerulosa which differs from the zona fasciculata (middle zone) and zona reticularis (inner zone), as a result of specialized enzymes which form hormones of the zona glomerulosa. The zona glomerulosa and its secretions are also different because they do not have 17α-hydroxylase enzyme activity needed to produce 17α-hydroxypregnenolone, an essential precursor in the production of cortisol and androgens in other zones. This process does not take place in the zona glomerulosa (Dutt et al. 2020).

7.3.3.1 Extra-Adrenal Organs and Tissues Synthesize Local Glucocorticoids and Mineralocorticoids

It was classically thought that glucocorticoids and mineralocorticoids produced exclusively only in the adrenal gland's cortex. But 11 β-hydroxysteroid dehydrogenase type 2, the enzyme involved in glucocorticoids conversation, has been localized and expressed in human epithelial tissues, the mammary and the salivary glands (Smith et al. 1996). It has been evidenced that these corticosteroids can be synthesized locally in several other tissues such as thymus, brain, skin, and maybe heart (Taves et al. 2011). Skin is a new source for glucocorticoids and the prominence of dermal glucocorticoidogenesis as a homeostatic action in human skin (Nikolakis and Zouboulis 2014). Intestinal mucosa is also an additional extra-adrenal that synthesizes glucocorticoids to regulate immunity and inflammation locally (Cima et al. 2004; Ahmed et al. 2019). Steroidogenic enzymes and higher local corticosteroid concentrations than blood levels are detected in those organs even after adrenalectomy. Similar to adrenal corticosteroids, local corticosteroid production can be regulated via expressed of local intermediaries of the hypothalamic-pituitary-adrenal axis or renin-angiotensin system. Similarly, local glucocorticoids regulate immune cells activity, while local mineralocorticoids control blood pressure and volume. Extra-adrenal (local) corticoids have physiological significance since their inhibition leads to main effects even if in normal (adrenal-intact) individuals. So, while adrenal production of glucocorticoids and mineralocorticoids in the circulation regulates various systematic functions in the body, local production of corticosteroids reveals high specific locative effect (Taves et al. 2011).

7.3.3.2 Characteristics of Adrenal's Cortex Hormones

Cortex hormones are steroids secreted by three zones of the cortex of the adrenal glands. They have long plasma half-life of 60–90 min due to binding to corticosteroid-binding globulin (CBG). Cortisol concentration falls throughout the day; the normal plasma concentration in the morning is 3–20 μg/dl which drops to half by four o'clock in the afternoon, then even more between ten o'clock at night and midnight, especially salivary cortisol which is present in the free form. It increases under stress conditions to about 60 μg/dl, especially after surgery. Seventy-five percent of cortisol is bound to globulin, 10% is in the free form, and 15% is bound to albumin. The amount of cortisol carried by CBG is around 25 μg/dl, while free cortisol represents about 1 μg/dl (Bullock et al. 1991). Diurnal salivary cortisol response may be linked with the level of risk exposure in special hazardous occupational task such as police work (particularly tactical police) compared with the work of universal population (Planche et al. 2019). Stresses also like night-shift work increase level cortisol (Cannizzaro et al. 2020).

Stages in the Synthesis of Adrenal Cortex Hormones This has been described in Chap. 2 (Fig. 2.4) and explained in the Steroid Hormones section of the chemical structure of hormones.

7.3.3.3 The Adrenal Cortex Zones

The adrenal cortex consists of three regular different cell zones, Fig. 7.4 (1, 2, 3). They are from internal to external direction: Zona reticularis, Zona fasciculata, Zona glomerulosa, in addition to the adrenocortical stem/progenitor area cells scattering from the adrenal capsule through the cortex. All the adrenal gland zones can remodel and expand to adapt the body to the stress or the environmental factors to maintain homeostasis.

Zona Reticularis

This is the innermost layer in the cortex. Its size is about equivalent to adult's zona glomerulosa. The zone reticularis secretes sex steroids, androgens such as **androstenedione**. Cortical androgens have limited functions, but act as precursors for the peripheral conversion into active androgens. **Oestrogens** are secreted also in insignificant amounts. It is involved in the growth and differentiation of the sex organs prior to sexual maturity and after menopause. It seems that this zone has an important functional role because its disruptions lead to defective sexual characteristics (Bullock et al. 1991).

Adrenarche The pubertal maturation of the deepest zone of the adrenal cortex, which is the zona reticularis. The starting of adrenarche happens in the age range of 6–8 years when dehydroepiandrosterone sulphate (DHEAS) levels rise (Witchel et al. 2020).

Functions and Unique Features of Adrenarche Adrenarche, the increase of DHEA and DHEAS at postnatal, the first unique feature in humans and the African

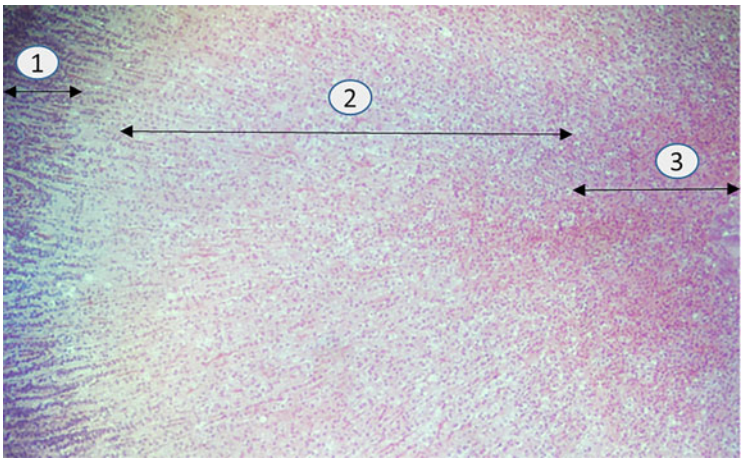


Fig. 7.4 Cross-section of the adrenal cortex showing its three zones: (1) the zona glomerulosa (dark pink) covers a narrow area, (2) middle: the zona fasciculate (pale pink) covers a wide area in the form of extended cords, and (3) the zona reticularis (H&E magnification 100×)

Apes. Humans DHEA has been linked to the growth of the left dorsolateral prefrontal cortex in the age between 4 and 8 years and the right temporoparietal junction in the age between 7 and 12 years. This link between these areas' growth with mentalizing in midst childhood DHEA may have performed an important role in the growth of the human brain. Human zona reticularis emerges at 3–4 years, along with the onset of DHEA/S synthesis. At the time of the weaning that is completed around 2½ years, while peaks of synaptogenesis about 5 years. It may be associated with post-weaning supplying by others (Campbell 2020).

- Despite it being similar to the zona fasciculata, in either in its histology or function but the zona reticularis is considered a distinctive structure because it characterized many unique features that are not present in the other cortex zones. The second individual feature is the comparatively delay in the growth and presence of this zone Adrenarche which points to the maturation of the zona reticularis leading to a rise in adrenal androgens accompanying with characteristics of secondary sexual, for example, the growth of the hair of specific areas in the body such as pubic, axillary, acne, and body odour (Mark et al. 2014; Bhagavan and Chung-Eun 2015).
- The third distinctive feature is its functional regression in adrenopause phase; the late stage of adulthood. The nearly possible cause of the age-linked decline in biosynthesis of adrenal androgen is an age-linked regression in the number of effective reticularis cells, without any main alteration in the differentiated features of the zone cells because of function of age (Endoh et al. 1996). Fourth feature, zona reticularis has a unique function that is the exclusive source of dehydroepiandrosterone sulphate (DHEAS) synthesis in the adulthood, due to the existence

of an enzyme termed a steroid sulfotransferase that links a sulphate to dehydroepiandrosterone (DHEA) (Mark et al. 2014; Bhagavan and Chung-Eun 2015).

- The perplexity of steroidogenesis of adrenal gland has increased with admission of the substitutional 'backdoor pathway' and the 11-oxo-androgens pathways. Classically, process steroids' sulphation such as DHEAS was seen as inefficient metabolites, but intracellular sulphated steroids may act as tissue-specified intracrine hormones particularly in the sources expressing steroid sulphatases like gonads and placenta (Witchel et al. 2020).
- The physiologic mechanisms commanding the onset of adrenarche are very important. The premature adrenarche in kids is a benign change of growth and a diagnosis of exception, those patients head to a higher BMI rate (Witchel et al. 2020).

Zona Fasciculata

This is the middle layer (Fig. 7.4, 2); it is the largest area and produces and secretes the glucocorticoids, the most important of which includes cortisol, cortisone, and corticosterone (Bullock et al. 1991; Burkitt et al. 1996).

Physiological Functions of the Zona Fasciculata Hormones

At physiological levels, glucocorticoids exert beneficial effects on various functions such as daily rhythm, cardiovascular, growth, metabolic, reproduction, and immunological effects. While pharmacological levels show their required curative effect for immune modification through the anti-inflammatory effect on cytokines, suppressing effect of cytokines-induced inflammation, and apoptotic effect on T lymphocytes, but also glucocorticoids lead to various unfavourable side effects, such as elevated susceptibility to contagion, increased weight as a result of increasing appetite, glucose intolerance, raised skin weakness, muscular inactivity, passive calcium equilibrium, and osteoporosis, cataracts, central nervous side effects (McKay and Cidlowski 2003; Ferris and Kahn 2012), exposure to excess glucocorticoid concentrations leads to intense metabolic disturbances of intermediary metabolism leading to abdominal and trunk fatness, insulin resistance and dyslipidemias, disturbance in body fat distribution (Akalestou et al. 2020).

- **Glucocorticoids participate in defining daily rhythm**: It plays a regulatory role in the circadian rhythm for the required metabolic, immunoregulatory, and cognitive daily activities like learning and memory and maintains the immediate response to a stressful stimulator. The hypothalamic-pituitary-adrenal axis plays a very important role in life. The concentration of cortisol in the blood undergoes diurnal variation; it reaches the peak at the early morning about (8:00 am) and falls to the lowest concentrations at midnight to 4:00 am. The retina provides the superchiasmatic nucleus in the hypothalamus with information on the light-dark changes to control the cortisol diurnal cycle (Lockley et al. 2007). The circadian rhythm originates by integrating numerous signals from the expression of clock-linked genes in a 24-h cycle. Most of the biological functions such as cell

proliferation, differentiation, energy storage, and immune and hormonal secretion and regulation are limited—in preference—to specified times. A gating system, controlled by the central and peripheral clocks, regulates the signals and paves for transiting to functions restricted to times in light or night. The variation in cortisol level with its receptor is critical in modifying these signals. Both glucocorticoids and the autonomous nervous system work as a connection between the suprachiasmatic master clock in the brain and all peripheral organ's clocks. This clocks system is promoted by peripheral corresponding functions such as metabolic flow and cytokines that steady this connected network. The pacemaker is magnified by peaks and bottoms in cortisol waves according to some factors including feeding, vigour, and inflammatory condition. So, if the glucocorticoid exposure manner is chronically continued at supraphysiologic levels such as Cushing's syndrome or low level such as adrenal's glucocorticoid insufficiency, this system is unsuccessful (Minnetti et al. 2020). Night-shift work changes the body's exposition to the natural light–dark program and disturbs daily rhythms. The most common example is security guards and their body reaction against stress. A physiological dominance of the vagal tone on the cardiocirculatory efficiency was in night shift. Cortisol concentrations and blood pressure are critical biomarkers for responding to intensive work stress. The outcome of shift-change happens at the end of the night shift since there is a considerable rise in concentrations of the cortisol prior and next the work shifts and an important variance in cardiovascular indices (Cannizzaro et al. 2020).

- **Glucocorticoids regulate many cellular functions** and are essential to facilitate normal physiological functions. Glucocorticoids transport their signal mostly via their intracellular receptors. While glucocorticoid receptors can act through several mechanisms, once linking with these receptors, glucocorticoids regulate the transcription of target genes via genomic glucocorticoid response elements by binding to DNA. These receptors trigger physiological and pathological responses of glucocorticoids (Kuo et al. 2013). The endogenous/internal steroids function on several cell kinds to exert many regulating actions such as gene expression that governs cellular metabolism, development, differentiation as well as apoptosis (Cain and Cidlowski 2015; Grad and Picard 2007). Also, these glucocorticoids act as a vital role in programming of health and disorder (Bolt et al. 2001). The receptor gene and protein of glucocorticoid are exposed to cellular processes, participating in signalling variety to enable glucocorticoid in its physiological and stress-induced concentrations to exert the cell-special functions (Whirledge and Cidlowski 2017).
- **Cortisol supports memory consolidation**: Stress and its stimulant hormonal cascade enhance consolidation of the long-term memory. In a non-stressful positive environment, cortisol also stimulates the memory broadening instead of a narrowing. This impact may be more notable in men (Wiemers and Wolf 2015). Increased level of cortisol benefits memory consolidation. Cortisol also interacts with sleep to support memory consolidation (Bennion et al. 2015). A reduction in adult hippocampal neurogenesis is related to age-linked cognitive diminishing (Schouten et al. 2020). Oscillations of glucocorticoids maintain a

pool of glucocorticoid receptor-expressing neural stem/precursor cells (NSPC) in old age, suppressing their activation, it could be achieved by nongenetic programming. This is a novel mechanism intermediated by glucocorticoids that regulate NSPC proliferation and preserves a quiescent NSPC population that may participate in reservation of neuroplasticity in the ageing brain. Therefore, in ageing, circadian pulsation of glucocorticoid maintains a population of adult neural stem cells of hippocampus in the brain (Fine et al. 2018).

- **Effect of glucocorticoids on Nutrition, metabolism, and cell permeability**: At physiological concentrations, glucocorticoids are vital for most of the homeostatic functions, such as euglycemic level. In human β-cells, corticosterone and cortisol and glucocorticoid's precursor's 11-dehydrocorticosterone (11-DHC) and cortisone inhibit voltage-dependent Ca^{2+} channel actin and Ca^{2+} fluxes. Though, main processes such as insulin release, top ATP/ADP responses to glucose level, and identification of βeta-cell did not change. Also, 11-DHC could be stopped by lipotoxicity accompanied with paracrine regulation of glucocorticoid effect. Glucocorticoids enhance cAMP to promote release of insulin although of disturbed ionic signals (Fine et al. 2018).
- **Carbohydrates**: Glucocorticoids counteract the effect of insulin and lead to hyperglycaemia and non-permeability of cells, especially during exertion. They maintain glucose levels in hunger and fasting situations, store glycogen in the liver to maintain carbohydrate levels, and increase the expression of enzymes needed to produce glucose from non-carbohydrate sources (gluconeogenesis). Glucocorticoids inhibit insulin-induced glucose uptake and employment and synthesis of glycogen. Glucocorticoid also plays a permissive function for catecholamine-stimulated glycogenolysis, to maintain the blood concentration of glucose, the main supply for the brain (Kuo et al. 2013). Extreme glucocorticoid exposure has been found to be a cause of insulin resistance and harmful for pancreatic βeta-cell endocrine functions and insulin production. Such cases lead to let-down of the protecting action of normal level of glucocorticoid that may participate in developing diabetes such as Cushing syndrome, which are associated with dyslipidemia (Bullock et al. 1991; Fine et al. 2018).
- **Proteins**: Glucocorticoids spend important metabolic effect on skeletal muscle. Glucocorticoids enhance protein breakdown and reduce protein synthesis. Then the free amino acids are moved from this skeletal muscle to serve as source for gluconeogenesis in the liver. This metabolic response is vital for surviving the body under stress status, such as fasting, hunger, and other stressors. While excess exposure to glucocorticoids may cause muscle's atrophy (Kuo et al. 2013) by two structures: ubiquitin-proteasome and autophagy lysosome. As glucocorticoids are very essential regulators of energy homeostasis, so in response to stress in case of realized danger or sever inflammation, glucocorticoids are released quickly mobilizing energy from different sources primarily carbohydrate, then fat and protein storage. In inflammation, rallied protein is vital for the quick formation of acute phase of response and an effective immune reaction to contagion. But in adaptive response to infection, chronic mobilization reveals a huge reduction in energy sources. Skeletal muscle is the main store of protein and can be extremely

atrophied under stresses of chronic inflammation. Protein formation is also inhibited at the translational inception, suppressing the synthesis of new myofibrillar protein. Glucocorticoids also prevent the anabolic regulators effect such as insulin further exacerbate the lack of protein and muscle block. The muscle atrophy in the chronic illness is a main feature of weakness and participates basically to morbidity and death rate (Braun and Marks 2015).

- **Fats**: Although the catecholamines and growth hormone facilitate the breakdown of fats into fatty acids, Stimson et al. (2017) revealed that cortisol's acute lipolytic effects require supraphysiological concentrations which are dependent on insulin and adrenaline and is observed in subcutaneous adipose tissue only. Its absence in visceral adipose tissue may contribute to the central accumulation of fat observed with chronic excessive glucocorticoid levels. In some pathological conditions, it causes the redistribution of fat in the body leading to fat deposits in the trunk and face (known as moon face) and at times in the abdomen (Bullock et al. 1991).
- **Exposure to excess glucocorticoid level can lead to obesity** due to increased appetite especially in case of exposing to stress in early life at specific phases of brain growth. As, extreme or chronic stress lead to long-term harmful effects on various physiological functions, because of group of factors that collectively increase appetite and induce dysmetabolism, but hypothalamic-pituitary-adrenal axis dysregulation is a main factor. In those phases; very early life phase, fatal phase and instantly postnatally, exposure to excessive psychosomatic stress like parent loss induce hypothalamic-pituitary-adrenal axis dysregulation, leading to high glucocorticoids level during life which chronically induces appetite for delicious foods and increases deposition of fat (Malik and Spencer 2019).
- **The effects of glucocorticoids could be summarized as below.**
  Glucocorticoids have key functions in responding to stress. There is a weak effect of glucocorticoids in the case of lack of food. In general, they maintain glucose and carbohydrate levels. In this way, the glucocorticoids provide amino acids from the muscles and free fatty acids from adipose tissue for using glucose synthesis. A lack of glucocorticoids causes hypoglycaemia. An increase in glucocorticoid level causes hyperinsulinemia and hyperglycaemia, increases appetite, poor fat distribution, weight gain, reduced protein synthesis, and muscle wasting.
- **Effects of glucocorticoid on reproduction**: In addition to the well-known functions of the sex steroidal hormones receptors in regulating puberty, fertility, growth, and reproductive functions. These processes are also facilitated by the hypothalamic-pituitary-adrenal axis in normal and stress statuses. Glucocorticoid has a permissive or an inhibitory effect in facilitating reproductive accomplishment. Glucocorticoids also control the other parts of the reproductive system. Moreover, in normal condition, homeostatic glucocorticoid signalling has a significant action on fertility and reproduction and on the hypothalamic-pituitary-gonadal axis. While in response to stress, glucocorticoid participates in the known suppression of the hypothalamic-pituitary-gonadal axis via the hypothalamus and pituitary. Certainly, as fundamental regulators of the immune reaction, glucocorticoids have a unique feature to counterbalance the intergradation of

body's contagious, inflammatory, stressors, metabolic, and nutritional condition throughout signalling of glucocorticoid receptor in their target tissues. Endocrine signalling that plays a role between tissues controlling the response to immune and stress and those regulating reproductive status offers positive benefit, accelerating the compromise between reproductive saving and offspring suitability (Whirledge and Cidlowski 2013). Glucocorticoid regulates reproductive function physiologically, under stress and in pathophysiological conditions according to its receptors (Whirledge and Cidlowski 2017). Glucocorticoids decrease response of gonadotrophins to GnRH in men and women. It is established that glucocorticoids, some hormones within the hypothalamic-pituitary-adrenal gland axis, and factors in the sympathetic system modify the axis of hypothalamic-pituitary-gonadal at three levels; at the hypothalamus level, they suppress GnRH release. At the pituitary level, they inhibit it to synthesize and release gonadotropin. At the gonad level, also inhibit synthesize and release of testosterone. Also affect gametogenesis and sexual attitude (Geraghty and Kaufer 2015).

- **Glucocorticoid influences functions of the circulatory and immune systems**: Glucocorticoids play critical role in the normal growth and function of the heart through glucocorticoids receptors signalling. While abnormal levels of glucocorticoids have negative effect on the cardiovascular system (Oakley and Cidlowski 2015). Glucocorticoids increase myocardial contraction and peripheral blood vessel tension as blood vessels respond to the vasoconstrictive hormones. Glucocorticoids inhibit inflammation and allergies through inhibition of the production of leukotrienes and proinflammatory agents. Also, prostaglandins are inhibited because of reduced phospholipase A_2 activity, the main enzyme needed for their production. They also influence the movement and function of white blood cells (WBCs) and reduce vessel permeability, leading to reduced migration of WBCs from the blood vessels. Administration or stress-induced glucocorticoid decreases the total WBCs count, and that of lymphocytes, monocytes, eosinophils, and basophils, while neutrophil count markedly increases. It also leads to atrophy of the thymus and reduced T lymphocytes count, leading to immunosuppression. This effect is used to reduce tissue transplantation rejection. The suppressive effect of glucocorticoids on basophils leads to the inhibition of histamine release, which is used to suppress allergies. Glucocorticoids increase neutrophils in the blood because of bone marrow stimulation but the ability of neutrophils to rotate on the blood vessel walls is reduced (Bullock et al. 1991; Nicolaides et al. 2000; Coutinho and Chapman 2011). Glucocorticoids have effective anti-inflammatory and immunosuppressive effects. Chronic increase of the endogenous glucocorticoid is observed after mental stress and continuous exposure to exogenous therapeutical glucocorticoids. Stimulation of the immunosuppressive transcription factor, in dendritic cells, leads to devastation of cancer treatment-educed anti-neoplastic immune responses, which in turn leads to unsuccessful therapy (Ma et al. 2020). While glucocorticoids have limited effect on red blood cells and haemoglobin (Bullock et al. 1991).

Effect of glucocorticoids on Digestive tract: There are two corticosteroid receptors (glucocorticoid and the mineralocorticoid receptors) which are members of the family of nuclear transactivating factors, the receptors are identified by existing zinc in the focal DNA binding domain, a COOH-terminal domain, and a changing NH2-terminal domain. Additionally, other corticosteroid receptors were detected in the intestine. Two putative corticosteroid receptors were also identified in epithelia of the intestinal, and other two least-affinity receptors in small intestine that are stimulated by corticosteroids and enhance CYP3A gene expression (Sheppard 2002). The CYP3A position contains all the members of the 3A subfamily of the cytochrome P450 genes which encode monooxygenases that stimulate reactions required in the synthesis of lipids, steroids, and lipoprotein (cholesterol) and drugs metabolism (Gellner et al. 2001). These receptors indicate the physiological function corticosteroid exert in the intestines. The intestinal mucosa shows steroidogenic enzymes activity; it synthesizes the glucocorticoid (corticosterone) in response to activation of T lymphocyte which leads to a rise in the expression of the steroidogenic enzymes that are enclosed in the crypts of the intestinal epithelial layer. The locally produced glucocorticoid shows dual effects, a reducing and a co-activating function on intestinal T cell stimulation. Since, in the lack of local intestinal glucocorticoid, administration of anti-CD3 leads to decreased CD69 expression and interferon-γ synthesis by intestinal T lymphocyte, while viral contamination activates T lymphocyte. The intestinal mucosa is an effective source of immunoregulatory glucocorticoid (Cima et al. 2004). In excess level, glucocorticoids increase intestinal secretion and decrease the proliferation of intestinal mucous cells, leading to ulcers during short or long-term cortisone treatment (Bullock et al. 1991). Short-term exposure—up to 28 days—to glucocorticoids is considerably linked with bleeding of peptic ulcer; this is dosage-dependent (Tseng et al. 2015).

- **Glucocorticoid influences the Central Nerve System (CNS)**: Glucocorticoids infiltrate to the target brain cells and connect with two types of internal receptors in the target cells: (1) glucocorticoid receptors expressed in areas such as glial cells and cerebral neurons and (2) mineralocorticoid receptors expressed essentially in limbic brain regions like the hippocampus. Cortisol connects with mineralocorticoid receptors with an affinity reaching ten times higher than those of glucocorticoid's receptors (de Kloet et al. 2016). Normal levels of glucocorticoid help to maintain mood and emotional balance as glucocorticoids act significantly in the homeostasis and the roles of CNS. But long-lasting exposure to high levels of glucocorticoids such as in Cushing's disease is connected with anatomical variations in the brain, elevated occurrence of psychiatric disorders, mental weakness, mood alterations (de Kloet et al. 2016; Bourdeau et al. 2005; Andela et al. 2015; Pivonello et al. 2015; Wolf et al. 2016). High glucocorticoid inhibits random eye movement (REM) sleep. Therapeutic doses cause exhilaration, psychosis, and possibly megalomania and depression. While low concentration, as occurs in Addison's disease leads to

depression, lack of interest and proneness to isolation and loss of temper (Bullock et al. 1991).

- **Glucocorticoid influences on skin**: The interconversion of cortisol and cortisone is catalysed within the endoplasmic reticulum by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD type 1) which is expressed broadly in the liver, adipose tissue, and CNS. In the skin, 11β-HSD type 1 controls adversely the propagation of epidermal cell—which produces keratin—and fibroblasts and heals dermal injury. So, 11β-HSD type 1 is a novel regulator for skin homeostasis, tissue repair, and treating of skin disease (Terao et al. 2011). Additionally, 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD), the enzyme that catalyses the conversion of inactive cortisone/11-dehydrocorticosterone into its active form cortisol/corticosterone in cells, has multiple functions in many organs, including the skin. These include cell proliferation, wound healing, inflammation (Wintermantel et al. 2005). Thus, endogenous glucocorticoids facilitate cellular function, while under stress it leads to the formation of anti-fibre progenitor cells and keratin cells, in addition to reducing wound healing. 11 beta-HSD type 1 is expressed in normal healthy skin in epidermis and dermal fibroblasts, while 11 beta-HSD type 2 is expressed in sweat glands. Weakness of skin glucocorticoidogenesis locally via harmful stimuli, like UVB, clarifies pathophysiology of some skin disorders such as rosacea. Plus, melanocytes keratinocytes and fibroblasts, dermal adnexus additionally act as an important role as sources and targets for glucocorticoids, since they express many glucocorticoidogenic enzymes. Glucocorticoid also contributes to the pathogenesis of pit wounds, producing sebum. Some enzymes required for steroidogenesis are upregulated in acne lesions such as 11β-hydroxysteroid dehydrogenase (Nikolakis and Zouboulis 2014).
- **Glucocorticoid effects on Breast**: Glucocorticoid is necessary for the mammary gland epithelium (Bullock et al. 1991). Several glucocorticoid receptor activities play significant role in mammary gland growth and lactation, in virgin females, the deficiency in the DNA binding function of glucocorticoid receptor weakens the development of ducts in the mammary gland, and this may be attributed to the reduction in proliferation of epithelial cells. Dissimilarity, lactating women have normally differentiated mammary glands and are completely eligible for milk protein synthesis by different molecular modes of action (Reichardt et al. 2001). Also, the epithelial glucocorticoid receptor is involved in the natural timing of cell propagation over the growth of lobuloalveolar of mammary gland but is unessential for milk formation (Wintermantel et al. 2005). Breastmilk differs from serum, as cortisone is extremely abundant than cortisol levels, because of the expression of 11β-HSD type 2 in the mammary glands (Smith et al. 1996). Breastmilk's glucocorticoids (cortisol and cortisone) exhibit a daily rhythm related to the activities of motherly hypothalamic-pituitary-adrenal axis, this influences the offspring's evolution and neurodevelopment. As there are elevated levels in the early morning, then decrease to the lowest bottom at night-time (Van der Voorn et al. 2016; Pundir et al. 2017). Also, there is no direct correlation between glucocorticoids and macronutrients (fat, protein, and carbohydrates) in human's

breastmilk (Hollanders et al. 2019). Glucocorticoids signalling plays as actors in the breast cancer (McNamara et al. 2018). Since elevation of stress hormones in the progress of breast cancer activates the glucocorticoid receptor at remote metastatic places, increases colonization, heterogeneity and metastasis, and decreases survival. The ablation of ROR1 (tyrosine-protein kinase transmembrane receptor) decreases metastatic evolution and extends survival in experimental animals (Obradović et al. 2019). Interaction of glucocorticoid receptors signalling in triple-negative breast cancer with androgen receptors signalling is the cause of glucocorticoid induced cell migration in those patients (Kanai et al. 2020).

- **Function of glucocorticoids on the lung**: In human, throughout the last prenatal phase of fatal lung growth, the synthesis of surfactant is vital for decreasing surface tension of alveoli's air-liquid boundary. In early gestation, the glucocorticoid receptor is expressed in lung of the fatal, to stimulate the synthesis of surfactant-related proteins A, D, or C that are expressed in fatal tissue and increase phospholipid production by activating phosphatidylcholine. Glucocorticoid also increases cellular growth and differentiation, antioxidant enzymes, reduces synthesis of DNA, alters constituents of interstitial tissue, and regulates metabolism of pulmonic fluid. The therapeutic effect of antenatal glucocorticoid is complemental one. Glucocorticoid is effective in treating the chronic lung disorders of prematurity, it regulates the inflammatory reaction via interface with transcription factors. Dexamethasone therapy decreases proinflammatory cells and chemokines and cytokines concentrations in bronchoalveolar liquid. Conversely, excessive or repetitive doses of corticosteroids for treating foetuses and preterm new-borns may lead to significant long-standing side effects including vital organs such as growth of brain and lung (Bolt et al. 2001; Hallman 2013). Among acute respiratory distress syndrome cases, glucocorticoids therapy is accompanied with a noteworthy decrease in mortality and period of mechanical ventilation, away from hospital-acquired infection possibility (Zayed et al. 2020), but in patients with severe virus-related pneumonia, corticosteroid administration is extremely debated (Yang et al. 2020). Although glucocorticoids are commonly used for treating multiple respiratory inflammatory disorders, they are regularly associated with important contrary effects. In COVID-19 pandemic happened in 2020, glucocorticoid treatment had decreased fever period but not mortality. The systemic glucocorticoid treatment extended the period of hospitalization in all patients with COVID-19, SARS and MERS led to hospital infections for influenza and late in viral clearance (Yang et al. 2020).
- **Glucocorticoids counter many hormones**: Increased concentrations of glucocorticoids lead to reduced synthesis and secretion of the thyroid hormones. It reduces the activity or response of gonadotrophins in men and women (Bullock et al. 1991). Glucocorticoid has anti-insulin effect, reduces the secretion of growth hormone (Ferris and Kahn 2012; Akalestou et al. 2020).
- **Glucocorticoids reduce growth, bones, and muscles**: High level of glucocorticoids reduces the secretion of growth hormone from the pituitary and therefore body growth is reduced. Increased levels slow down growth in children

and analyse proteins. The anti-insulin effect leads to a substantial reduction in anabolic processes in the body. Reduce bone deposition, which weakens bone synthesis and leads to osteoporosis which results from an increase in glucocorticoids. The mechanism of reducing bone formation is through inhibiting increases in RNA, collagen, and hyaluronate (Bullock et al. 1991; Mandel 1982). Normal concentration of corticosteroids is essential for muscle physiology but change in glucocorticoid or mineralocorticoid concentration leads to myopathy (Mandel 1982). Elevated glucocorticoid concentration results in muscle weakening because of its catabolic action on protein metabolism. While corticosteroid deficiency results in reduced capacity of striated muscle's function, faintness, and exhaustion. This response is attributed to an insufficiency of the circulation system instead of disproportions of electrolyte and carbohydrate. In case of long-lasting administration of glucocorticoid, it induces osteoporosis, a severe warning risk in steroids therapy, glucocorticoid mediate its effects through: (1) Suppresses bone remodelling by straightforwardly moderating functions of bones cells (osteoclast, osteoblast, and osteocyte), (2) elevates calcium elimination from kidney, and (3) reduces calcium absorption by intestinal membrane, leading to reduction in calcium in the circulation which stimulates parathyroid hormone and its sensitivity. PTH stimulates osteoclast function. There are other side effects for high therapeutics doses of glucocorticoids on the musculoskeletal system such as aseptic (Richards et al. 1980), avascular necrosis of bone (Chan-Lam et al. 1994), and tendon split which probably through changes in metabolism of collagen (David et al. 1970; Patschan et al. 2001). While recently Liu et al. (2020) prepared gel comprised of sialic acid-modulated dexamethasone lipid calcium phosphate essence nanoparticles to treat acute kidney damage. In addition to the improving effect of the nanoparticles gel on the kidney function, it reduced the proinflammatory and regulated the oxidative stress elements and apoptotic proteins. Furthermore, they noticed that there were slight side effects on mineral mass of the bone and glucose concentration in the circulation.

- **Effect of glucocorticoids on water and minerals**: Glucocorticoids help in excretion of water, reduce calcium reabsorption from the kidney and intestines, and reduce the absorption of phosphates and magnesium from the intestines. However, treatment with cortisone leads to the retention of water and minerals in the body. Glucocorticoids link to particular sites in cellular membrane stimulating drive alterations of electrolytes (Suyemitsu and Terayama 1975; Avanzino et al. 1987). The hypothalamic-pituitary-adrenal axis is essential in regulating body fluid homeostasis, glucocorticoids act their centric actions on neurohormones of the posterior pituitary (oxytocin and vasopressin) in response to severe and chronic variations of plasma osmolality and volume. Glucocorticoids do not only contribute to rapid secretion but also in the transcriptional steps resulting in reduced production of these neurohormones according to different changes of fluid tonicity and volume (Ruginsk et al. 2009). Glucocorticoids invert a dilute hyponatremia through suppressing the route of vasopressin receptor in rats suffering from heart failure (Zhu et al. 2020).

Zona Glomerulosa

This is the outer layer (Fig. 7.4), which synthesizes and secretes the mineralocorticoids: A**ldosterone and 11-deoxycorticosterone**. Aldosterone is the major hormone of the adrenal cortex. Cortisol also plays a vital role as a mineralocorticoid but its activity is low in the kidneys because it is broken down there. As discussed above, glomerulosa does not include the enzyme 17 alpha-hydroxylase, pregnenolone the only compound that could be transformed into progesterone through multiple steps including 3-beta-dehydrogenase; 21-hydroxylase induces conversion to 11-deoxycorticosterone; 11-beta-hydroxylase stimulates transformation to corticosterone. Then, aldosterone synthase, which exists in the glomerulosa zona only and is controlled by angiotensin II, transforms corticosterone to aldosterone (Dutt et al. 2020). Mineralocorticoids are steroid hormones characterized by **s**hort half-life of 15–20 min. Up to 50% mineralocorticoids are in the free form in the plasma and bind weakly to globulin. These steroids are secreted at a rate of 50–250 μg/day when the required sodium level is available (Bullock et al. 2001).

Main Functions of Aldosterone

- **Circadian rhythm**: Nikolaeva et al. (2012) reported that time-dependent changes in plasma aldosterone levels were clear in wild mice. To understand the contribution of adrenal hormones particularly aldosterone to the circadian rhythm, it is important to know that the molecular clock that works in the suprachiasmatic nucleus of the brain is the central clock, but there is a peripheral clock in liver. These two clocks work together to coordinate rhythmic fluctuations in behaviour and metabolism. Other molecular clocks are present in peripheral tissues including the kidney (Gumz 2016). The molecular clock acts as a master controller of gene expression.
- **Homeostasis**: Aldosterone is targeted by the kidney to control mineral homeostasis, a very important function. The hormone acts by regulating electrolytes, particularly sodium and potassium exchange. In the blood and extracellular fluid, aldosterone reabsorbs sodium and potassium and eliminates chloride and potassium from the distal renal tubules. This requires reabsorption of water for dissolution of the minerals in it to maintain the volume of body fluids.
- **Aldosterone** facilitates entry of sodium via the Na^+/K^+-ATPase pump into the cell; therefore, both aldosterone essentially as well as antidiuretic hormone as needed work synergistically to maintain the volume of water in the body.
- **Cardiomyocytes**: Mineralocorticoid signal targets its receptor in cardiomyocytes and plays roles in the development and progression of cardiac disease (Oakley and Cidlowski 2015).

Regulation of Aldosterone Secretion

- The hypothalamic-pituitary-adrenal axis regulates the blood aldosterone levels. CRH is produced by the hypothalamus, and ACTH is produced by the pituitary gland (Fig. 7.5).
- The renin-angiotensin system in the kidneys regulates the circulation level of aldosterone.

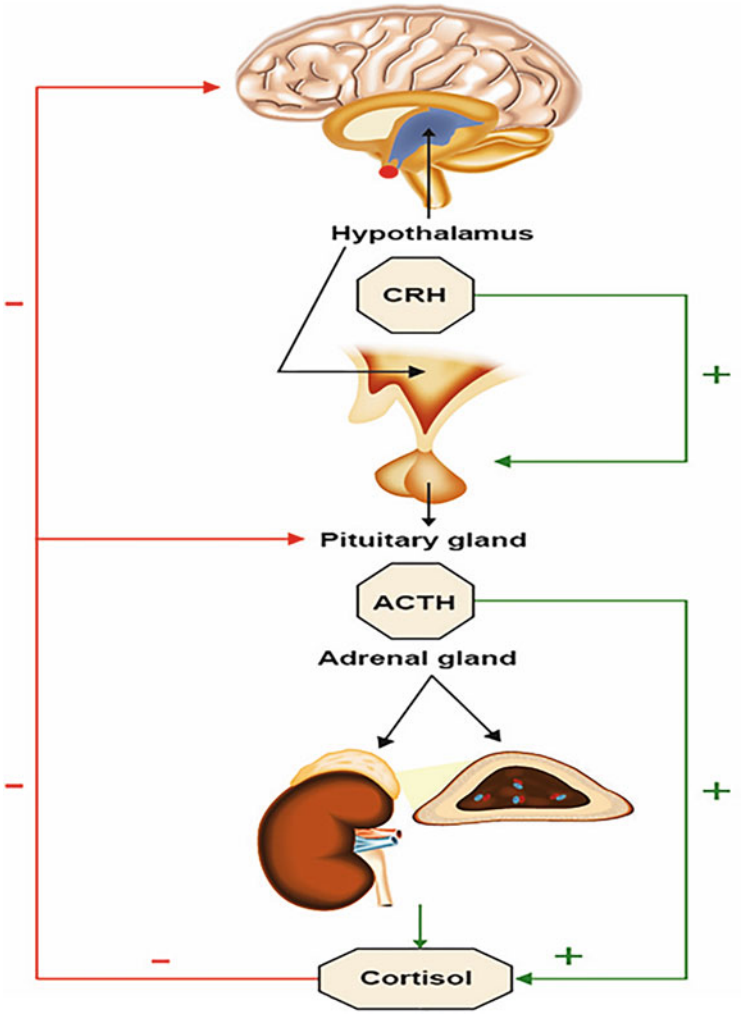


Fig. 7.5 Mechanisms of secretion of the adrenal cortex hormones through (the hypothalamus-pituitary-adrenal gland axis)

- Some dopamine receptors control blood pressure by affecting renal function and releasing some mineral regulators such as renin, aldosterone, and vasopressin.
- Mineral levels in the plasma, especially ionic sodium and potassium levels influence the release of aldosterone.

Regulation of the Total Adrenal Cortex

- CRH is released by the hypothalamus and stimulates ACTH production by the pituitary. This induces the adrenal cortex to produce and secrete its hormones, this is called the hypothalamic-pituitary-adrenal (HPA) axis.

- Negative feedback: Cortisol is the only hormone among the corticoids that can stimulate the pituitary short-axis effect on ACTH secretion and stimulation of the hypothalamus long-axis effect on CRH secretion, which increases the level of glucocorticoids in the blood; the reverse is also true (Fig. 7.5).
- HPA axis. It plays a regulatory role in the circadian rhythm through the pulsatile rate of cortisol secretion during the day cycle. Pulsed secretion and circadian rhythm of ACTH influences glucocorticoids levels. CRH and ACTH release occurs as bursts model, the rate of the bursts forms the circadian rhythm (diurnal cycle of the hormones) in related to sleep-wake and light-dark cycles in human. This daily cycle of CRH and ACTH and stress-induced release of these hormones are activated by serotonin released from the brain. Therefore, serotonin-antagonist drugs inhibit rhythmic ACTH release. Then ACTH influences the glucocorticoids release.
- Activation of acetylcholine secreting neurons stimulates the basic and stress-induced release of ACTH from the pituitary, the mechanism happens through muscarinic and nicotinic receptors on CRH neurosecretory cells in the hypothalamus, therefore stimulates ACTH secretion.
- Activation of adrenaline and noradrenaline-secreting neurons inhibits CRH secretion, via their action on β adrenergic receptors on CRH neurosecretory cells in the hypothalamus and then inhibits ACTH release from pituitary. But, under stress conditions, adrenaline and noradrenaline may stimulate the pituitary directly to release ACTH by stimulating α and β adrenergic receptors on the corticotrophs in the pituitary.
- Dopamine also inhibits CRH release from the hypothalamus.
- Stress has a stimulatory effect on the response of the hypothalamus-pituitary-cortex axis. Such as exposure to pain, trauma, psychological factors, surgical burns, acute suffocation, temperature triggers, hypoglycemia, bleeding, and exercise.
- A significant hypermetabolic response follows extensive burn injury that lasts up to 2 years after the burn. It includes many-fold increase in plasma catecholamines, cortisol, and glucagon which lead to the entire body catabolism and higher resting energy expenditure.
- Adrenocortical stem/progenitor cell populations: play a critical role in the adrenal homeostasis and self-renewal. Adrenal gland cortical cells of different zones are continuously differentiating and renewed. These functions are regulated by multiple endocrine and paracrine signals including ACTH, angiotensin II, LH, insulin-related growth hormones, inhibin, and activin. Zonation and regeneration of adrenal cortex are also regulated by developmental signalling pathways, such as fibroblast growth factor and others (Pihlajoki et al. 2015; Lerario et al. 2017; Bullock et al. 1991, 2001; Bennett and Whitehead 1983; Williams and Herndon 2017).
- Electronic waste (e-waste) related metal such as chromium (Cr) and nickel (Ni) in the blood circulation link positively with the hormones (CRH, ACTH, and cortisol) and with two biomarkers of oxidative stress (malondialdehyde and 8-isoprostane). So, exposure to elevated levels of Cr and Ni—as in e-waste

reprocessing places—induces oxidative injury in e-waste individuals. The regulating effect of HPA axis plays the significant function throughout this route (Li et al. 2020).

Disorders of the adrenal cortex may lead to some disturbances in the corticoids blood levels. Increased secretion causes Cushing's syndrome in which the patient suffers rapid weight gain and poor fat distribution in the body, with a change in facial features (moon face), a tendency to develop osteoporosis and several psychological symptoms (Bullock et al. 1991). This is because of increasing use of cortisol levels (Debono and Newell-Price 2016). While lack of secretion of this hormone leads to Addison's syndrome which manifests as several symptoms of varying degrees of severity such as weakness, fatigue, dizziness, vomiting, loss of weight, patchy skin pigmentation, digestive tract disorders, low blood pressure, and difficulty in concentrating. Hyperaldosteronism is an increase in aldosterone blood levels. Congenital adrenal hyperplasia is a group of autosomal disorders that result from lack of pathway of steroidogenesis enzymes in the adrenal gland which leads to reduction in biosynthesis of cortisol (El-Maouche et al. 2017).

7.3.3.4 Adrenal Stem Cells: Stress-Inducible Stem Cells in Adrenal Glands

The adrenal gland as known is a multi-endocrine gland with three layers steroidogenic mesenchymal cortex and an inner catecholamines-producing medulla originated from neuroendocrine source. After embryonic development, this plastic organ suffers from physiological postnatal remodelling. Clarifying these complicated developments is essential to know the basics of functional endocrine syndromes and tumours disturbing the mature gland (Poli et al. 2019). Figure 7.6 shows the sites of adrenal stem cells.

The stem cells sites and function intruduced breifly in the bigninig of this chapter in Sect. 7.3.1. In this section, stem cell role in front of stress will be discussed. Humaneness is permanatly face stressors leading to adaptation response. Since the adrenal gland plays an essential function in this response to physiological confront. Thus, keeping of the adrenal partly requires adult progenitors and stem cells in the cortex and medulla that proliferate and differentiate in response to the stress. A subpopulation of adrenocortical progenitors is characterized and interconnected as a response to adrenomedullary stress which activate and mobilize adrenocortical progenitors producing steroidogenic cells. Furthermore, there is a synchronized action of stress-inducible stem (adrenomedullary stress-dependent progenitors) that leads to tissue remodelling and adaptation of cells and functions to stress. These cells have emerging effects in disease related to endocrine, metabolism, and psychological status (Bornstein et al. 2018). The adrenal glan plays a role in the continuous replacement of senescent cells by recently differentiated cells. An extraordinary capacity of plasticity showed by the adrenal is important to maintain homeostasis in response to multiple physiological requests. This comes from the proliferation and differentiation steps of progenitors of adult adrenal. A nestin pool of adrenocortical progenitors that placed beneath the adrenal capsule and distributed through the

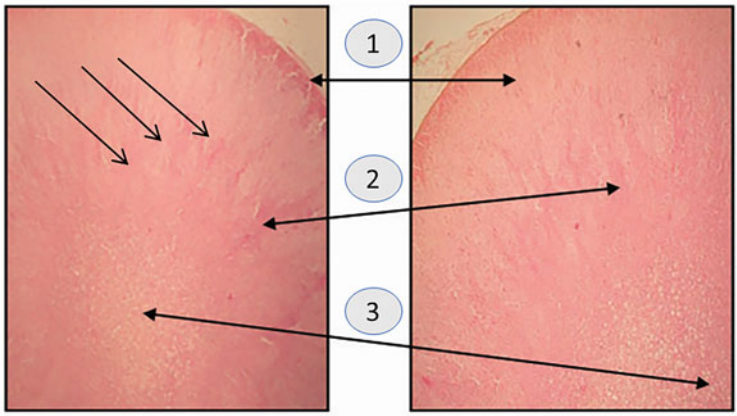


Fig. 7.6 Cross-section of the adrenal cortex shows (small arrows) the possible sites of adrenal stem cells. (1) The zona glomerulosa (dark pink) covers a narrow area, (2) middle: the zona fasciculate (pale pink) covers a wide area in the form of extended cords, and (3) the zona reticularis, H&E magnification 100×

adrenal cortex zone, in addition, these cells interrelated with medulla's progenitors. In regular status this pool is not active and migrates gently and centrally, while in stress, the migration is activated signifacntly, and the cells differentiate into mature cells: glucocorticoid and mineralocorticoid-secreting cells. Nestin cells play a role in the adrenal gland homeostasis and highlighting their action under stressors which made them a potential home for cell substitute for treating adrenal deficiency (Steenblock et al. 2017; Bornstein et al. 2020). Stress factor influences stem and progenitor cells which leads to a new mechanism which impacts the newly formed stem cell in the initial stage of postnatal embryogenesis. It may cause diseases in adults. Stress inhibits the negative impact on stem and progenitor cells that can delay the onset of disease and improve the health. Stress-induced lack of stem cells of melanocyte is not related to immune aggression or stress by adrenal gland hormones. But, hair greysh colour is a result of the effect of sympathetic nerves that innervate the niche of melanocyte stem cell. The stimulation of sympathetic effect leads to outbreak secretion of the noradrenaline leading to rapid change in quiescent melanocyte stem cells in term susequets events including proliferation, differentiation, migration, and constant defcincy from the niche. Stress-induced hair greying could be prevented by transitory reduction of those events in melanocyte stem cells. Neurotransmitter effect stimulated by acute stress can lead to a quick and permanent lack of somatic stem cells; it shows an example that the sustenance of somatic stem cells is immediately affected by the whole physiological status of the live body (Zhang et al. 2020).

7.4 Pineal Gland

This is a small neuroendocrine gland which is present on upper area of the diencephalon in the brain as one of the circumventricular organs. These organs are generally characterized by being well vascularized with permeable capillaries; they contain neural tissue because some of them function as secretory bodies like the pineal gland and therefore need neuroendocrine connections. It produces an important hormone, melatonin (Brown 1994). Melatonin is used as a marker of circadian phase in human. The timing of the endogenous melatonin rhythm is the most trustworthy marker of hypothalamic suprachiasmatic nuclei clock timing. It is used to estimate and provide information on circadian phase in humans (Johnston and Skene 2015).

7.4.1 Pineal Size and Cellular Structure

The pineal gland, also known as *pineal body*, is attached to the posterior side of the third ventricle by a short stem containing sympathetic neural axes that penetrate the gland tissue and connect with the hypothalamus. Its size decreases at puberty. It measures 5 × 10 × 8 mm, and weighs 120 mg, its weight varies based on seasonal variations. It is surrounded by a capsule (Fig. 7.7) which penetrates it in the form of septa (Volkova and Milovidova 1980). Its tissue consists of several types of cells (Fig. 7.8). There are variations in the form, size, and ultrastructural of the cellular components of the pineal (Volkova and Milovidova 1980).

- **Pinealocytes**, the majority of which are called **Chief cells**. These are modified neural cells in the form of capillary-rich cords or clusters. In both children and adults, the pinealocytes are categorized into light and dark pinealocytes based on shape, cytoplasmic contents, staining density, and infolding of the nucleus (Fig. 7.8). The number of light pinealocytes (round or oval cell shape) exceeds the dark pinealocytes that vary in the shape and pigmented cytoplasm (Al-Hussain 2006).
- **Neuroglial cells** which are similar to the nervous system's astrocytes found inside the chief cell clusters (Kaur and Ling 2017).
- **Interstitial cells**: A very small cell category with slim and elongated shape contains packed vacuoles with flocculent content and increase of probable secretion in the extracellular space (Al-Hussain 2006). The interstitial cell is a non-neuronal cyte similar to the astrocyte, dark stained, and has small nucleus. It is located round blood vessels and between collections of pinealocytes to backing the pineal gland.
- **Perivascular phagocytes**: immune cells are located adjacent to the rich blood vessels existing in the pineal. These perivascular phagocytes are acting as antigen presenting cells. Moreover, these cells also include MHC class II, the recognition protein that usually present on the immune cells (Møller et al. 2006).

Fig. 7.7 Cross-section of the pineal gland showing the capsule enveloping the pineal tissue (H&E magnification 100×)

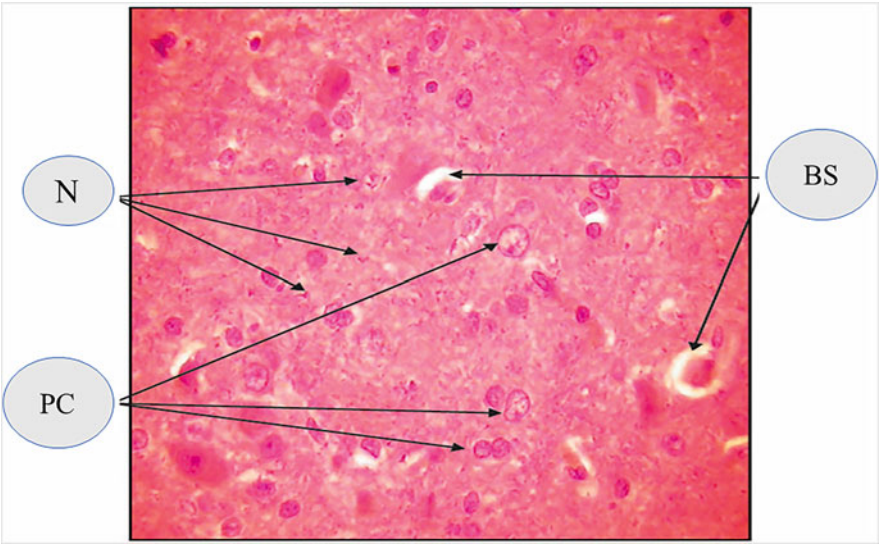


Fig. 7.8 Cross-section of a calcified pineal gland showing the multi-nuclear poorly stained cytoplasm, pineal chief cells (PC) neuroglia (N) and pineal brain sand (BS) H&E magnification 100×)

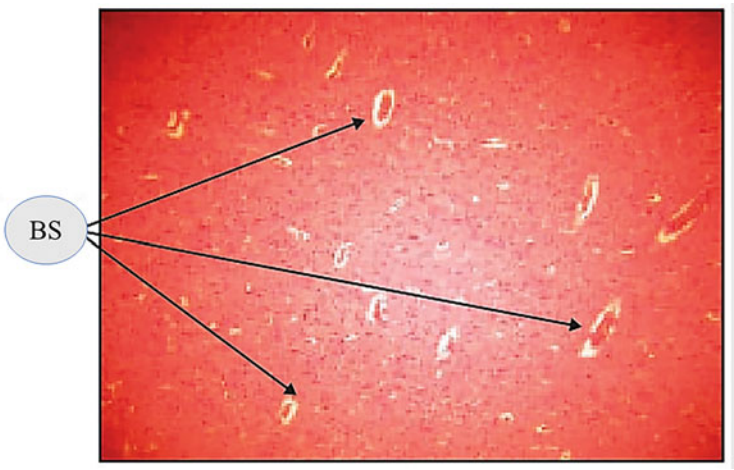


Fig. 7.9 Cross-section of a calcified pineal gland showing the pineal tissue and pineal brain sand (BS) H&E magnification 100×

- **Pineal brain sands**: In old age, the pineal gland is characterized by the presence of pineal brain sand which is a non-cellular calcified concretions basophilic body which forms due to the deposition of calcium and magnesium phosphates (Figs. 7.8, 7.9, and 7.10). Sands are unique biomineral constructions (Sergina et al. 2018).

7.4.2 Pineal Gland Hormones

The most important of these hormones is melatonin, it is a neuroendocrine peptide hormone. Another group of hormones is secreted from the pineal like serotonin, many polypeptides and indoles.

7.4.3 Melatonin Synthesis

Melatonin is a methoxyindole (*N*-acetyl-5-methoxytryptamine) an amino-acid derived hormone synthesized from tryptophan. The melatonin synthesizing pathway has specific properties such as photosensitivity and diurnal rhythmicity. It secreted at night. The body collects tryptophan during the daylight hours with the help of special receptors especially on the retina. At night, it is converted via several steps into serotonin, a precursor of melatonin; the highest concentration is at night when melatonin is secreted into the blood and cerebrospinal fluid. Its release adapts to night length as light can either inhibit or orchestrate melatonin synthesis based on the program of light (Claustrat and Leston 2015).

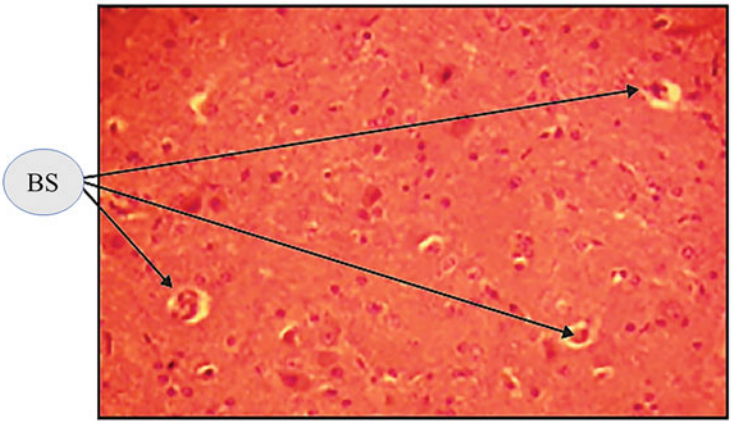


Fig. 7.10 Cross-section of a calcified pineal gland showing the pineal tissue and pineal brain sand. Dark and light cell are present (H&E magnification 400×)

7.4.4 Pineal Gland Functions and the Physiological Roles of Melatonin

- **Pineal gland regulates the circadian rhythm**: The pineal gland adjusts the function of many endocrine glands. The main physiological function of melatonin is to transfer information of the daily cycle of day and night to body systems to organize the functions that respond to photoperiod alteration which includes the cyclic rhythms. Daily melatonin is secreted as a night signal to organize, stabilize, and support combination circadian rhythms such as core temperature, sleep-wake rhythms. This organization for other physiological functions like, antioxidant, immunity, glucose, and haemostasis depends on the melatonin signal. But there is variance between physiological and therapeutically effects of melatonin based on dose, the controlling system of melatonin release is complicated as it is based on central and autonomic signal pathways. So, their disturbance exerts many patho-physiological disorders. Melatonin receptors show a very widespread distribution in the organs which made supposed therapeutic signs of this hormone is various (Smolensky et al. 2016). The endogenous daily rhythm of melatonin has a role in the synchrony's maintenance between circadian clocks throughout the body in adult. Melatonin acts as an endocrine daily, seasonal calendar. The daily melatonin signal symbolizes endogenous circadian time and also encodes seasonal information (Brown 1994). In addition to the brain and suprachiasmatic nuclei of the hypothalamus, melatonin produced by mammalian (Brown 1994) and the human pineal gland provides additional circadian pacemaker effects at night (Smolensky et al. 2016). Melatonin participates clearly in human circadian rhythm. Thus, its disruption, as well as that of other circadian pacemakers is considered a novel clinical view for disease pathology and treatment plans. Along with the glucocorticoids, melatonin regulates chronobiological/daily rhythm as a

function of daylight and light/dark transition. So, melatonin is a major factor for chronobiological research studies.

- **Melatonin could be estimated as a marker** of circadian phase in several biomaterials, directly such as plasma and saliva samples, or indirect method in urine sample as a metabolite, 6-sulphatoxymelatonin (Skene and Arendt 2006). Melatonin is least influenced by activity, sleep, rest, meals, and exertion when compared with body temperature and cortisol hormone rhythms. Melatonin is recommended to be investigated as a biomarker for different disorders in different ages.
- Melatonin regulates sleep and waking. It has a therapeutic effect in the treatment of disorders that associate with biological rhythm disturbances such as sleep trouble (Srinivasan 1989). Many of blind individuals could not realize the light, so they suffer constant circadian desynchrony via a failure of providing light information to the hypothalamus's circadian clock, leading to periodic occurrence of poor sleep and disorder in daytime. Daily treatment with melatonin is a hopeful therapeutic plan; it leads to daily alternation synchronizing "time plexus", but it needs more investigation (Lockley et al. 2007).
- **Melatonin has a physiological relationship with puberty** in both sexes. In females, during the puberty phase, either intermediate decreases in melatonin levels or a decrease in melatonin peak may be considered as an indicator of pubertal progression (Crowley et al. 2012).
- **Melatonin has different role on reproduction**: In males, melatonin has essential functions on testicular physiology, steroidogenesis, and spermatogenesis. In Leydig cells, melatonin functions locally as a modulator for endocrine functions. In sertoli cells, melatonin impacts cells growth and proliferation, the oxidation state and energy metabolism. In patients who have idiopathic infertility, melatonin hormone has antiproliferative and anti-inflammatory properties on macrophages, and a protective role against oxidative stress in mast cells in the testis. Melatonin has local action in testis' somatic cells (Frungieri et al. 2017). Pineal gland hormone successfully protects spermatogonia from chemotherapy and oxidation stress and shows the base molecular action, which will help in fertility protection clinically. The mechanism by which melatonin saves spermatogonia from apoptosis is neutralization of reactive oxidative species (ROS) induced by the chemotherapy (busulfan) and retrieved the phosphorylation of ATM and p53 to regular normal concentration, which avoid apoptosis in progenitor cells of spermatogonia (Zhang et al. 2019). Serotonin secreted by the pineal gland reduces the activity of the sex hormones because it inhibits the production of GnRH which inhibits the production and secretion of anterior pituitary gonadotropins, and these, in turn, inhibit the gonads and reproductive function. It has a lipophilic feature, enabling it to cross the placenta and regulate perinatal physiology (Johnston and Skene 2015).
- **Melatonin and corticosteroids participate in responding to the stress** of food **depletion**. Physiological adaptation to variable conditions of food availability is not only visible at the behavioural level, but also at endocrine system/hormonal level. So, melatonin, adrenal corticosteroids, adipokines (leptin/ghrelin), insulin/

glucagon, orexins and T4, T3 which display rhythmic profiles of release in ad libitum feeding status are sensitive to raise and/or reduction in energy stock. Also, they are influenced when food sources become limited or unobtainable at usual times (Gesmundo et al. 2017). Melatonin exhibits insulinotropic or insulinostatic effects (Hyder et al. 2017).

- **Melatonin protects against heat stress** which enable living subjects to perform their functions physiologically (Hyder et al. 2017). It has many physiological effects, including free radical detoxification, antioxidant, participation in bone formation, regulation of body mass index, immune, and cardiovascular systems (Tordjman et al. 2017). Melatonin protects against cardiac microvascular ischemia/reperfusion injury in mice (Zhou et al. 2017). Detoxification of free radicals is one of the functions of melatonin, thus it protects key molecules from the hurtful properties of oxidative stress happened in some cases such as ischemia/reperfusion injury. This could be exerted via the receptor-independent effects of melatonin (Reiter et al. 2014).
- **Melatonin hormone has promtional effect on Central Nerve System**: It has neuroprotective actions. Melatonin is also known to have counteractive effects. For example, it alleviates experimentally the symptoms of Parkinson's disease, and this may be due to its effect on sodium and potassium balance in the brain (Sharma et al. 2007). Melatonin prevents memory impairment induced by consuming high-fat diet (HFD) in rats, by preventing changes of oxidative stress in the hippocampus in the brain, as melatonin prevents HFD-induced suppression in glutathione concentrations and ratio of glutathione (GSH)/reduced glutathione (GSSG), and rise in GSSG. Melatonin also prevents decrease in the catalase activity in hippocampus of HFD animals (Alzoubi et al. 2018). It encourages propagation of neural stem cells (NSCs) in hyperglycaemia via the extracellular controlled protein kinases path. Additionally, it acts as a direct free radical scavenger, melatonin reduced apoptosis of NSCs in to hyperglycaemia. So, in diabetic gestation, melatonin treatment might act as a key role in protection of neural malformations (Liu et al. 2015). Thus, melatonin plays a comprehensive leading role in NSCs for its propagation, differentiation, and endurance. Therefore, its roles can be modified by several factors such as neurotrophic, transcription factor, apoptotic genes, MAPK/ERK signalling pathway, and histone acetylation (Chu et al. 2016).
- **Melatonin is used in stem cell-based therapy**: It plays a significant function in regulating stem cells either its physiological or pathological functions. Melatonin promotes cell propagation, immigration, and differentiation. Thus, melatonin cooperates with stem cell transplantation revealing favourable therapeutically application potency in neurodegenerative illness, osteoporosis, liver cirrhosis, myocardial infarction, kidney ischemia and wounds injury (Zhou et al. 2017), etc. These curing effects of melatonin are done through its unique properties such as antioxidant, anti-inflammatory, antiapoptotic, and anti-ageing effects Melatonin with mesenchymal stem cells plays a critical for treating liver cancer in a mode of functional integrity (Elmahallawy et al. 2020). Melatonin is a promising tool but therapeutic and protective effects need to be assessed in future studies.

7.4.5 Regulation of Melatonin Secretion

The hormone level increases during dark hours, and melatonin levels depend on daylight length. During daylight hours melatonin levels fall and serotonin levels increase, while the opposite occurs during the hours of darkness. Melatonin production is controlled by the sympathetic system and the hypothalamic-pituitary-adrenal axis. The secretion of norepinephrine from the sympathetic nerves which innervate the pineal gland is affected by light previously perceived by the retina. It was observed that hypoglycaemia leads to increased secretion of melatonin. While the physiological function of melatonin decreases with age.

7.4.6 Stem Cell/Progenitors in Pineal Gland

About 16% of entirely cloneable pineal cells are multipotent precursors. The foetal pineal could be looked as an ideal multipotent structure (Watanabe et al. 1988). The embryonic growth of the pineal gland is still unknowable, while the pineal progenitors derive from the side margin of the frontal neural laminate. In zebrafish, the pineal progenitors initiate, partially from the non-neural ectoderm. The non-neural original source of the pineal gland uncovers an essential resemblance in the creation of both pineal and pituitary glands. Each of CNS neuroendocrine organs might demand a non-neural involvement for neurosecretory cells formation (Staudt et al. 2019).

7.5 Conclusion

In addition to the essential functions of the gland's cortex and medulla regions, the adrenal can act antagonistically to enable melatonin from the pineal gland to protect against heat. To adjust the body homeostasis and to harmonize the activities to day-night cycles (24 h), the biologic clock system has been developed that regulates physiological functions in a circadian manner. Stress system is quietly associated with the circadian clock's system, adrenal corticoids, and catecholamines contribute significantly in this clock system. Any disturbance in circadian rhythm may lead to functional disorders, the matter which draws the attention of scientists to consider circadian rhythm disturbance in general as a basis for disease and treatment plan. Occupational stress can provoke a disruption in homeostasis that the body should adapt through the triggering two systems, the first one is the hypothalamic-pituitary-adrenal cortex axis, and the second one is sympathetic nervous system. The utmost impact of the duty shifts is the disturbance of circadian rhythms. The chapter described the admirable coordination between the adrenal and pineal glands, location, structure, adrenocortical stem/progenitor cells. The adrenal medulla, productions of the adrenal medulla, regulation of catecholamines secretion, physiological functions of catecholamines, and adrenomedullin. Hormones of adrenal cortex have physiological characteristics. The three adrenal cortex zones, Zona

glomerulosa, Zona fasciculata, Zona reticularis) briefed with detailed physiological functions of the zona fasciculata hormones with regulation of the adrenal cortex. Description about the neuroendocrine gland known as Pineal gland is provided along with Pineal size and structural features, Pineal gland hormones group, melatonin synthesis, regulation of melatonin secretion, Pineal gland functions, and the physiological roles of melatonin are discussed. Recent information on pineal and adrenocortical stem/progenitor cells were indicated including localization in the adrenal capsule, subcapsular region, juxtamedullary region, or between the zona glomerulosa and the zona fasciculata as well as their functions. All the adrenal zones can remodel and expand to adapt the body to the stress or the environmental factors to maintain homeostasis. Glucocorticoid concentration and melatonin with other factors act in modulating the clock-related tasks.

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Endocrine Pancreas and Glucose Metabolism

8

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Abstract

Pancreas gland located in the upper abdomen region plays two important roles as digestive exocrine gland and hormones releasing endocrine gland. Exocrine gland composed of tiny masses called "acini" secretes enzymes for digestion. Pancreatic islets (Langerhans) as clusters or islets are responsible for important hormones secretion such as peptide hormone insulin, somatostatin, glucagon, and pancreatic polypeptide. Dysfunction in pancreatic islet leads to metabolic disorders including diabetes mellitus. The cells of pancreatic islets (α, β and δ cells) involve in the physiological and metabolic functions of insulin, correlation between immunity/insulin imbalances, cardiovascular functions. The α cells make up 20–25% of pancreatic islet cells in humans whereas β cells comprise

60–80% of islet cells in humans and mammals and δ cells comprise approximately 3–5% of islet cells. In addition, pancreas also contains polypeptide cells which are known as pancreatic polypeptide cells and these make up around 5% of pancreatic islet cells. Physiological and pathological conditions of different pancreatic hormones are also discussed in great details with suitable examples. Pancreatic progenitor or stem cells are found in rodents that β cell's self-renewal, they form new β cells promoted by other pancreatic cells such as non β islet cells, duct cells, and acinar cells. In addition to extra pancreatic cells like neural, liver and stem or progenitor cells. In humans also, β cell neogenesis from non- β cells origin of β cell self-renewal as particularly in adulthood, restricted beta cell self-renewal happens. This chapter discusses topics related to endocrine pancreas and glucose metabolism.

Keywords

Endocrine pancreas · Pancreatic hormones · Pancreatic physiology · Diseases and glucose metabolism

Abbreviations

Ca^{2+}	Ionized calcium
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
DM	Diabetes mellitus
GHIH	Growth hormone-inhibiting hormone
GLUT-1	Glucose transporter-1
GLUT-2	Glucose transporter-2
GLUT-3	Glucose transporter-3
GLUT-4	Glucose transporter-4
H&E	Hematoxylin and eosin stain
hiPSC	Human-induced pluripotent stem cell
IDE	Insulin-degrading enzyme
MSC	Mesenchymal stem cells
Na^+/K^+ ATPase	Sodium-potassium adenosine triphosphatase
NPY	Neuropeptide Y
NPY4	Neuropeptide Y receptor type 4
PDI	Protein disulfide isomerase
PP	Pancreatic polypeptide
PTH	Parathyroid hormone
PYY	Peptide YY
RNA	Ribonucleic acid

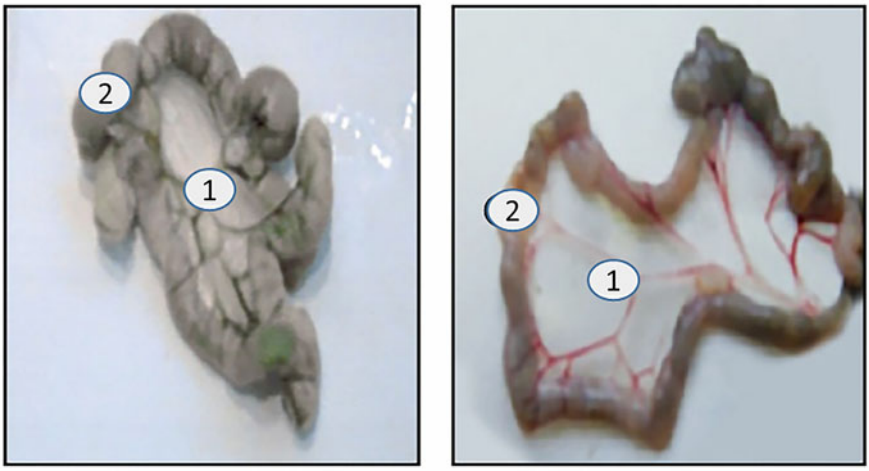


Fig. 8.1 It shows the location of the pancreas (1) between the two bends of the duodenum (2) in mammals

8.1 Introduction

Pancreas gland located in the upper abdomen region plays two important roles as digestive exocrine gland and hormones releasing endocrine gland. Exocrine gland composed of tiny masses called "acini" secretes enzymes for digestion. Pancreatic islets (Langerhans) as clusters or islets are responsible for important hormones secretion such as peptide hormone insulin, somatostatin, glucagon, and pancreatic polypeptide. Dysfunction in pancreatic islet leads to metabolic disorders including diabetes mellitus. The chapter details the cells of pancreatic islets (α, β, and δ cells), physiological and metabolic functions of insulin, correlation between immunity/insulin imbalance, cardiovascular functions with insulin imbalance, β cells role in producing insulin. In particular, secretory vesicles of beta cells secretions, insulin components, glucose transporters, carbohydrate metabolism in liver, muscle tissues, adipose tissue and protein metabolism in liver and muscle, Fat metabolism in muscles and adipose tissue were explained. Factors influencing the insulin secretion, pathological conditions (obesity) analyzed along with regulation of glucagon secretion and physiological functions of glucagon and somatostatin. The sources, receptors of pancreatic polypeptide hormone, discussed with pancreatic progenitor/stem cells.

The pancreas is a long gland located between the two bends of the duodenum, and is pale red in color (Fig. 8.1). It is a mixed gland as it consists of:

- Acini as the pancreas is a partly exocrine gland responsible for the secretion of pancreatic juices that are transported to the intestines via the pancreatic duct.

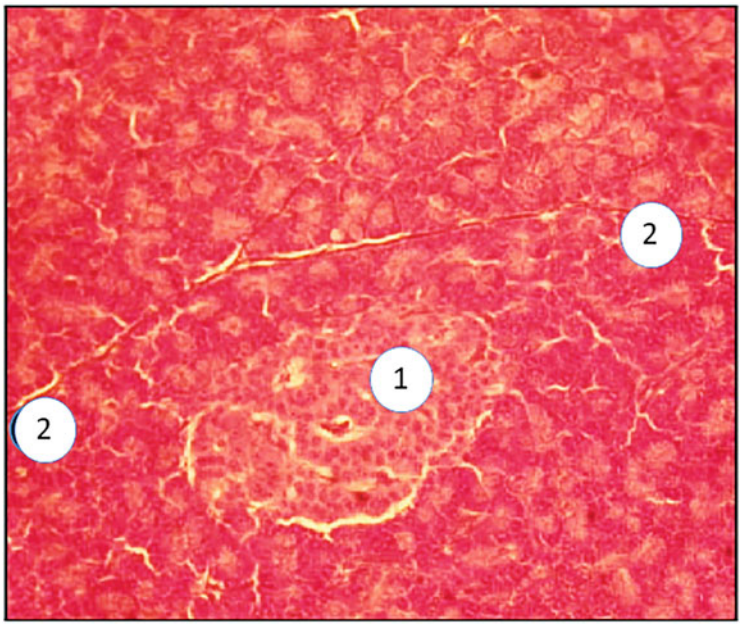


Fig. 8.2 Cross-section of the mammalian pancreas showing the pancreatic islets (1) as a partly endocrine gland and the exocrine acini (2) H&E magnification 200×

- Pancreas islets which are responsible for endocrine secretion (hormones) and are arranged in the form of clusters or islets in the pancreatic tissue (Fig. 8.2). The islets are lighter in color than the acini.

The pancreas islets are an extremely important endocrine gland, and any defects in its hormone secretion or receptors lead to complex metabolic disorders, the most serious of which is diabetes mellitus.

8.2 Structure of Pancreatic Islets

The pancreas contains tens of thousands of islets whose sizes are less than 1 mm. These islets comprise 1–2% of the total pancreatic tissue, which weighs approximately 2 g in adults. These islets are much vascularized and the blood supply to the islets is about ten times higher than that reaching the ductal or exocrine part. In addition, the flow of blood which transports hormones in the endocrine portion of the pancreas enables the hormones to act via paracrine signals (between the islet cells). For example, the beta cells produce insulin which inhibits the secretion of glucagon by alpha cells. Also, somatostatin secreted from delta cells inhibits glucagon secretion from the alpha cells. Moreover, the hormonal secretions of the pancreatic islets are released directly into the bloodstream (endocrine signals) and affect target tissues

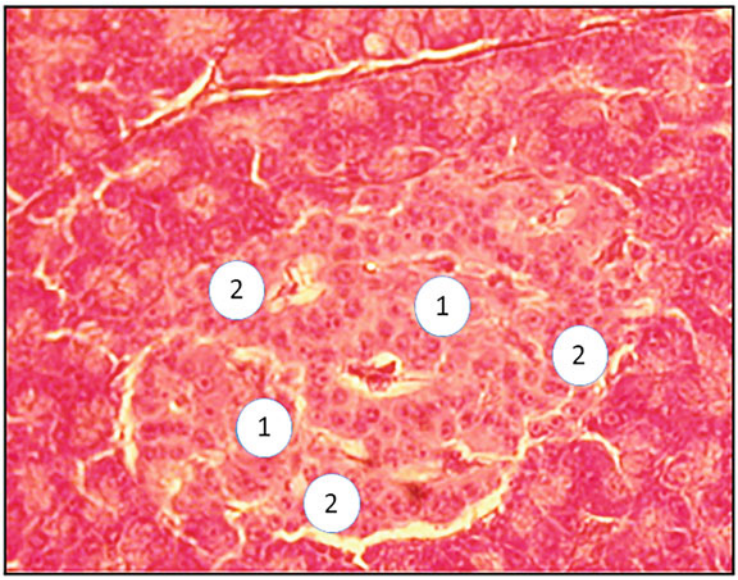


Fig. 8.3 Cross-section of a pancreatic islet showing (1) the location of β cells (insulin-secreting cells) at the center and (2) the location of a cells (glucagon secreting cells) at the periphery. H&E magnification 200×

in various parts of the body. The hormonal secretions do not pass through the pancreatic ducts at all.

Alpha Cells (α Cells) These make up 20–25% of pancreatic islet cells in humans. The alpha cells often have a peripheral position in the islets and secrete the hormone glucagon (Fig. 8.3). In birds, they occur in the form of separate or mixed islets; they are larger in size as birds have a greater need for glucagon and higher glucose requirements for energy production.

Beta Cells (β Cells) These comprise 60–80% of islet cells in humans and mammals, but there are fewer of them in birds. Beta cells are found in a central position in the pancreatic islets and secrete the hormone insulin (Fig. 8.3). In humans and other animals, the sustainment of normal glucose homeostasis, is performed by the release of insulin from pancreatic β cells. It has been reported that defective insulin secretion is responsible for all forms of diabetes mellitus, as the destruction/damaging of β cells is accountable for Type 1 diabetes, and a decrease in β cell population and loss of secretory function of insulin is implicated in Type 2 diabetes (Rutter et al. 2015).

Delta Cells (δ Cells) These comprise approximately 3–5% of islet cells and secrete somatostatin. This hormone is also secreted from the hypothalamus, as mentioned in Chap. 4. It has been reported that δ-cells contain ATP-sensitive potassium channels

normally open when glucose level is low, and it closes when the glucose level is increased. This process caused membrane depolarization and electrical activity, and which caused for an increased in the secretion of somatostatin (Rorsman and Huising 2018).

Pancreatic Polypeptide Cells These make up around 5% of pancreatic islet cells and secrete pancreatic polypeptide (Burkitt et al. 1996; Guyton 1986). The pancreatic polypeptide is 36-amino acid peptide, and this peptide is a significant feedback inhibitor of pancreatic secretion after a meal. It originates from both islet and acinar cells of the pancreas (Lonovics et al. 1981).

8.3 Pancreatic Innervation

The pancreatic islets have a sympathetic nerve supply which secretes catecholamines which stimulate alpha cells and inhibit beta cells, in addition to a parasympathetic nerve supply which secretes acetylcholine to stimulate beta cells when glucose levels are high. Glucagon and insulin secretion from islet cells are controlled by the intracellular glucose signaling pathway, in addition to being indirectly regulated through the autonomic nervous system that splendidly innervates the pancreatic gland (Thorens 2014). The physiological activity of the pancreatic islet cells can be seen from the microscopic structure of the tissue (active—medium activity—low activity) as shown in Figs. 8.4, 8.5, 8.6, and 8.7.

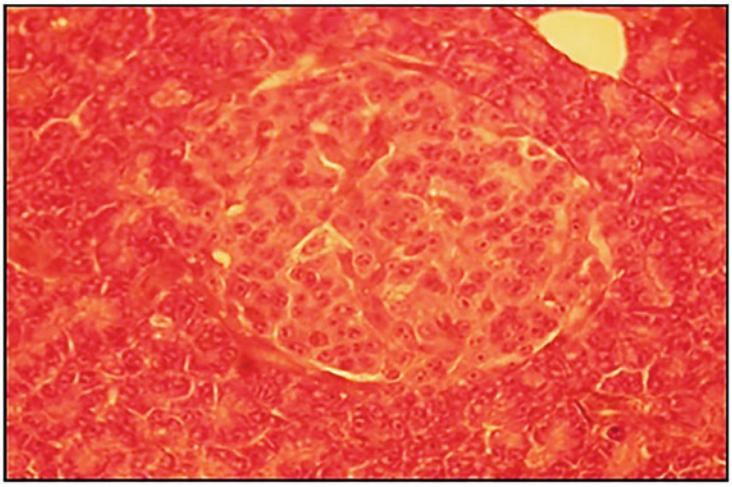


Fig. 8.4 Cross-section of the pancreas showing inactive islet cells in terms of secretion; they are filled with the secretion which can be seen from the more intense cytoplasmic staining with the absence of lacunae. H&E magnification 200×

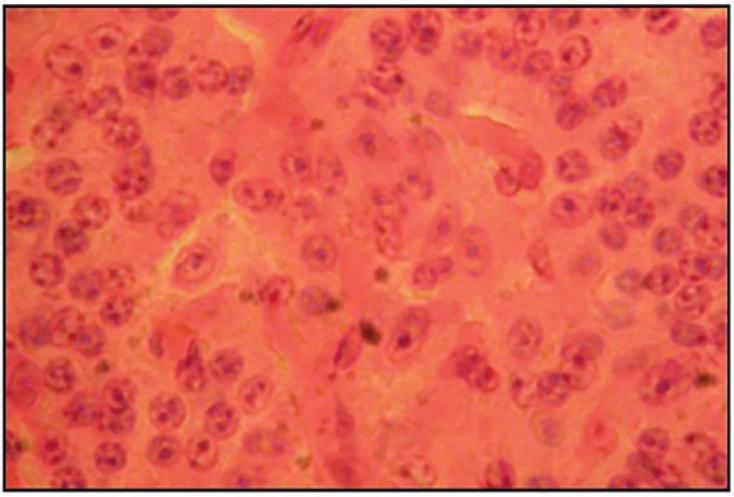


Fig. 8.5 Inactive islet cells in terms of secretion. They are filled with the secretion; this can be seen from the more intense cytoplasmic staining with the absence of lacunae (magnified). H&E magnification 400×

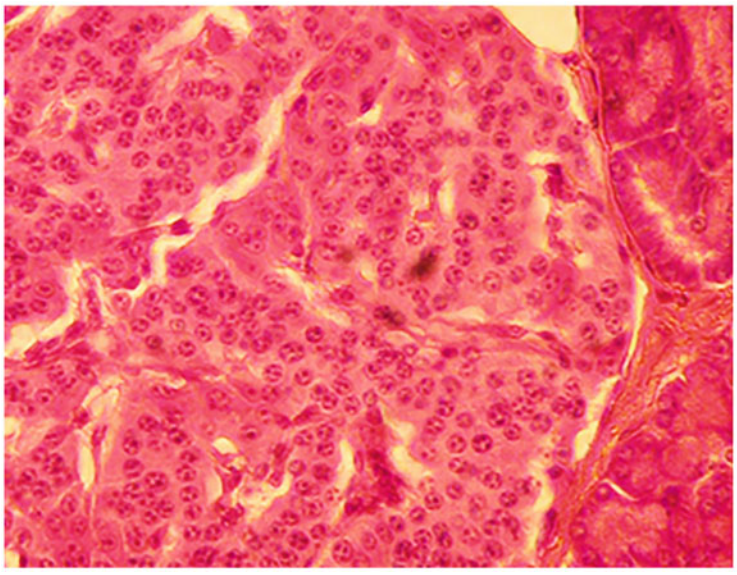


Fig. 8.6 Cross-section of the pancreas showing some islet cells with low activity which have released some of their secretions, as shown by the presence of several lacunae in the cytoplasm. H&E magnification 400×

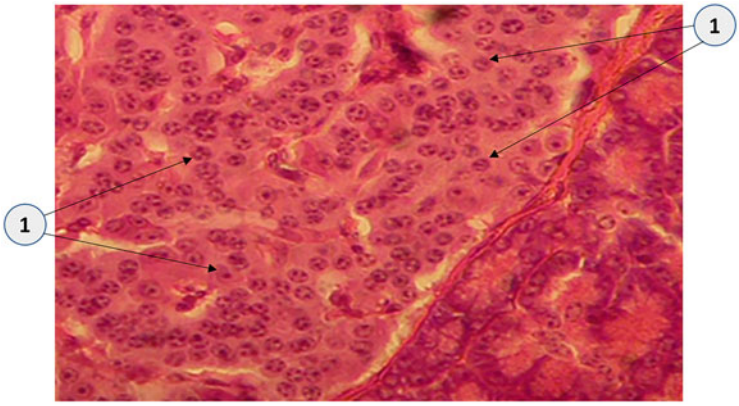


Fig. 8.7 Cross-section of the pancreas showing some islet cells with low activity (1) which have released some of their secretions, as shown by the presence of several lacunae in the cytoplasm H&E magnification 400×

8.4 Beta Cell Hormones

The most important hormone secreted by the beta cells is the polypeptide—insulin

- After a stimulatory signal reaches the beta cells, the nucleus sends the messenger RNA responsible for its production to the ribosomes to initiate the steps leading to the formation of **preproinsulin** in the endoplasmic reticulum of beta cells with molecules includes (A-chain, B-chain), and signal sequence.
- The signal sequence is detached from the amine-terminus of the peptide by the signal peptidase, and parting proinsulin.
- **Proinsulin** is a polypeptide of 86 amino acids synthesizes in the beta cells, as prohormone (precursor) of insulin. Proinsulin consisting of three chains of peptides A, B, and C.
- In Golgi apparatus, proinsulin is further cleaved to form insulin, packaged and produced into vesicles.
- The connecting C domain **(C-peptide)** of proinsulin molecule is detached by a specialized group of enzymes activity, which acts within the mature secretory granules.
- Once the C-peptide is removed, it leaves the A-chain bounds with B-chain by disulfide bonds forming the insulin molecule.
- The complete hormone, **insulin**, is then stored in specialized secretory vesicles as microcrystalline arrays of (zinc insulin hexamers) for secretion into the bloodstream.
- Proinsulin is secreted into the bloodstream and is less active than insulin. Its half-life is four times that of insulin because it is only broken down in the kidneys and is not eliminated by the liver.

- There is another pancreatic hormone like ghrelin (Weiss et al. 2000; Guyton and Hall 2016).

8.4.1 Insulin and C-Peptide

A polypeptide of 31 amino acids, it binds A-chain of insulin with its B-chain in the proinsulin molecule. It is produced during the conversion of proinsulin to insulin. It has a half-life of up to four times that of insulin because it is only eliminated by the kidneys and not the liver. The secretory vesicles of beta cells which are ready to release their secretions contain equal quantities of insulin, C-peptide as well as a small amount of proinsulin, which means that not all the proinsulin is converted to insulin (Bullock et al. 1991, 2001; Guyton 1986; Guyton and Hall 2006, 2016; Cohen et al. 1979).

Functions of C-Peptides

- The C-peptide of proinsulin is very vital for synthesis of insulin, however it was thought that it is biologically inefficient. Later, it is indicated that it has many important physiological functions.
- C-peptide in the nanomolar concentrations range targets cell membrane and binds a G protein-coupled surface receptor, then stimulates Ca (2+)-dependent intracellular signals.
- There is no cross reaction with proinsulin, insulin, insulin growth factors I and II (formerly called somatomedins), or neuropeptide Y.
- C-peptide activates the enzymes such as Na-K ATPase and endothelial nitric oxide *synthase.* Both enzymes have several physiological functions.
- C-peptide is produced in equimolar amount to endogenous insulin but is secreted at a steadier rate through a longer time.
- There are potential uses and applications of c-peptide in clinical practice.
- Diabetes mellitus type 1 patients who don't produce insulin will commonly have significantly reduced concentrations of C-peptides.
- C-peptide administration accompanies with increased blood flow in skin and skeletal muscle, decreased glomerular hyper filtration and reduced albumin excretion in the urine.
- It improved the activity of nerve in type 1 diabetic patients who have insufficient C-peptide, but not in healthy ones.
- Replacement of C-peptide with administration of insulin in type 1 diabetes, may prohibit the progress of long-term complications.
- C-peptide is exceedingly used as an estimation of pancreatic beta cell functions.
- Its estimation includes urine and serum samples. Recent assay detects concentrations of c-peptide could be used as a guide for diagnosis and management of diabetes. But glucagon stimulation c-peptide assay has balance of practicality and sensitivity. C-peptide concentrations are linked with diabetes mellitus (DM) types and its duration. So, a c-peptide concentration lesser than 0.2 nmol/l is associated with a diagnosis of DM type 1. C-peptide concentration

may correlate also with micro- and macro-vascular complications, and the future use of insulin treatment (Guyton and Hall 2016; Wahren et al. 2000; Leighton et al. 2017).

Insulin

- Insulin is a 51 residue (amino acids) anabolic polypeptide. Insulin comprises two polypeptide chains linked by two disulfide bonds. It is produced by the beta cells.
- Insulin circulates in the bloodstream in an unbound form, because it has half-life in the circulation ranges 3–6 min and mainly cleared from the blood circulation within 10–15 min except that amount of insulin that binds with its receptors in the target cells.
- Insulin differs from the other molecules secreted by the beta cells in that half-life of it, as it is degraded mostly in the liver and to a lesser degree in the kidneys and muscles. The degradation is done by the enzyme *insulinase.*
- The rapid degradation, removal, and clearance of insulin from the plasma is important because at time, its importance to speedily turn off the regulation function of insulin as it is to turn them on.

Baseline Insulin Secretion and Concentration The beta cells secrete a baseline insulin level into the bloodstream of normal individuals at a concentration of 0.4 ng/ml (10 μU/ml) when the normal glucose level is 80–100 mg/dl. The insulin level starts to rise 8 min after eating a meal and peaks at 45 min, in which case it can reach a concentration of 100 μU/ml in normal individuals. After this, it returns to its normal baseline level within 90–120 min. Insulin has been produced in vitro from the bacteria *Escherichia coli* in sufficient amounts for use to compensate for insulin deficiency in humans.

8.4.2 Physiological and Metabolic Functions of Insulin

Glucose Metabolism The normal glucose level in the blood is 75–100 mg/100 ml. The most common of the pancreatic islet disorder is diabetes mellitus, which occurs due to destruction of β cells, and consequently, leads to insufficient insulin secretion, or as a result of deficient insulin activity or resistance as is the case with obesity. This leads to higher than normal glucose levels which results in hyperglycemia and glucose in the urine along with a host of metabolic symptoms. Chronic lack of regulation gives rise to many complications including kidney and retinal disorders, a weak immune system, and so on. Diabetes happens when pancreatic β cells fail to produce and secrete sufficient insulin to maintain glucose homeostasis. It also occurs as a result of insulin resistance.

Type 2 diabetes mellitus is a metabolic disease triggered by the dedifferentiation of pancreatic β cells. In vitro, a high glucose environment mimics hyperglycemia in vivo and beta cells grown in this medium over a prolonged period undergo dedifferentiation (Neelankal John et al. 2017). On the other hand, excessive insulin secretion or hyper-insulinism leads to hypoglycemia, followed by loss of

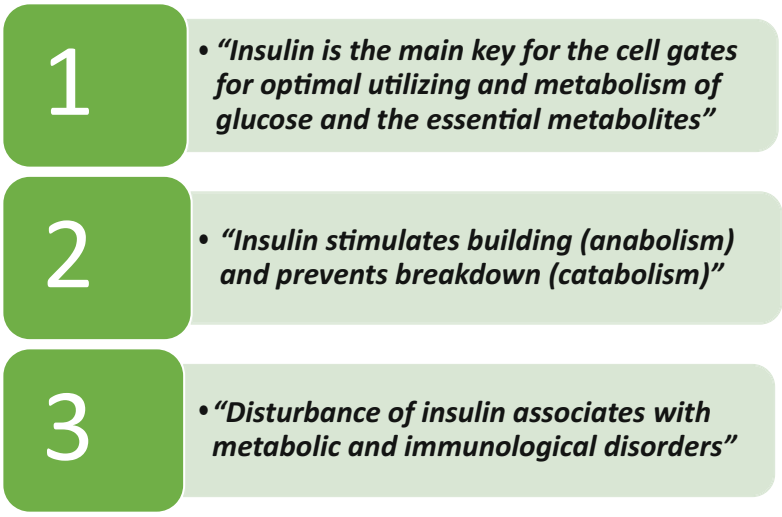


Fig. 8.8 Three main principles of insulin effects

consciousness due to lack of glucose needed for the brain and energy production. Insulin basically acts in the main metabolic organs which are the liver, muscles, adipose tissue and other organs via endocrine signals. It is also involved in metabolic regulation based on three main principles Fig. 8.8.

8.4.3 Glucose Transporters

- It should be noted that the brain only uses glucose for energy production because the membranes of its cells are permeable to hydrophilic substances such as glucose. This is why glucose in the circulation must be regulated within levels above the critical value, because levels below 50–60 mg/100 ml of blood lead to loss of consciousness from hypoglycemia.
- Entry of glucose into the tissues of the brain, liver, red blood cells, and epithelial cells of the intestines and kidneys is independent of insulin, but insulin supports this process in the liver.
- All cell membranes require glucose transporters as they comprise a lipid bilayer.
- The kidneys and intestines use active transport via the sodium pump. But other cells use passive diffusion from higher to lower concentrations.

There are 13 forms of glucose transporters, some of which are dependent on insulin, while others do not. The four most important of these are:

- **GLUT-1**: This has a very high affinity for glucose and is used to transport glucose even at low concentrations as is the case with the baseline level. It is found in

most cells and is very important for the blood–brain barrier to ensure moderate glucose transport to the central nervous system.

- **GLUT-2**: It has very little affinity for glucose. It seems that it transports glucose in cases where glucose concentration is high. It is the main transporter of glucose to the liver cells, intestinal epithelium and kidneys because glucose enters these tissues when its concentration is high. Additionally, this characteristic of GLUT-2 reduces glucose uptake by the liver when its concentration is low, for example during fasting.
- **GLUT-3**: It has a very high affinity for glucose and is also found in all tissues. It is the main transporter of glucose to the surface of nerve cells.
- **GLUT-4**: This is found in the main insulin-sensitive organs (the muscles and adipose tissue) and only functions as a glucose transporter for these tissues once it receives a signal from insulin leading to the transfer of GLUT-4 to cell membrane to facilitate the entry of glucose into these tissues which store glucose after a meal (Gardner and Shoback 2007).

The Relation Between Immunity and Insulin Imbalance The innate immune system is impaired in diabetes mellitus, which is considered the main reason for infections as there is an inhibitory effect on many molecular immune signals and pathways, Hansen et al. (2017) reported that the endothelial barrier reduces its functions clearly in response to hyperglycemia which leads to disease. Many molecular findings confirmed that biological or physical barriers, protein function, specific immunity, and inflammatory pathways are subjected to risk by hyperglycemia, and that hyperglycemic effects alone should be taken in consideration as risk factors for different human diseases. For examples:

- Glucose levels and insulin sensitivity may be controlled by activating the immunity to gut macrobiotic interface (Pomié et al. 2016).
- Also, in experimentally diabetic rats, probiotics restore immune and gut macrophage activities (Maciel et al. 2016).
- Macrophages have specific receptors to insulin which make hyperglycemia a cause of impaired macrophage activity and immunity.

Effect of Insulin Imbalance on Cardiovascular Performance There is a different regulation in cardiac function, immunity and intracardiac (cytokines[1]) by (rapamycin[2]) in healthy and diabetic rats (Luck et al. 2017).

[1] Cytokines are diverse groups of biochemical secretions by immune and adipocyte cells.

[2] Rapamycin is a macrolide compound could be gotten from *Streptomyces hygroscopicus*.

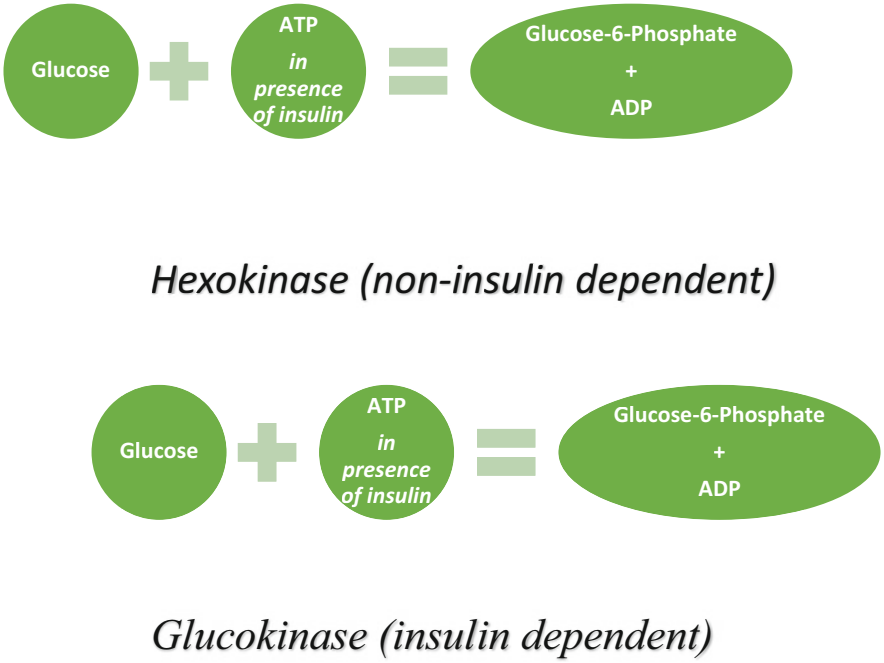


Fig. 8.9 The main reactions for glucose oxidation by the enzymes Hexokinase (without insulin) and Glucokinase (with insulin)

8.4.4 Carbohydrate Metabolism

8.4.4.1 Carbohydrate Metabolism in the Liver

Insulin supports the production of glycogen and stores up to 110 g of it. Glucose uptake by the liver takes place easily and without limitation because the liver is very permeable to glucose even without insulin, although the presence of insulin increases the efficiency of the process. These processes require the oxidation of monosaccharides such as glucose to glucose-6-phosphate in order to retain phosphorylated glucose in the cell and prevent it from diffusing out of the cell. This process as showed Fig. 8.9 involves two enzymes:

- Hexokinase (non-insulin dependent).
- Glucokinase (insulin dependent).
- Insulin stimulates the enzyme phosphofructokinase needed for the second step after glucose phosphorylation, as well as the enzyme glycogen synthetase responsible for crystallization of monosaccharide molecules into glycogen complex, Fig. 8.10.
- Insulin inhibits the glycogen breakdown and glucose production from it.

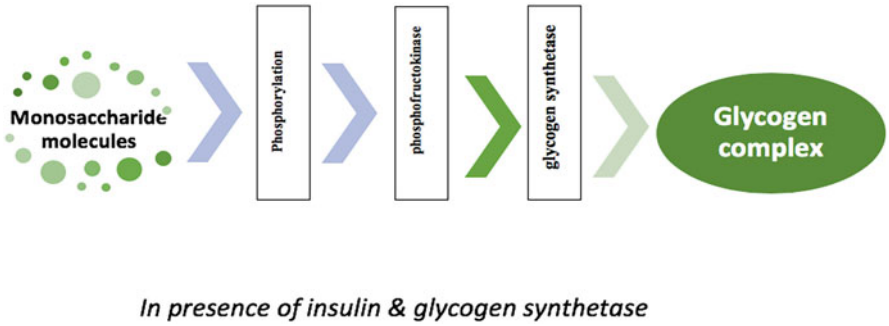


Fig. 8.10 Insulin stimulates the enzyme phosphofructokinase for the second step after glucose phosphorylation, then the enzyme glycogen synthetase for crystallization of monosaccharide molecules into glycogen complex

- Insulin inhibits (*Gluconeogenesis*) glucose production from any other non-carbohydrate sources by suppressing the quantity and activity of the liver enzymes required for the process.
- Insulin stimulates conversion of exceed glucose into fatty acids which are packaged later as triglycerides in the form of very low-density lipoproteins to be brought by the circulation to the adipose tissue and stored as fat.

8.4.4.2 Carbohydrate Metabolism in the Muscle Tissues

- Glucose is transported by passive diffusion into the skeletal and cardiac muscle cells with the help of insulin.
- Insulin also boosts the consumption of glucose by muscles. It increases intracellular glucose concentration in muscle cells. In the absence of insulin, the intracellular glucose concentration may decrease significantly although high extracellular glucose concentrations.
- Insulin boosts the production of glycogen in the muscles by stimulating the enzymes needed for its production. The amount of glycogen stored in the muscles is about 500–600 g in a person weighing 70 kg. Glucose is stored as muscle glycogen reached a limit of 2–3% concentration to be used later for energy for short period of severe exercise, and also for anaerobic energy by glycolytic breakdown of the glycogen to lactic acid even in the absence of oxygen. Muscle glycogen can only be used slightly as a glucose source.
- The need for insulin for glucose transport in the muscles is different in the case of rest compared to physical exertion situations.

8.4.4.3 Carbohydrate Metabolism in Adipose Tissue

Insulin is the principal stimulatory factor for glucose uptake by adipose tissue and is vital for the synthesis of *α-glycerophosphate*, the substance needed for the esterification of free fatty acids and whose absence prevents esterification and leads to the release of free fatty acids from fat cells.

8.4.5 Protein Metabolism

8.4.5.1 Protein Metabolism in the Liver

Insulin is a protein-building hormone in the liver. Liver plays a significant role in glucose, lipid homeostasis and detoxification. It has been found that disruption of glucose or lipid metabolism in the liver is a major feature in the development of type 2 diabetes. In addition, the main distinctive of these metabolic diseases is the buildup of extra lipid, which is recognized as fatty liver (Nagarajan et al. 2017).

8.4.5.2 Protein Metabolism in Muscle Tissue

- Insulin is **protein-building** in the muscles as it boosts the entry of amino acids into the cells, stimulates their joining together and the synthesis of proteins in the cells. When insulin is absent, amino acids in the blood increase.
- At the same time, insulin is an anti-catabolic hormone as it prevents protein oxidation and breakdown.

8.4.6 Fat Metabolism

8.4.6.1 Fat Metabolism in the Liver

- Insulin is considered to be both lipogenic and anti-lipolytic hormone. The liver is an important site of lipogenesis, more so than adipose tissue, and insulin boosts the synthesis of triglycerides and cholesterol (low-density lipoprotein) in the liver.
- Insulin deficiency promotes converting fatty acids by the liver to cholesterol and phospholipid in high concentrations in the plasma. These two substances along with excess triglycerides formed by the liver at the same time are released to the bloodstream increasing the lipoproteins to three folds in the absence of insulin more than the normal concentrations leading to high levels of lipids especially cholesterol.

8.4.6.2 Fat Metabolism in the Muscles

Insulin enhances glucose metabolism and lipid oxidation in muscles. It has been reported that acute exercise enhances insulin stimulated GLUT4 translocation. There is an increase GLUT4 protein in the muscle which content contribute to this effect. In addition, physical exercises enhance the insulin sensitivity via multiple alterations in glucose transport and metabolism (Borghouts and Keizer 2000).

8.4.6.3 Fat Metabolism in Adipose Tissue

Fat in the form of triglycerides is the active form of energy storage as it supplies nine kilocalories per gram, whereas carbohydrates give only four in normal individuals and this is why lipogenic insulin in adipose tissue boosts energy production.

When carbohydrates are available in the presence of insulin, they are oxidized to produce energy due to complete combustion of the carbohydrate material such that no ketones are produced. However, in the absence of insulin, the body resorts to

excessive fat oxidization to obtain the energy it needs. In this type of oxidation, combustion is not complete and leaves behind substances that give rise to harmful ketone bodies whose odor is apparent in the urine and breath. Ketone bodies are toxic and can lead to what is called glycemic loss of consciousness as well as blood acidity and kidney failure. Insulin counteracts the production of these ketone bodies.

- Insulin promotes the formation of fatty acids in adipose tissue whereas its absence reduces this. Insulin inhibits lipolysis (triglycerides) in adipose tissue cells.
- It stimulates the production of *lipoprotein lipase* in adipose tissue which leads to the breakdown of triglycerides in the circulation and in this way, prepares fatty acids to enter adipose tissue, removing low-density lipoproteins and triglycerides from the blood.
- The absence of insulin also provides an opportunity for *the enzyme hormone-sensitive lipase* and *triglyceride lipase* which break down fats into free fatty acids that increase in the circulation blood within minutes acting as the main source of energy essentially for all body tissues except the brain. On the other hand, the presence of insulin inhibits this enzyme and when there is an insulin shortage, high levels of fats, especially cholesterol, lead to the possibility of strokes in individuals with uncontrolled chronic diabetes (Guyton and Hall 2016; Bullock et al. 1991; Greenspan and Forsham 1986; Waugh and Grant 2006).

8.4.7 Insulin Maintains Weight

- Preventing the oxidation of proteins in the body.
- Preventing glucose production from non-carbohydrate sources; in other words, insulin prevents gluconeogenesis.
- Acting on fat metabolization to prevent their use as an energy source.
- Boosts protein production in the muscles and prevents their catabolization.
- Weight loss may occur in the absence of insulin.

Insulin therapy is applied in type 2 diabetic patients. It has been found that this group of patients make 25% of all type 2 diabetic patients. In contrast, patients with 2 diabetes who take insulin therapy gain weight which may reduce the predictive benefit of improved glycemia (Hodish 2018).

Insulin functions on the metabolites could be summarized as in Fig. 8.11.

8.4.8 Updates on Insulin Physiology on Brain: Source and Target

8.4.8.1 Is Brain a Source of Insulin/C-Peptides?

Brain is an insulin-insensitive system, the latest evidence for the location of system of (insulin and insulin receptors) is very significant knowledge to utilize it as accountable hormone/ligand for many physiological functions and as well to use this concept as a therapeutic target for metabolic and neurodegenerative disorders.

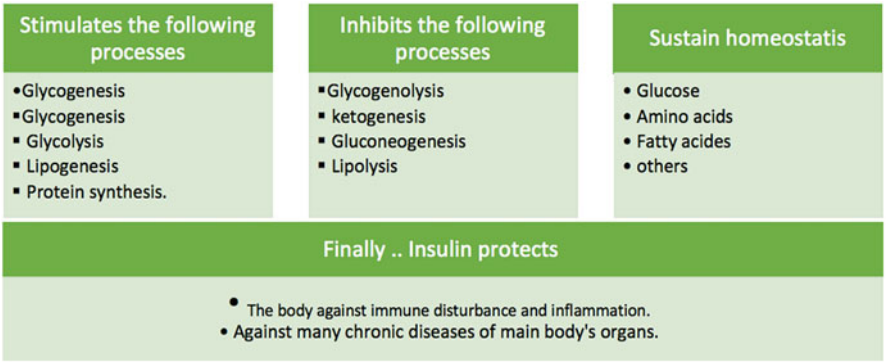


Fig. 8.11 Summary of the main insulin effects on the metabolites

In human, C-peptide is a metabolic production during I biosynthesis of insulin, it was proven that it localizes in neurons as extra-pancreatic insulin production immunoreactivitally in the soma's cytoplasm and in some pyramidal cells in the Neocortex particularly in the proximal area of the apical dendrites as well as in Hippocampus (Dorn et al. 1982). The brain localization of insulin and C-peptide were observed using different methods such as indirect immunofluorescence, peroxidase-anti-peroxidase technique, and radio-immunoassay which showed that the concentration of insulin and C-peptide is higher in the human brain than the blood, and the highest level was found in the hypothalamus, this supported the hypothesis that the brain insulin formed in the brain (Dorn et al. 1983). C-peptide of proinsulin is biologically active, since the expression of anti-C-peptide of human preproinsulin-like peptide 7 was detected in the various brain regions. Preproinsulin-like peptide 7 acts as a signaling molecule which is independent from insulin 7 in the rat brain (Hills and Brunskill 2008; Brailoiu et al. 2009). The origin of insulin either from central or peripheral sources is highly functional in brain regardless its source of production, it is a legend for its specific receptors in the brain and behaves molecularly signals and functions similar to those peripheral molecular functions except some functions of glucose metabolism in brain (Blázquez et al. 2014).

8.4.8.2 Local Synthesis of Insulin in the Brain

It was found that immunoreactive insulin is present in the rat brain 10–100 times higher in concentrations than in the plasma (Havrankova et al. 1978), but this was denied by subsequent findings (Baskin et al. 1985), assuming that little or no insulin is formed in the brain (Hansen et al. 2017). Insulin's original source is produced not only by the beta pancreatic cells as known earlier but also synthesized in neurons derived from the hippocampus and olfactory bulb in adult. Paracrine Wnt3 signal acts main function to upregulate insulin expression in both olfactory bulb-derived neural stem cells and hippocampal. Neural progenitor derived from experimental diabetic adult animals possesses the ability to differentiate to insulin-producing cell (Kuwabara et al. 2011), It has been shown that Ins2 gene expression in the rat brain

throughout development (Devaskar et al. 1993). Expression of insulin mRNAs was also detected in the hippocampus or olfactory bulb in rat brain (Kuwabara et al. 2011). The expression of INS mRNA was observed in the hippocampus, amygdala, and temporal lobe, olfactory bulb, cerebellar and pontine regions in human brain (Mehran et al. 2012).

It has been found that excitatory pyramidal neurons contained Ins2 mRNA, whereas Ins2 mRNA was not expressed in GABAergic neurons and astroglial cells (Molnár et al. 2014). Molnár et al. (2014) first reported that external insulin is effective in quashing spontaneous excitatory potentials in neurons of the neocortex, then, using local delivery of glucose to neuro-gliaform interneurons (Ins2 mRNA) and forced the release of an endogenous substance that also suppressed spontaneous excitatory potentials. Peripheral blood insulin-producing cells (PB-IPCs) were enhanced into an inhabitance of astrocyte-like cells. In case of limiting effect on proliferation by ATRA, the neurotrophic effect could be applied as this unique CD45+ cell population can play a protective function to manage neurodegenerative disorders (Li et al. 2015).

8.4.8.3 Insulin Physiology on Brain

Insulin acts on insulin receptor (IR), and IGF-1 receptor (IGF-1R) to regulate body functions. In addition, insulin also plays a significant role in synthesis of neurotransmitters, brain cholesterol, and also in the mitochondrial function. Any disruption of insulin action in the brain may cause abnormalities in neuronal function and synaptogenesis (Kleinridders et al. 2014). Furthermore, IRs and IGF-1Rs are expressed in the brain and the highest expression of the IR was found in the olfactory bulb (Fernandez and Torres-Alemán 2012; Zhao et al. 2004; Dou et al. 2005) while, the expressions of IGF-1R were highest in the cortex, hippocampus, and thalamus (Fernandez and Torres-Alemán 2012). Actions of insulin are widely several in CNS, according to different stimuli: (1) hormone-induced glucose uptake stimulated by lower activity of insulin-sensitive GLUT-4, available of GLUT-1 and GLUT-3. (2) brai's insulin regulates nutrient homeostasis, reproduction, cognition, memory, neurotrophic, neuroprotective, and neuromodulatory functions. Disturbances in these functions may participate in of many diseases such as central insulin resistance, T2DM, as well as Alzheimer. There is a clear connection between T2DM and Alzheimer as it possibility is higher "Type 3 diabetes" for this connection. The link between Alzheimer and T2DM is mediated by changes in mitochondria, oxidative stress, dysfunction in energy and metabolism of glucose, cholesterol, Aβ, protein O-GlcNAcylation as well as synthesis of amyloidal plaque, tau hyperphosphorylation. This information may result in developing treatment to prevent such diseases (Blázquez et al. 2014).

C-peptide protects hippocampal from apoptosis and cognitive dysfunctions. Exchange of C-peptide in T1DM has various functions on this dysfunction. C-peptide acts widely diabetic encephalopathy, supporting its useful on neurological complexity in T1DM (Sima et al. 2008).

Lower insulin release significantly associates with disorder named (hippocampal and parahippocampal gyrus atrophy) in old T2DM patients. The suggesting the

hypothesis that insulin-signaling dysfunction is required in the pathophysiology of Alzheimer (Adachi et al. 2021).

It has been suggested that insulin is synthesized by a subpopulation of neurons in the cerebral cortex and neural progenitor cells of the hippocampus. Modulation of insulin production by brain neurons via glucagon-like peptide 1 (GLP-1) agonists might be useful in counteracting diabetes, obesity, and neurodegenerative diseases. A viable therapy for diabetic patients is the removal of lost pancreatic β cells by autologous transplantation of insulin-producing neural progenitor (Csajbók and Tamás 2016). Insulin has diverse effects in the body as it has been that v insulin's role in the regulation of brain glucose and energy homeostasis, memory, and mood (Lee et al. 2016). It has been reported that insulin is present in the cerebrospinal fluid where it can be transported to the brain (Gray and Barrett 2018). There has been a substantial connection between the pathophysiology of Alzheimer's disease and related dementias (ADRDs) and type 2 diabetes mellitus (T2DM) diseases. It has been suggested that insulin resistance is a core feature of T2DM and is emerged as a possibly significant feature of ADRDs (Arnold et al. 2018). Recent studies have suggested a relationship between systemic insulin resistance and higher occurrence of neurodegeneration, dementia, and minor cognitive impairment. Some of these pathological conditions could be due to chronic hyperglycemia, hyper-insulinemia, and dyslipidemia (Maciejczyk et al. 2019). In T1DM, insulin and C-peptide concentrations reduce in both CNS and periphery. C-peptide promotes the regulatory activities of insulin. Combination—administration of intranasal of C-peptide and insulin effectively activates insulin system functions in the hypothalamus that is impaired at T1DM. This combination was better than treatment with insulin only while single therapy with C-peptide only was useless (Derkach et al. 2019). In human, insulin role in the brain (hypothalamus) may regulate pancreatic as hypothalamus is the site that may initiate insulin resistance. So, patients with increased insulin sensitivity by hypothalamus, the brain insulin stimulates second-phase of pancreatic insulin release from beta cells. This may contribute to late postprandial glucose control via inhibiting synthesis of hepatic glucose (Heni et al. 2020).

8.4.9 Effect of Insulin Imbalance on Cardiovascular Performance

It has been reported that under normal physiology condition, insulin performs vasodilatory and pro-survival actions through the phosphatidylinositol 3-kinase (PI3-kinase) pathway while insulin produces vasoconstrictive and mitogenic actions through the mitogen-activated protein kinase (MAPK) pathway in the vasculature. In the situation where insulin develops resistance, insulin action on PI3-kinase pathway are become dysfunctional but its signals through the MAPK cascade remain intact. This caused an imbalance in insulin in the insulin resistant patients to hypertension and atherosclerosis (Liu 2006). Insulin activating mitochondrial Akt is required for transmitting the insulin signal which activates oxidation of cardiac glucose directly, suggesting novel therapeutic for cardiac insulin sensitivity in heart failure or metabolic diseases (Karwi et al. 2020).

8.4.10 Other Functions

- Insulin also causes an increase in the permeability of many ions (potassium, magnesium, and phosphates) needed for cell function in the muscle tissue. It is also involved in the polarization of muscle cell membranes.
- Beta cells of the pancreas contribute to the coupling between bone and fat tissue. Insulin, preptin, and amylin are co-released from beta cells in response to high glucose levels after meal. Also, they are in high circulating concentrations in obesity. Also, Peptide hormones released from the gastrointestinal tract after feeding can act as mediators of the connection between bone and fat cells (Naot and Cornish 2014).
- In general, insulin is acting as growth/metabolic hormone regulates the alternative isoform expression of the signal of the key kinase in neuronal cells results in promoting neuronal survival (Apostolatos et al. 2012).
- In another study, a relationship of leptin hormone with insulin and glucose has been reported in Arabian camel. It has been found that leptin levels were affected by season variation, as it increases in winter than summer in female and vice versa in males. In addition, there was positive correlation between leptin and age in males and negative one in females (Al-Suhaimi et al. 2009).

8.5 Factors Affecting Insulin Secretion

Monosaccharides The most potent stimulators of insulin secretion are the monosaccharides, if glucose levels suddenly rise beyond the normal fasting limits **(75–100 mg/dl)**, insulin secretion increases in two stages. It alternates these stages with growth hormone which acts when physiological sugar levels fall:

Stage 1: There is a sharp increase in insulin due to secretion of large amounts of it by the beta cells, up to ten times the baseline level within minutes; this does not last and the level falls to approximately half within 15 min.

Stage 2: This begins 15–20 min later. Insulin levels begin to rise gradually in a moderate and constant manner until they reach a plateau after 2–3 h.

Amino Acids and Fatty Acid The availability of amino acids, particularly arginine, increases glucose stimulation of insulin secretion and their oral consumption has more of an effect than receiving them via the veins because of gut microflora supporting effect and stimulation of the intestinal hormones such as gastrin.

Fats, on the other hand, have very little effect on increasing the insulin level.

Glucose-stimulated insulin secretion requires both **cAMP** and **ionized calcium**. Also, other stimulators use cGMP as a second messenger (Park et al. 2015). As soon as the glucose trigger reaches the beta cell, cAMP and/or cGMP is produced, followed by an ionized calcium from the mitochondria and other organelles into the cytoplasm. This increases its concentration inside more than outside the cell

leading to a change in membrane ion permeability. Glucose also acts on calcium uptake by its beta cells and traps calcium inside until there is a response.

Digestive Tract Hormones Insulin levels increase after oral consumption of glucose in a greater proportion compared to intravenous glucose because gut microflora or/and oral glucose cause the secretion of intestinal hormones such as gastrin, secretin, and cholecystokinin.

Paracrine Signals of Pancreatic Hormones The pancreatic hormones act also locally other than through the blood stream. Glucagon secreted by the alpha cells has a stimulating effect on insulin secretion from the beta cells in the same islet.

Some medicinal products and drugs inhibit insulin secretion.

Other Hormones Insulin levels exchange alternatively with glucagon and growth hormone throughout the day depending on meals times.

Additionally**, glucagon and growth hormone** induce an increase in the baseline insulin level. There is also some interaction between certain hormones and the effect of insulin such as PTH and certain adrenal cortex hormones and female steroids at pregnancy. Cortisol increases glucose levels by reducing insulin's efficacy by decreasing the number of receptors.

Other insulinotropic or inhibitory polypeptides like ghrelin, glucagon-like peptide, glucose-dependent, or the inhibitory peptide somatostatin (Guyton and Hall 2016).

Brain derived neuropeptide hormones: Melatonin, galanin, and other show neuroendocrine control for beta cells and have potential therapeutic for the treatment and management of diabetes and obesity (Gesmundo et al. 2017).

The regulatory effect of nerves:

The axon terminal ends penetrate the pancreas islets:

- Stimulation of the vagus nerve increases insulin's response to glucose.
- Stimulation of the sympathetic nervous system, which secretes catecholamines; this prevents insulin secretion from the pancreas, leading to an increase in the blood glucose level.
- On the other hand, stimulation of the parasympathetic nervous system which secretes acetylcholine; this activates insulin secretion which leads to a decrease in blood glucose levels.

Brain Control of Insulin and Glucagon Secretion The production of insulin and glucagon hormones in the islets of pancreas are important for glucose homeostasis. It is well known fact that insulin is a necessity for life, and disruption in the insulin production or release may cause deregulation of blood glucose. It has been found that islets are fully capable of detecting glucose fluctuations and it can alter hormone release appropriately (Osundiji and Evans 2013).

8.6 Circadian Clocks and Insulin

Circadian clock is located in the hypothalamic supra-chiasmatic nucleus and is responsible for the management of glucose metabolism in humans. The central clock is responsible for the regulation of insulin sensitivity, food intake, and energy usage, these actions are more closely monitored by local peripheral clocks (Stenvers et al. 2019).

8.7 The Therapeutic Utility of Insulin in Diabetes, and the Challenges and Status of Oral Insulin Therapy

In the patients who are suffering from low supply of insulin, it's necessary to provide them insulin externally. It has been found that daily insulin injection is standard management for people with diabetes, but its painful process of insulin injection. Recently other forms of delivery have been applied where insulin is delivered oral routes. It has been reported that oral management of insulin has possible benefits in decreasing pain and chances of skin infection, improving the portal levels of insulin and avoiding sides. Yet oral delivery of insulin is best administration route, there are several physiological issues such as low oral bioavailability, susceptibility to enzymatic proteolysis and low diffusion rate across the mucin barrier which needs to be resolved (Wong et al. 2016).

8.8 View of Point on the Synthesis and Physiology of Sex Steroids in Pancreatic B-Cells

8.8.1 Proof of Local Islet Steroidogenesis

Neurosteroids are steroids made by the brain from cholesterol (Baulieu and Robel 1990). The pancreas also synthesizes steroids. Cytochrome P450scc was detected in dog pancreas (Morales et al. 1999). The enzymatic activities of 17 β-hydroxysteroid dehydrogenase have been reported in rats, and humans (Martel et al. 1992) as well as in canine pancreas (Mendoza-Hernandez et al. 1988). The mRNA of type 17 β-hydroxysteroid dehydrogenase is expressed in the human pancreas (Miettinen et al. 1996), and the type 12 form was entirely observed in the islets of Langerhans (Sakurai et al. 2006). P-450scc, and P-45017 α were found to be co-localized in islet β-cells of a rat. This suggests that P4 is intracellularly produced and is converted to androstenedione (Ogishima et al. 2008). Co-localization of P-450scc and 3-β-hydroxysteroid dehydrogenase (3βHSD) was also found in rat β-cells (Ogishima et al. 2008). This suggests that P4 is intracellularly produced in rat β-cells and transformed to androstenedione. Similarly, the activity of 3βHSD was exhibited in the mitochondrial fraction of dog pancreas homogenates (Mendoza-Hernandez et al. 1990). Aromatase and 5α-reductase activities were detected in human pancreatic carcinoma (Iqbal et al. 1983). Therefore, β-cells could generate testosterone,

dihydrotestosterone (DHT), and E2, which would act as local steroids in the islets. In the case of neurosteroids, their local concentration is thought to surpass that of the steroids in plasma (Baulieu and Robel 1990). Therefore, locally produced islet steroids could directly and efficiently interact with ER and AR (Labrie 2015).

8.8.2 Sex Steroids Play Roles in β Cell Function, Growth, and Survival

The sex-related biological factors that can be connected to gender-based prevention of and therapy for diabetes (Gannon et al. 2018). Globally, diabetes is more dominant in men than in women. In most animal models, male animals are more likely to develop obesity, insulin resistance, and hyperglycemia than females in response to nutritional challenges. Medical and experimental observations evidence the protective actions of endogenous estrogens, mainly through estrogen receptor α activation in various tissues. On the path to precision medicine, further interpreting sex-specific traits in energy balance and glucose homeostasis is indeed a priority topic to optimize individual advances in type 2 diabetes prevention and therapy (Tramunt et al. 2020).

Gonads are endocrine glands that produce sex steroids such as estrogens, androgens, and progesterone and these gonadal steroids are involved in sexual differentiation, puberty, and reproduction. Gonadal steroids play a significant role in sex-specific aspects of energy metabolism in different physiological conditions. In that respect, gonadal steroids also influence the secretion of insulin in a sex-specific manner.

Estrogens The role of female hormone E2 and related estrogens via ERα, ERβ, and the G protein-coupled ER (GPER) in islet biology has been recently reviewed by Naot and Cornish (2014). It has been reported that ERα is involved in insulin biosynthesis, and nutrient homeostasis though ERβ enhances GSIS. The G-protein coupled ER is implicated in GSIS and islet survival.

Testosterone Testosterone is secreted by the testicles binds AR in β-cells, intensifies (+) the insulinotropic effect of the β-cell GLP-1 receptor (GLP-1R) that is activated by islet-derived GLP-1 and GLP-1R agonists (GLP-1RA). Gut GLP-1 acts in a paracrine manner on GLP-1Rs in the guts portal vein to relay signals via the vagal nerve to the brain which then signals to the β-cells to enhance insulin secretion (+) (Mauvais-Jarvis 2016). Deficiency of testosterone deficiency may lead to type 2 diabetes in men, whereas, androgen excess production may cause hyperglycemia in woman. In males, testosterone action on AR in β-cells enhances glucose-stimulated insulin secretion by potentiating the insulin-tropic action of glucagon-like peptide-1. In females, excess testosterone action via AR in β-cells promotes insulin hypersecretion leading to oxidative injury, which in turn predisposes to type 2 diabetes (Xu et al. 2019).

Progesterone Female and male rats with progesterone (P4) stimulated β cell proliferation. This effect was not observed in gonadectomized mice (Nieuwenhuizen et al. 1999) or cultured rat islet cells (Sorenson et al. 1993), signifying that P4 needs the intact gonadal function to induce islet cell proliferation. Similarly, in the perfused pancreas of ovariectomized rats, E2 increased insulin release but P4 alone did not, while P4 enhanced the effect of E2 (Sutter-Dub 1979). P4 has been shown to induce β-cell apoptosis in cultured rat islets and clonal insulin-secreting cells (Nunes et al. 2014).

Male and female β-cells express receptors for estrogens, androgens, and progestogens. Although nutrient-induced insulin secretion is exhibited in the same way in male and female mammals, evidence demonstrates that gonadal steroids can regulated (in a sex-specific manner) the fine-tuning of insulin secretion. Thus, ERs are directed to improve functional β-cell mass and modulate immune function in T1D. However, AR improves GLP-1-stimulated insulin secretion in the male. In contrast, excess AR activation in female fetal and adult β-cells produces β-cell dysfunction in the adult. The role of the PR in females is more complex and depends on the reproductive status.

Apparently, due to of the systemic side effects, general treatments by estrogens and androgens cannot be used for β-cell treatment. Therefore, further studies are needed to understand the mechanisms behind estrogen, androgen, and progestin, as they represent avenues for gender-specific protection of β-cell functional mass in diabetes and consequently precision treatment (Mauvais-Jarvis 2016).

In clinical trials hormone replacement treatment has been found to reduce type 2 diabetes (Kanaya et al. 2003; Margolis et al. 2004). New selective estrogen receptor modulators have been found to facilitate the protective actions of estrogens on glucose metabolism with limited side effects, which can mostly benefit menopausal women (Gourdy et al. 2018). Tissue-specific targeting could also be a relevant plan (Finan et al. 2012).

Apoptosis is programmed cell death and it has been reported that leptin caused pro-apoptotic effects induced by menadione in HepG2 cells. It was found that menadione produced a dose and time dependent anti-viability effect by suppressing leptin pathway and activation caspase 3 and P53 signals depending on ROS generation (Al-Suhaimi 2014).

8.9 Alpha Cell Hormones

8.9.1 Glucagon

A hyperglycemic hormone consisting of a single peptide series of 29 amino acids. It is secreted by the endocrine cells of the pancreas (α cells) and intestines. As shown in Fig. 8.3:

- It is synthesized as shown in Fig 2.1 from a prohormone, proglucagon. Glucagon has a half-life of 3–6 min.

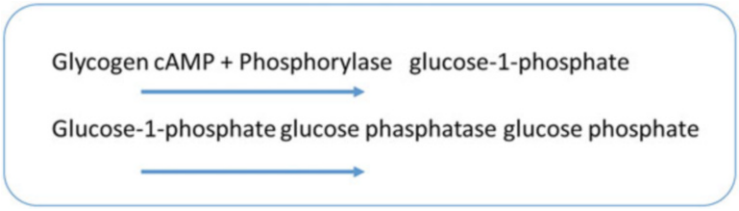
- Its concentration in the plasma in normal individuals is 75 pg/ml (Bullock et al. 1991).
- This includes molecules that are cleaved off such as proglucagon, glicentin, and oxyntomodulin.
- Glicentin contains the whole glucagon sequence at residues number 64–92. So, it accomplishes one of the requirements for being a glucagon precursor "proglucagon" (Holst 1980).

8.9.2 Physiological Functions of Glucagon

Most of its functions are the opposite of those of insulin, the most important of which is its involvement in the regulation of glucose levels in the blood whereby it prevents the glucose level falling below normal which saves energy for the body, especially between meals.

8.9.2.1 Physiological Functions of Glucagon on the Liver: On the Carbohydrates

- Glucagon raises blood glucose within 20 min of the body being exposed to it.
- As soon as glucagon arrives, the enzyme adenylate cyclase is stimulated leading to production of cAMP in the liver cells and this leads to the breakdown of glucagon to glucose (**glycogenolysis**) after the removal of phosphates from it (dephosphorylation), allowing free glucose to be released from the cell into bloodstream. Between meals glucose is released from the liver (the lack of insulin along with increase of glucagon).



- Glucagon does not oppose glucose consumption processes in the peripheral tissues.
- Additionally, it stimulates the glucagon-dependent enzyme cAMP, an important factor in glucose synthesis from non-carbohydrate sources (such as amino acids) in the liver (gluconeogenesis). These two processes make glucose available to all organs in the body.
- The processes are aided by the hormone adrenaline which boosts glucagon and inhibits insulin.

8.9.2.2 Effects of Glucagon on the Fat

- Glucagon breaks down triglycerides (lipolytic hormone) and prevents their storage in the liver which means that the liver cannot remove fatty acids from the blood.
- It stimulates the enzyme triglyceride lipase in the cells, contrary to insulin which inhibits it. Consequently, fatty acids and glycerol levels in the blood increase to make fatty acids available for energy production.
  It helps produce energy from fats via oxidation of fatty acids in the liver and the formation of ketone bodies in the absence of insulin (which opposes this process).

8.9.2.3 Proteolytic Effect of Glucagon on Proteins

Glucagon has a proteolytic effect on proteins in the liver in addition to its anti-protein building effect. It is involved in the production of glucose from non-carbohydrate sources which leads to an increase in amino acid oxidation and metabolites such as urea.

8.9.2.4 Novel View of Glucagon on Brain

Recently it has been reported that brain glucagon play a critical role in the regulation of peripheral homeostasis. The brain glucagon action has been found in feeding and in the regulation of glucose. The action of glucagon is mainly reported in the central nervous system specifically in the medio-basal hypothalamus and the dorsal vagal complex respectively. These novel findings may help to develop future therapies for the treatment of diabetes and obesity (Abraham and Lam 2016).

8.9.2.5 Other Functions

High glucagon concentration (1) enhances cardiac output; (2) increases blood flow in some tissues particularly kidney's tissue; (3) stimulates bile secretion; and (4) inhibits gastric juices (Hall 2016; Bullock et al. 1991; Waugh and Grant 2006).

8.9.3 Regulation of Glucagon Secretion

1. **Metabolites**
   - **Glucose**: There is an inverse relationship between hormone concentration and glucose concentration: a glucose shortage leads to an increase in glucagon and vice versa.
   - **Fatty acids** increase in the bloodstream, inhibits the secretion of glucagon.
   - **Amino acids** increase levels in the circulation after a meal, particularly the amino acids alanine and arginine, stimulate glucagon and insulin. This mechanism is important for the two hormones because insulin brings in amino acids and lowers glucose in the cells. This is a process that is stopped by glucagon stimulated by amino acids. Amino acids generally differ in their ability to stimulate glucagon.
2. **Gastric hormones** such as gastrin and cholecystokinin stimulate the secretion of glucagon.

3. Glucagon is stimulated by the **vagus** nerve and catecholamines released by the sympathetic nerve endings which innervate the islets.
4. **Strenuous exercise** increases the secretion of glucagon, the amino acids is one of the factors which can intermediate the process (Bullock et al. 1991, 2001).

It is concluded that glucagon

- Has a hyperglycemic effect.
- Stimulates several processes such as glycogenolysis, gluconeogenesis, lipolysis, ketogenesis, proteolysis.
- While it inhibits processes like: Glycogenesis, lipogenesis, protein synthesis.

8.10 Insulin and Glucagon Degradation

Hormonal degradation is an important as hormone secretion, the biological roles of insulin clearance and degradation are to inactivate and then remove insulin from the circulation.

- Insulin degradation is an organized process plays a function in regulating insulin activities by removing and inactivating the hormone. Disturbance in insulin clearance is existing in many diseases such as type 2 diabetes and obesity and contributes in producing clinical problems. The reception, uptake, processing, and degradation of insulin by cells and clearance are group of complex processes of cellular pathways (Duckworth et al. 1975; Duckworth and Kitabchi 1974).
- Insulin and Glucagon are degraded in the liver, kidneys, and other tissues (Duckworth et al. 1975; Duckworth and Kitabchi 1974).
- Increased glucose inhibits glucagon secretion.
- The activities of insulin- and glucagon-degrading could not be distinguished by the effect of some reagents like sulfhydryl, pH, or heat inactivation. Insulin acts as a competitive suppressor of glucagon degradation and glucagon serves as a competitive suppressor of the degradation of insulin, so it seems experimentally, that both hormones can be degraded by the same enzyme which exists in the soluble portion of rat skeletal muscle cells homogenate (Duckworth et al. 1975; Duckworth and Kitabchi 1974).
- Insulin and glucagon as peptides can be proteolytically degraded by an enzyme separated from insulin-sensitive tissues (skeletal muscle). It acts on intact insulin molecule (Duckworth et al. 1975; Duckworth and Kitabchi 1974).
- Insulin-degrading enzymes (IDE) like: A proteolytic activity, insulinase are found in all cells, not only insulin-sensitive tissues and cells. IDE is the main degradative enzymatic mechanism involved in insulin metabolism (Duckworth et al. 1998).
- **Protein Disulfide Isomerase** (PDI) is also the primary enzyme required in insulin metabolism, it was known previously (the enzyme glutathione insulin transhydrogenase). PDI cleavages the disulfide bound and degrades insulin. The

two essential enzymes PDI and IDE required for insulin metabolism (Duckworth et al. 1998).
- Lysosomes and different enzymes also, participate certainly to insulin metabolism (Duckworth and Kitabchi 1981).

8.11 Somatostatin (SS)

SS is a growth hormone–inhibiting hormone (GHIH), and a polypeptide/tetradecapeptide hormone isolated from sheep hypothalamus in 1970s. SS has two active forms secreted by the alternatively cleavage of its precursor, preproprotein: one has 14 amino acids (Somatostatin-14), while the other of 28 amino acids (Somatostatin-28). SS is secreted by pancreatic islet δ-cells, and by extra-islet neuroendocrine cells of the hypothalamus. It is also found in the central and the peripheral nerve system as a neuropeptide exerting several biological actions. It is present in most organs of the body and produced abundantly from intestinal enteroendocrine cells.

SS shows a variety of neuroendocrine, neuromodulatory, and gastrointestinal physiological functions through five different receptor subtypes (SS1–SS5). SS2 and SS5 are the major mediators of the gastrointestinal actions of the hormone. The native somatostatin has a short half-life in the circulation (1–3 min). Its normal concentration in humans is 80 pg/ml. Its secretion is stimulated by most metabolites such as glucose, amino acids and fatty acids (Bullock et al. 1991).

8.11.1 Physiological Functions of Somatostatin

Somatostatin acts as a classical endocrine hormone, locally as a paracrine regulator signal inside the islets to inhibit both insulin and glucagon or as a neurotransmitter.

As Endocrine/Paracrine Hormone
- Somatostatin is also called growth hormone–inhibiting hormone.
- Somatostatin is released into the blood circulation after a meal and works in it as an endocrine hormone.
- It inhibits the growth hormone and thyroid-stimulating hormone.
- SS receptors are found on α- and β-islet cells. Endogenous and exogenous somatostatin suppress insulin and glucagon release consistent with its roles in regulating α- and β-cell functions. Islet δ-cells secrete SS that fulfills various roles as a paracrine signal of Islet functions (Hauge-Evans et al. 2009).
- SS facilitates the islet response to cholinergic stimulation (Hauge-Evans et al. 2009).
- SS regulates cell differentiation, it has an antiproliferative effect. But the use of somatostatin analogues as antitumor treatment is still in debate.
- It has effects on the immunity.

8.11.2 As Neurohormone

- SS is synthesized in the hypothalamus and acts as a neurohormone.
- It is brought through the portal vessels of the pituitary gland's stalk to the growth hormone and thyroid-stimulating hormone-producing cells.

8.11.3 As Neuromodulator Peptide/Neurotransmitter

- Somatostatin was identified widely in the brain. It has receptors in the central nervous system, and hypothalamus.
- Brain somatostatin receptor 2 plays a role in regulating the feeding and the drinking behavior (Stengel et al. 2015).
- Hippocampal somatostatin receptors have different neuromodulatory effects in cognitive functions, learning anxiety, and depression, locomotor activity (Prévôt et al. 2017).

8.11.4 As Gastrointestinal Local Hormone

- Somatostatin acts as an autocrine/paracrine signal in the gastrointestinal tract.
- In the gastrointestinal tract, it inhibits the release of several gut hormones that control gastrointestinal functions. SS exerts a wide domain of physiological functions, as an inhibitory, of which inhibition of gastric acid secretion is a main response. The hormone influences both the epithelial transport function and motility function of the digestive tract. It slows down digestion, in general. It has a regulatory role for the absorption and the secretion of water and electrolytes (Bullock et al. 1991; Dharmsathaphorn 1985; Martinez 2013; Ando 2016).

8.12 Pancreatic Polypeptide Hormone

Pancreatic polypeptide hormone is a family of peptides was discovered in the avian pancreas, then in mammalian and human pancreatic tissue. Pancreatic polypeptide hormone consists of:

- Pancreatic polypeptide (PP) was isolated from pancreatic extracts.
- Peptide YY (PYY) was isolated from intestinal mucosa.
- Neuropeptide Y (NPY) was isolated from brain extracts.

8.12.1 Sources of Pancreatic Polypeptide Hormone

The polypeptides U-shaped tertiary construction leads to name them (PP-fold peptide family) alternatively. The entire three peptides contain 36 amino acids. PP concentration in normal individuals is 24 pmol/l. PP is synthesized and secreted by polypeptide **F cells** lying in the periphery areas of pancreatic islets and little clumps dispersed through the pancreatic acini. PYY is co-synthesized with the glucagon-like peptides in **L cells** mainly present either at the end of the ileum or in the colon. PYY is mostly stored in these cells, 40% of the circulating hormone form is the so-called (3-36PYY), and its N-terminal dipeptide was deleted by *dipeptidylpeptidase* IV. Both PYY forms are active biologically. PYY is also secreted by central and peripheral neurons.

8.12.2 Pancreatic Polypeptide Receptors

The symmetry tertiary structure of the PP-fold peptides permits them to link with the same subfamily receptors, but with various levels of affinity. Five distinct isoforms of G-protein coupled receptors exist in the brain and intestines mediating the mechanism of actions of these peptides. PP relative receptor is the NPY4 receptor which is expressed in the hypothalamus, the brainstem, the small and large intestines.

- Physiological roles of pancreatic polypeptide hormone.
- Pancreatic polypeptide hormone acts as a satiety hormone.
- It has an inhibitory effect on the secretion of the exocrine pancreas.
- It is slowing stomach emptying.
- PYY may regulate metabolism.
- In general, PP, PYY, and NPY have inhibitory effects on gut functions, they inhibit gastric acid secretion and gastrointestinal motility, to regulate the post-prandial status.
- NPY has effects on the cardiovascular, endocrine glands, and central nervous systems.

8.12.3 Pancreatic Polypeptide Hormone Regulating Factors

- PP and PYY are limited to endocrine cells of the pancreas and distal gut epithelium. They are released within moments in response to feeding or mixed meal under the regulation of the vagus nerve.
- PP increases with age and certain illnesses such as kidney failure.
- NPY is limited to nervous tissue and is released in response to nerve activation as a neurotransmitter (Bullock et al. 1991; Mannon 2004; Goodman 2009; Tan and Bloom 2013).

8.13 A Glance, Pancreatic Progenitor/Stem Cells: Beta Cell's Self-Renewal and Promising Strategy for Diabetes

Transplantation neuronal progenitors into the pancreas of experimentally diabetic animals decreases glucose concentrations showing direct effect adult's stem cells between organs, regardless genes' induction (Kuwabara et al. 2011).

Pancreatic progenitor/stem cells are found in rodents that β cell's self-renewal seems to be the predominant origin for the new β cells promoted by other pancreatic cells such as non- β islet cells, acinar cells, and duct cells. In addition to extra-pancreatic cells like neural, liver, and stem or progenitor cells. In humans also, β cell neogenesis from non-beta cells seems to be the predominant origin of beta cell self-renewal as particularly in adulthood, restricted β cell self-renewal happens (Cerf 2013).

As a part of endocrine system, pancreatic hormones secreting beta and alpha cells play main functions in maintaining glucose homeostasis from fetal to adult stages. Beta and alpha cells play regulatory strategies to insure maturation and proliferation at different developmental times synchronously. The heterogeneity of juvenile β cells shows dissimilar cell-cycling phases, origins, and maturation states, while adult β cells are homogeneous at the transcriptomic level (Qiu et al. 2017).

Human-induced pluripotent stem cells (hiPSCs)-derived glucose-responsive insulin-secreting cells could be a promising subjective drug and cell transplantation therapy in type I diabetes mellitus. In vitro protocol emulates in vivo pancreatic organogenesis by guiding cells through phases like ultimate endoderm, primal gut-tube endoderm, hind foregut, pancreatic endoderm, and endocrine precursor. The generated cells showed many features of effective β cells such as expression of pivotal β cells transcription gen factors, secreting C-peptide in response to high glucose levels and the synthesis of mature endocrine secretory granules. The protocol revealed more than 70% insulin-secreting cells capable response to glucose levels five times higher than the basal level (Rajaei et al. 2017).

Recently, it is found that the fibroblast cells of mouse embryo contain a population of mesenchymal stem cells (MSC) which differentiates into insulin-producing cells expressing up-regulation of islets markers such as (insulin, glucagon, and somatostatin, and down-regulation of MSC markers such as Vimentin and Nestin. This could be extrapolated for isolation of human MSCs, for the treatment of type 1 diabetic patients. It is worth to mention that this is a reprogramming technique of mouse embryo fibroblasts into functional islets without genetic management techniques (Chandravanshi and Bhonde 2018). In addition, it has been reported that human limbal fibroblast-like cells can be successfully differentiated into pancreatic beta islet cells (Dravida et al. 2005). Human embryonic stem cells (hESCs) also hold great potential as they can also possess tremendous capability to differentiate into pancreatic beta islet cells (Khan et al. 2018). The differentiation of embryonic stem cells induced pluripotent stem cells and mesenchymal stem cells into β cells is illustrated in Fig. 8.12.

An effective strategy to neutralize the disease developing condition is to reform the beta cell from residual islet cells or substitution by beta-like cells derived from stem cells is a promising strategy to prevent disease progression. Knowledge on

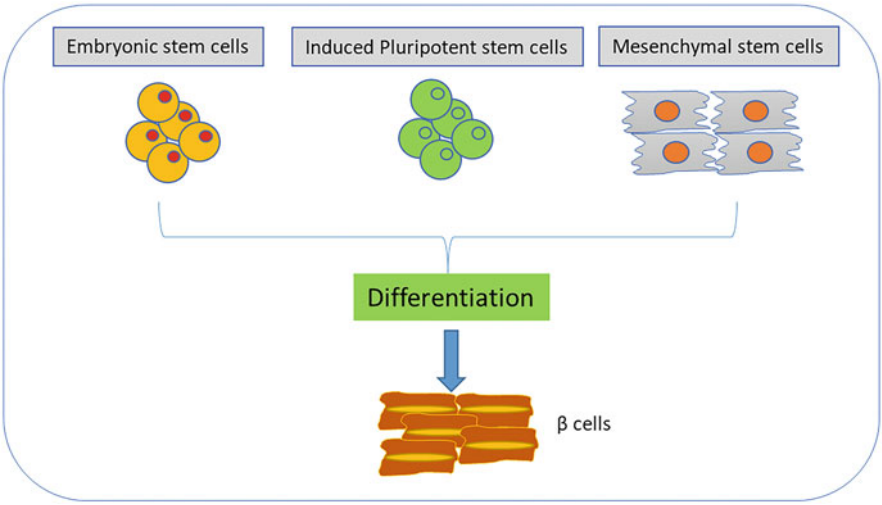


Fig. 8.12 Showing differentiation of embryonic stem cells, induced pluripotent stem cells and mesenchymal stem cells into β cells

human pancreas organogenesis is limited because of shortage on primary tissues needed for comparative models of beta cell in health and disease before pre-clinical and clinical researches. The latest knowledge is key steps to know the development of human pancreas such as pancreas' organoids, stages of stem cell differentiation, primary micro-islets and pseudo-islets, bioengineering and microfluidic schemes (Bakhti et al. 2019).

Tissue and stem cell encapsulation and transplantation are promising approaches in treating diabetes mellitus. Microfluidic technique was utilized to study in vitro and in vivo based on trabecular meshwork mesenchymal stem cells (TM-MSC) encapsulation in insulin-producing cells (IPCs). Presence of cellular differentiation was detected in both 3D- and 2D-based cell culture. Pancreatic islet makers were detecting by molecular analysis of mRNA and protein expression studies. In addition, insulin release was calculated based on cellular response to environmental glucose tolerance test. In that undifferentiated cells in microfibers in vitro culture were regulated the glucose levels in diabetic induced animals. Microfluidic fabrication of Mesenchymal stem cells (MSCs) differentiation in alginate microfibers tends to reduce in differentiation of stem cells. Methods of using inner functionalization causes numerous cells loses (Barati et al. 2018).

8.14 Conclusion

Pancreas gland located in the upper abdomen region plays two important roles as digestive exocrine gland and hormones releasing endocrine gland. Exocrine gland composed of tiny masses called "acini" secretes enzymes for digestion. Pancreatic

islets (Langerhans) as clusters or islets are responsible for important hormones secretion such as peptide hormone insulin, somatostatin, glucagon, and pancreatic polypeptide. Dysfunction in pancreatic islet leads to metabolic disorders including diabetes mellitus. The cells of pancreatic islets (α, β and δ cells) involve in the physiological and metabolic functions of insulin, correlation between immunity/insulin imbalances, cardiovascular functions. The α cells make up 20–25% of pancreatic islet cells in humans whereas β cells comprise 60–80% of islet cells in humans and mammals and δ cells comprise approximately 3–5% of islet cells. In addition, pancreas also contains polypeptide cells which are known as pancreatic polypeptide cells and these make up around 5% of pancreatic islet cells. Physiological and pathological conditions of different pancreatic hormones are also discussed in great details with suitable examples. Pancreatic progenitor or stem cells are found in rodents that β cell's self-renewal seems to be the predominant origin for the new beta cells promoted by other pancreatic cells such as non- β islet cells, acinar cells, and duct cells. In addition to extra-pancreatic cells like neural, liver, and stem/progenitor cells. In humans also, β cell neogenesis from non-β cells seems to be the predominant origin of beta cell self-renewal as particularly in adulthood, restricted beta cell self-renewal happens.

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Regulation of Male and Female Reproductive Functions

9

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Abstract

Reproduction is an important biological process of species evolution, it is leading to new offspring from parents. The pituitary gland (the master gland) in the endocrine system in coordination with the hypothalamus plays a vital role in the reproductive system, differentiation, and different physiological functions in the entire stages of life and its circadian rhythm in both males and females. The chapter deals with the prominent role played by the brain, endocrine system, and gonads axis through complex communicating signals. The male gonads are the location of testicles, interstitial tissue (Leydig cells), and peritubular myoid cells. Sertoli cells act as "nurse and stem" cells, spermatogenesis, spermiogenesis were explained. Gonad's steroid hormones (Androgens) characteristics are specified in male reproductive activity, biological actions along with the regulator hormones (follicle-stimulating hormone, luteinizing hormone, and hypothalamic–pituitary–Leydig cell axis. Ovaries are female reproductive glands. The chapter describes the tissue zones of ovaries, puberty, and two main functions (exocrine and endocrine) controlled and coordinated by the hypothalamus and the pituitary. Female sex hormones in pre-puberty (Estrogen) and post-puberty (estradiol, estrone, progesterone, and inhibin), and sources (ovarian follicle and corpus luteum) were discussed in detail. Structure of steroid hormones discussed with the role of the endometrium, regulation of ovarian functions, and puberty by endocrine and immune system. The different phases of the ovarian cycle are explained to regulate gonadotropins, follicular growth, steroid synthesis, non-functional corpus albicans (infertile ovum), and regulation of the ovarian

cycle (pre-ovulatory phase, ovulation phase, and post-ovulatory phase). The involvement of estradiol metabolites, enzyme aromatase, the hormone oxytocin, matrix metalloprotease, cytokines, and vasoconstriction in corpus luteum formation is related along with maintenance and regression. Synthesis of ovarian hormones (β-estradiol, estrone, and estriol) after puberty discussed with important functions of progesterone, regulatory roles of inhibin, activin, and follistatin in the physiology of testis and ovary. Dehydroepiandrosterone (DHEA) involvement was discussed for menopause in elderly women and andropause in men. The chapter declares that the classic theory of cessation of oocytes production after birth was canceled. Both human neonatal and adult ovarian germline stem-cell precursors (ovarian surface cells) have the capability for oogenic/differentiating and producing functional oocytes, so it renews the oocyte pool (neo-oogenesis) and ensures renewal during the prime reproductive period, with follicular cooperation under the regulation of the endocrine, immune systems, and cellular support. After the prime reproductive period, aging starts, and menopause occurs because of the immunoregulatory changes that cause cessation and terminate neo-oogenesis and follicular renewal in vivo despite the existence of germline stem cell precursors. The rest of the oocytes in the primordial follicles retain ovarian function but advancing age (aging oocytes) correlates positively with the occurrence of fetal chromosomal abnormality. This chapter discusses the topics related to regulation of male and female reproductive functions.

Keywords

Follicle-stimulating hormone · Luteinizing hormone · Ovary · Testis · Reproductive hormone · Stem cell

Abbreviations

16-keto-E2	16-Keto-estradiol
2N	Diploid
2-ME2	2-Methoxyestradiol
4-OHE1	4-Hydroxyestrone
ACTH	Adrenocorticotropic hormone
AMH	Anti-Müllerian hormone
BMP	Bone morphogenetic protein
BTB	Blood–testis barrier
Ca^{2+}	Ionic calcium
Ca^{2+}/CaMK	Ca^{2+}/calmodulin-dependent protein kinase
CaM	Calcium-modulated protein
CRH	Corticotropin-releasing hormone
DFF	Dominant follicular fluid
DHEA	Dehydroepiandrosterone
DNA	Deoxyribonucleic acid
FSH	Follicle-stimulating hormone

FSHRH	Follicle-stimulating hormone-releasing hormone
FSTL1	Follistatin-related protein 1
GDF	Growth differentiation factor
GDF-9	Growth differentiation factor-9
GMP	Guanosine monophosphate
GnIH	Gonadotropin-inhibitory hormone
GnRH	Gonadotropin-releasing hormone
H&E	Hematoxylin and eosin stain
hCG	Human chorionic gonadotropin
ICSH	Interstitial cell–stimulating hormone
IGF-1	Insulin-like growth factor 1
IGF-2	Insulin-like growth factor 2
IGFBP-2	Insulin-like growth factor binding protein 2
IGFBP-3	Insulin-like growth factor binding protein 3
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
mRNA	Messenger ribonucleic acid
N	Haploid
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
TGF	Transforming growth factor
TGF-beta	Transforming growth factor beta
TNFα	Tumor necrosis factor alpha

9.1 Introduction

Reproduction refers to multiple biological processes that maintain the survival of humankind and all living creatures, by producing new individual "offspring" from their parents. Reproduction is a prominent biological feature. The endocrine system, especially the pituitary gland in coordination with the neuroendocrine gland in the central nervous system, the hypothalamus, controls and organizes the reproductive system growth, differentiation, physiological functions and its circadian rhythm in males and females, throughout life, even in the menopausal or andropause phase.

Fully integrative hormonal and neurotransmitter signals act through several systems to produce a synchronized physiological result. The human reproductive function is regulated by a network of complex communication systems including many organs and tissues such as the brain, endocrine system and gonads by circulation and local signals. The hypothalamic-pituitary-gonadal (testicular/ovarian) axis plays a key role in regulating this biological feature with other endocrine, paracrine, and autocrine signals in a very exquisite harmony. The functional paracrine and autocrine signals and mechanisms in the gonads have been recommended as

therapeutic targets for the infertility cases in both females and males (Rudolph et al. 2016a, b).

9.2 Gonad Hormones and Male Reproduction

9.2.1 Testes Structure

The testes are a pair of loose, oval-shaped glands measuring; length 3.6–5 cm, width 2.5–3 cm, and weight 10–45 g. The size varies according the mammal's species (Fig. 9.1).

9.2.2 External Location of Tests

Each testicular gland is surrounded by two fibrous membranes. In order to provide ideal conditions for spermatogenesis, testicular/scrotal thermoregulation is a very important complex process controlled by various local mechanisms within the testes. Spermatogenesis in humans and mammals is a serial biological process that occurs within the seminiferous tubules of the testes. This process involves a controlled

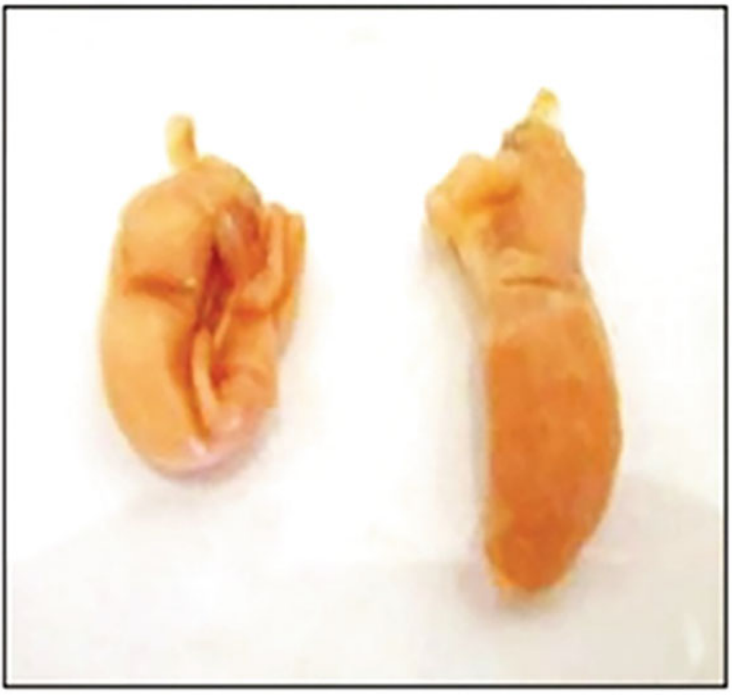

Fig. 9.1 Morphology of the testes in rabbits (Fixed in 10% formalin)

balance of cell proliferation, differentiation, transformation, and apoptosis. For these precise processes, the testes are located outside the body cavity in the scrotum, at a temperature 2–7 °C lower than temperature of the core body, and with a circulation that is not affected by body changes (Reyes et al. 2012). Many studies have reported the damaging effects of heat on the testes' weight, endocrinology, physiology, histology, and biochemistry, also on sperm count, motility, fertilizing ability, and on the growth of embryos produced if sperms from heated testes fertilize normal ova and the possibility of abnormalities in male reproduction in humans and animals. It was found that elevated testis temperature in humans, either due to occupational risks or clothes style may contribute significantly to infertility disorders (Mieusset and Bujan 1995; Parazzini et al. 1995; Thonneau et al. 1997). Heating method was considered as a potential contraceptive tool (Kandeel and Swerdloff 1988). Also, global heating may a potential reason of the decline of sperm counts in human (Setchell 1998).

9.2.3 Puberty

At the time of puberty, certain physical changes occur in human body along with functional changes including various sexual maturations ranging from gonadal differentiation during the first trimester of fetus growth to other changes evident at later stages.

In the second trimester of fetus growth, it is observed that FSH and LH levels are equivalent to those in adults while the levels are found to be lower during the last trimester. This could be because of the maternal and placental sex steroids that regulate negative feedback.

The concentration of serum FSH in infant girls may be similar to adults while the level of LH in such individuals elevates gradually to reach the lower levels in adults. In case of males, FSH levels as well as LH level show a gradual rise in childhood and early puberty.

The levels of FSH and LH are retained at a lower level by the endocrine system during the period from 2 years' age to puberty and the juvenile pause. This may be attributed to the suppression of melatonin secretion by the pineal gland. The pulse amplitude is specifically found to be higher at the time of puberty. Consequently, gonads are stimulated, and pituitary gland becomes more sensitive to GnRH stimulation (Copeland and Chernausek 2016).

In animals, the onset of male puberty is controlled by the timing of early pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus (Byrne et al. 2017). While in human, the onset of puberty is between the ages of 12 and 16 years, although this can vary from one geographical area in the world to another as a function of diet, growth, genetics, health, and environmental factors. These factors influence several metabolic and reproductive hormones which in turn influence endocrine functions of the hypothalamic–pituitary–testicular axis. Puberty is also influenced by the hormone melatonin as mentioned in Chap. 7. The signs of puberty may not appear until the age of 16 years (Copeland and Chernausek 2016).

In addition, puberty follows a sigmoidal growth curve, with a major variation testicular growth and adult testicular volume. The increase in Sertoli cells caused testicular growth early in puberty. Largest and fastest growth of testicular due to the increase in the diameter of the seminiferous tubules, first due to spermatogonial proliferation phase and then due to the expansion of meiotic and haploid germ cells. Moreover, FSH stimulates Sertoli cells and spermatogonial proliferation, whereas LH or testosterone is mandatory to complete spermatogenesis (Koskenniemi et al. 2017).

9.2.4 Physiological Functions of the Testicles

- Endocrine function: Synthesis of the sex hormones (steroidogenesis), as well as of inhibin, activin, and other hormones.
- Exocrine function: Spermatogenesis and spermiogenesis.

The parenchymatous tissue of the testis consists of two functionally interconnected components (Fig. 9.2). The two tissues are separated by partition tissue which includes the basal membrane (Al-Motabagani 2008; Burkitt et al. 1996; Young and Heath 2000).

9.2.4.1 Seminiferous Tubules

Each testicle is divided deeply by the tunica albuginea into small lobules. Each lobule contains multiple seminiferous tubules. The conical seminiferous tubules number around 250–300. These comprise 90% of the testicular volume and make up a total length of 400 m per testis. They are responsible for the production of around 30 million sperm every day, starting from puberty and continuing throughout life.

Sex Cells (Spermatogonia and Spermatogenesis)

Spermatogenesis occurs according to the following steps.

Two essential phases are required:

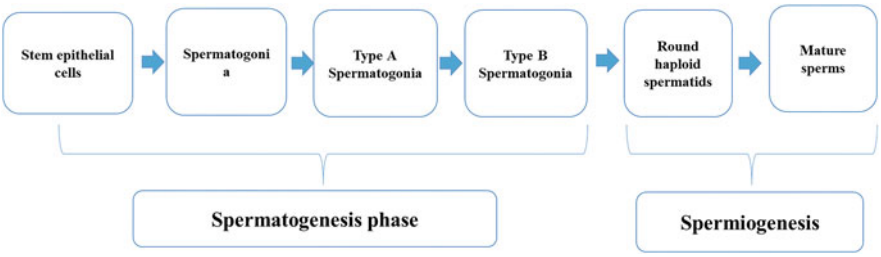

Fig. 9.2 Stages of spermatogenesis and spermiogenesis

Spermiogenesis and Spermiogenesis

- The process starts with the proliferative phase (spermatogonia): Type A spermatogonia, present and in contact with the basement membrane of the seminiferous tubules start to differentiate. Once spermatogonia enter into the process of spermatogenesis, they change from stem cells into germ cells ("progenitor cells") (Fig. 9.5).
- Mitotic phase: After enlargement, spermatogonia develop into type B spermatogonia which undergo one last division by mitosis to produce two primary spermatocytes (2n) (spermatocyte I) and then secondary spermatocytes (1n) (spermatocyte II).

Spermiogenesis

- The day-long process of conversion of a round spermatid into a sperm cell is called Spermiogenesis. The four processes involved in spermiogenesis are as follows:
- Nuclear condensation: In this process, the nucleus shrinks resulting in closely packed contents within nucleus depicting pear shape.
- Acrosome formation: In this process, a cap-like structure called acrosome is created by the Golgi apparatus on the anterior part of sperm cell. These created structures perform the same functions as performed by lysosome and these structures also contain lysosomal enzymes like hyaluronidase and acrosin which are responsible for the disruption of outer ovum membrane.
- Development of flagellum: In this process, the flagellum is produced by a centriole. The four main body parts of a flagellum are neck, middle piece, the main piece, and the tail. It consists of nine outer microtubules doublets as well as two single ones in the center. The flagella move with the help of energy obtained from the mitochondria within the middle piece.
- Cytoplasmic reduction: In this process, the Sertoli cells eliminate the extra and unneeded cytoplasmic components through Phagocytosis. At this point, the sperm cell is not able to swim. It becomes able to swim when it passes through the epididymis (O'Donnell 2015).
- In this phase round-shaped spermatids (**1n**) turn into mature sperms, the process which is free from cellular division. At the end of meiosis, the **haploid spermatids** change biochemically and morphologically without any cellular division, which leads to the formation of **mature sperm (spermatozoa)** (Sèdes et al. 2018; Guyton 1986; Guyton and Hall 2006, 2016). This is summarized in Fig. 9.2.

Somatic Cells of the Testes (Functions of Sertoli Cells and Peritubular)

Spermatogenesis, from the beginning of the formation of sperms to their secretion into the tubule cavity, takes approximately 64 days, but this can vary a great deal. Mature sperms are then transported through the epididymis to the ejaculatory duct over a period of 12–21 days.

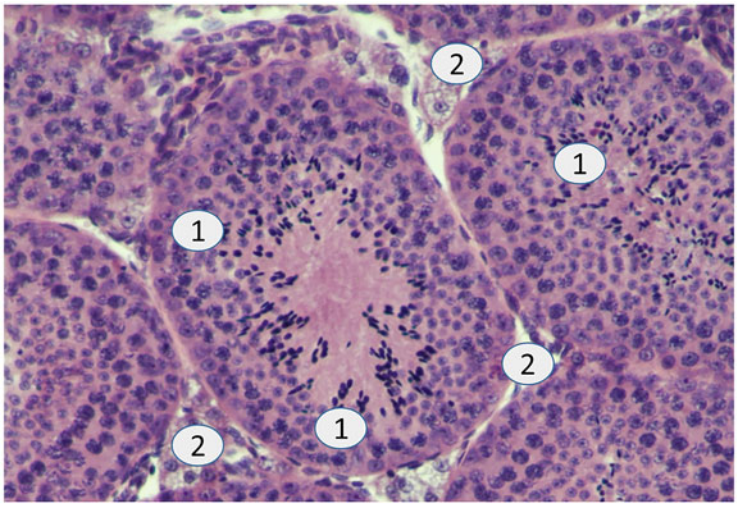

Fig. 9.3 Cross-section of the testis showing the normal structure of the seminiferous tubules in which cells in various stages of spermatogenesis can be seen (1) and the interstitial tissue (2) (H&E magnification 400×)

Stages of Spermatogenesis

Stages of spermatogenesis are explained as showed in Figs. 9.3, 9.4a, b, and 9.5.

The Seminiferous Tubules Contain Three Types of Cells

1. Sex cells (spermatogonia): These are the stem cells that differentiate into different cell lines during spermatogenesis.
2. Different cell lines necessary for the synthesis of spermatocytes and sperms.
3. Somatic cells of the testis, including
   (a) Large, elongated "nurse" cells called Sertoli cells (sustentacular cells) which are found in the seminiferous tubule between sections of spermatogonia. These are the only cells located in the basal membrane.
   (b) Peritubular myoid cells: These cells provide structural integrity to the seminiferous tubules. Thus, these somatic cells surround the seminiferous tubules within the testis. The cells are connected by junctional complexes similar to epithelial cells. Due to their structural function, the peritubular myoid cells contain cytoskeletal proteins, mainly abundant actin filaments, myosin, desmin, or vimentin and alpha-actinin.

Functions of Peritubular Myoid Cells

- They are contractile cells.
- They facilitate the transport of sperms and testicular fluid within the tubules.
- Peritubular myoid cell produce substances such as extracellular matrix components (fibronectin, types I and IV collagen, proteoglycans, and growth factors such as transforming growth factor beta (TGF-beta), insulin-like growth

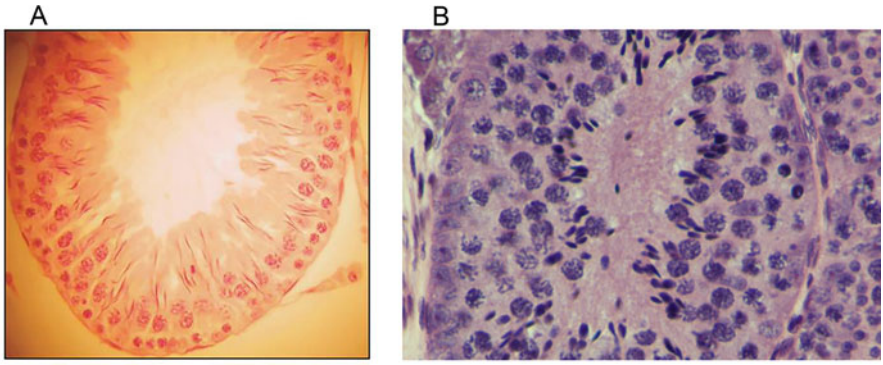

Fig. 9.4 (**a**) Cross-section of the testis: Microscopic structure of seminiferous tubule where spermatids can be seen (one of the stages of spermatogenesis) (H&E magnification 100×). (**b**) Cross-section of the testis: Microscopic structure of seminiferous tubule where spermatids can be seen (one of the stages of spermatogenesis) (H&E magnification 400×)

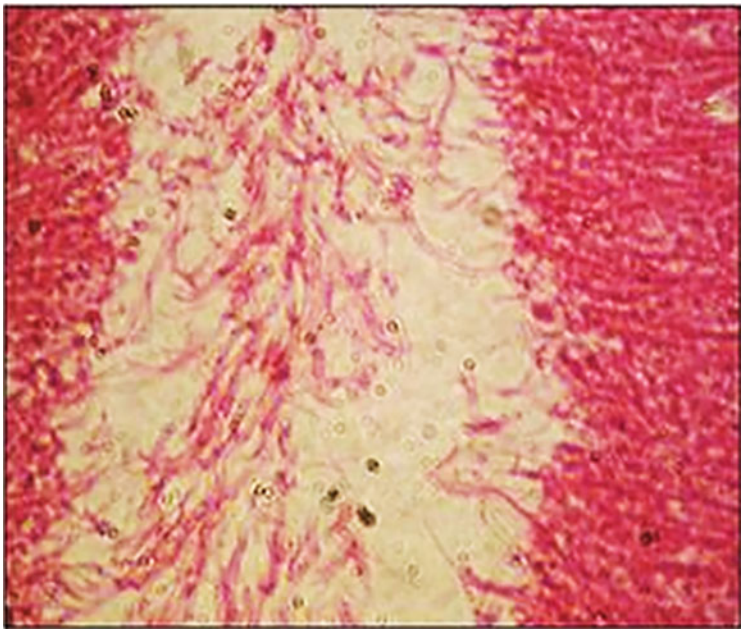

Fig. 9.5 Cross-section of the testis showing the presence of sperms inside the cavity of the seminiferous tubule (H&E magnification 400×)

factor, and activin A). As will be seen by the end of this chapter, these substances affect the functions of Sertoli and Leydig cells, and other hormones.

- Peritubular myoid cells express androgen receptors required in vitamin A/retinol processing.

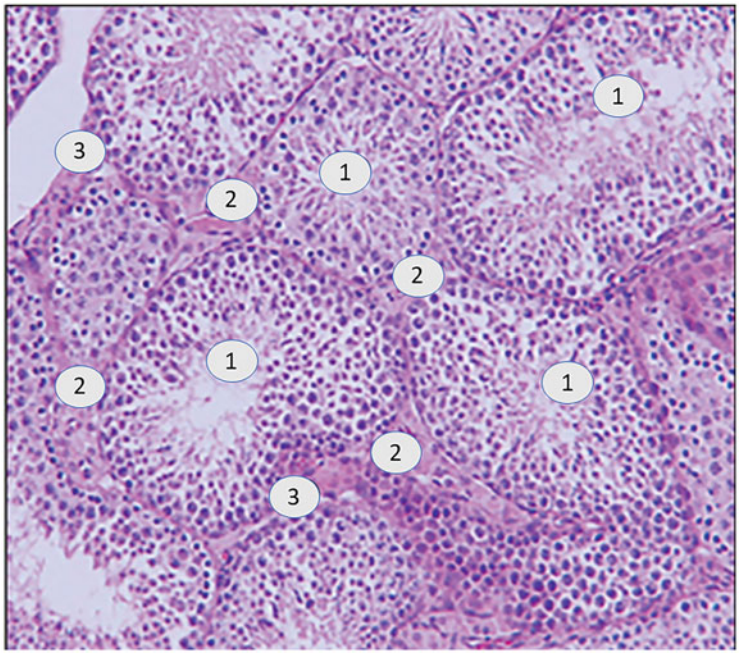

Fig. 9.6 Cross-section of the testes showing the normal structure of several seminiferous tubules (1) and the interstitial tissue between them (2) Peritubular myoid cells (3) (H&E magnification 10×)

- It is clear that peritubular myoid cells don't only provide integrity for the structure of the tubules, but also play a partly regulatory role in spermatogenesis and testicular function (Maekawa et al. 1996).

Functions of Sertoli Cells: The Nurse Cells

1. Sertoli cells act as sustentacular or "nurse" cells, and so are characterized by special properties proportional to their functions. Sertoli cells form Blood–Testis Barrier (BTB).
   - Sertoli cells are located on the basal membrane of the seminiferous tubules and fill the narrow spaces between nests of spermatogonia. Their functionally suitable structure extends between the basal membrane of the tubule and its antrum (Fig. 9.6). The Blood–Testis Barrier (BTB) consists of a unique type of tight junctional complex between adjacent Sertoli cells in the basal seminiferous tubule's epithelium. These connections take the form of secure extensions, with the complexes lying in the direction of the basal membrane to divide the tubule into two portions, a basal portion and the antrum which contains the spermatids. This is a barrier that regulates the passage of nutrients and materials through and within the testis. BTB physically divides the meiotic spermatocytes from post-meiotic spermatids away from testicular blood

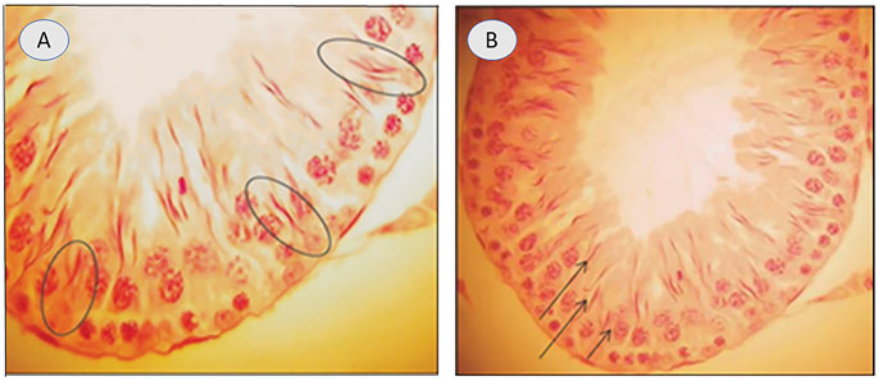

Fig. 9.7 Locations of stem cells within seminiferous tubule—Sertoli cells act as stem cell (**a**). Stem cells distributed equally across all seminiferous tubule stages (**b**). (H&E magnification 100×)

vessels, thereby preventing the autoimmune activity of the immune system against the immunogenic germ cells.

- Under the control of androgens, vitamin A compounds and thyroid hormones, Sertoli cells form the BTB at puberty, which regulates the passage of substances, drugs and toxic materials and prevents autoimmune disorders.
- Paracrine signals, such as the TGF-beta superfamily of cytokines (TGF-beta 3, activin A) and vitamin A (retinoid) signaling, act as potential factors for junction assembly and disassembly during the process of spermatocyte translocation.
- Endocrine and locally-produced testicular factors play a participatory role in the regulation of the BTB (De França et al. 1995; Willems et al. 2010; Tarulli et al. 2012; Stanton 2016).

2. Sertoli cells nuclei are located at the base while the cytoplasm is extensive, irregular, and constantly changing to allow sperms to move upwards to the surface of the tubule cavity (Fig. 9.7).
3. Sertoli cells act as "nurse" cells, and protective cells for developing spermatocytes by providing mechanical support, in addition to metabolic support by providing nutrition. Sertoli secretes a diversity of cytokines and immunosuppressive factors, to provide adequate nutritional supply and immune defense for sperm's development.
   - They secrete a fluid rich in certain ions that contribute to directing mature sperms in the right direction to the epididymis.
   - They are involved in the phagocytosis of excess cytoplasm released from the spermatids after they are enveloped.
   - Sertoli cells release many transporter proteins that facilitate transportation of transferrin, androgen-binding protein, and retinoid-binding protein across BTB (Porter et al. 1985; Sylvester and Griswold 1994; Mruk and Cheng 2004). The androgen-binding protein is synthesized by the cells under the control of FSH.

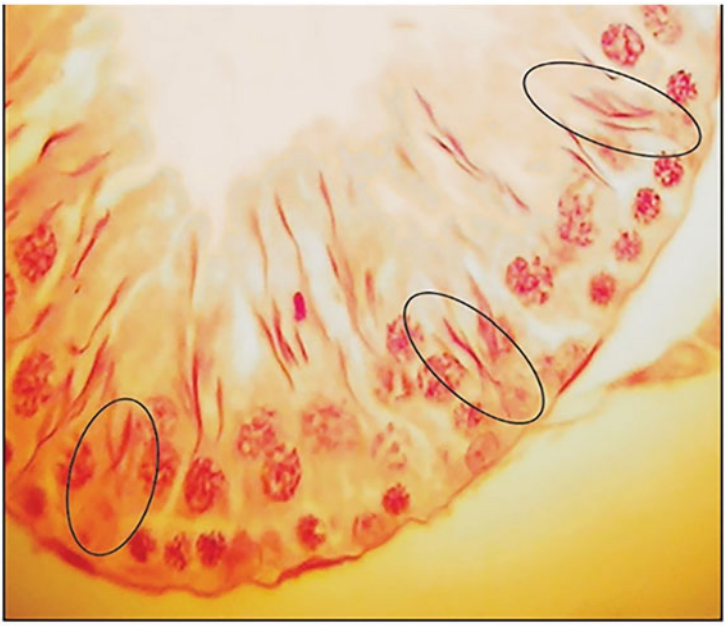

Fig. 9.8 Cross-section of the testis showing the structure of a seminiferous tubule, indicating the direction of the spermatids toward the Sertoli "nurse" cells present on the basal membrane of the seminiferous tubule (H&E magnification 100×)

- They secrete inhibin, which inhibits FSH secretion by the pituitary.
- They produce several substances such as estradiol, insulin-like growth factor, transferrin, and other compounds.
- In male fetuses, they are involved in the organogenesis of the testis.
- During male sex differentiation, fetal Sertoli cells produce a hormone called Mullerian-inhibiting factor or Anti-Mullerian Hormone (AMH). AMH mainly causes the regression of the female organs (Mullerian ducts, the anlage for uterus and Fallopian tubes) (Josso et al. 2005).
- Sertoli cell is a type of mesenchymal stem cells (Fig. 9.8).

9.2.4.2 Endocrine Cells of the Testes (Interstitial Tissue)

- **Interstitial tissue**: This includes Leydig cells and stem cells.
- **Leydig cells:** which are somatic cells and represent the endocrine tissue in the testis. These cells occur in the interstitial tissue either individually or in nests and make up 10% of the space between seminiferous tubules (Figs. 9.4 and 9.6).
- **Stem Leydig cells:** Adult Leydig cells develop from undifferentiated mesenchyme-like stem cells (stem Leydig cells) and exist in the same interstitial tissue during the early postnatal period (Fig. 9.9). Stem Leydig cells have been

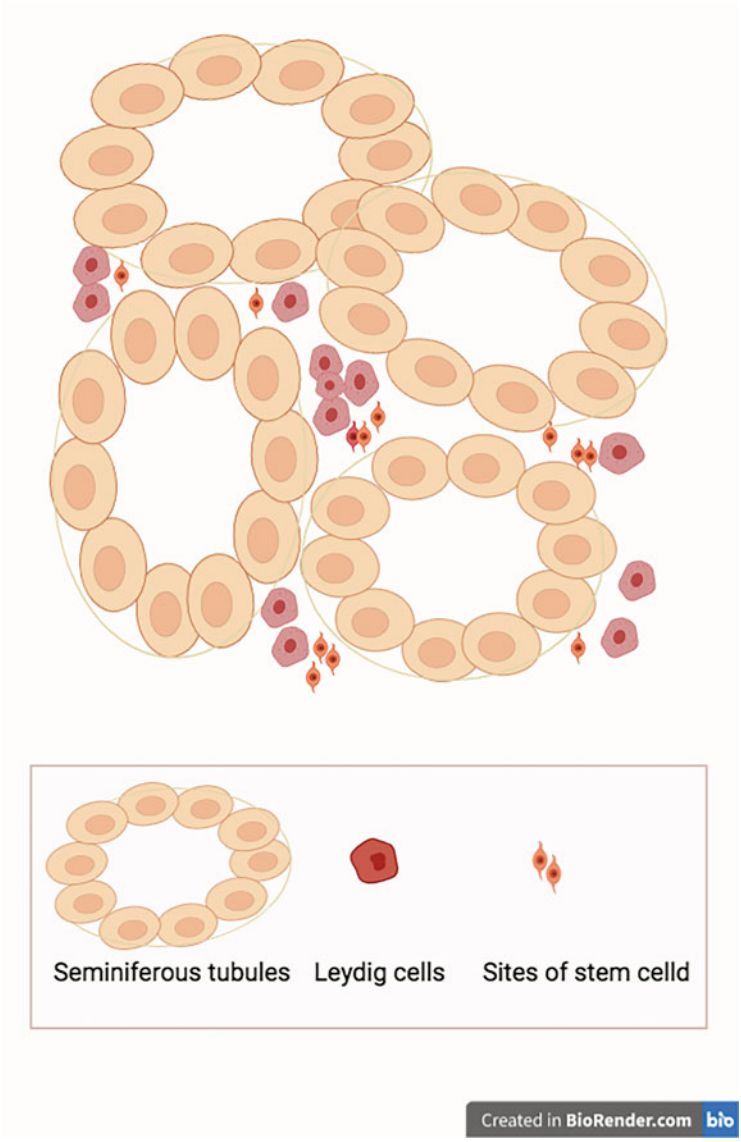

Fig. 9.9 Locations of Testis stem cells in interstitial tissue. (Reproduced from Al-Suhaimi and Aljafary (2019))

identified in peritubular and perivascular sites in adult testis to regenerate new Leydig cells instead of the loss of the adult cells (Chen et al. 2017a, b).

Physiological states for endocrine Leydig cell activity in the interstitial tissue of the testis (Figs. 9.9 and 9.10).

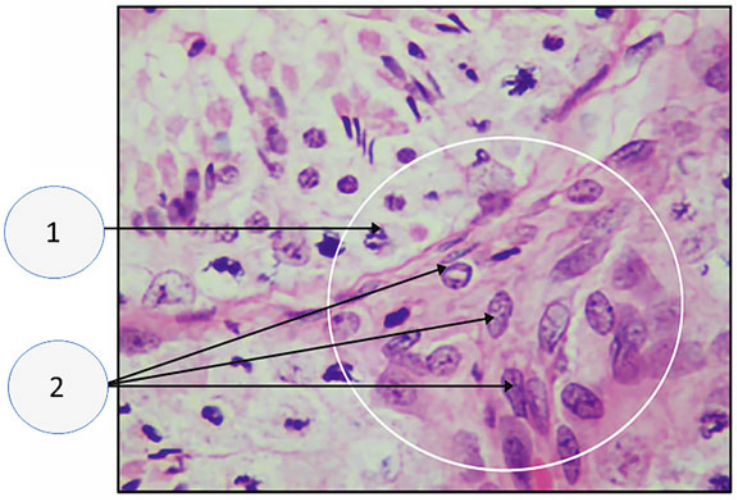

Fig. 9.10 Cross-section of the testis showing the interstitial tissue (1) as well as testosterone-producing endocrine Leydig cells (2) (H&E magnification 200×)

Endocrine Leydig Cells

- The Leydig cells produce testicular hormones called androgens.
- Testosterone and dihydrotestosterone are the main (more than 90%) source of circulating androgens synthesized and released by the testes into the spermatic venous blood; the remaining is synthesized and released by other tissues such as the zona reticularis of the adrenal glands in humans.
- The testes also produce estrogen, estradiol, and progesterone; these hormones contribute to the biosynthesis of androgens from cholesterol as a steroid precursor (Fig. 9.11).

9.2.4.3 Characteristics of Androgens

- Androgens are steroid hormones.
- Synthesis: refer to Fig. 2.4, Chap. 2.
- Testosterone is formed and secreted mainly from the Leydig cells.
- They are secreted in smaller quantities by the adrenal cortex.
- They circulate mainly in the blood, 60% of which is bound to a sex-hormone binding protein, globulin with high affinity and limited capacity, and 38% is bound to albumin which has lesser strongly and great total capacity; 1–3% of testosterone also occurs in the free form, allowing it to enter target cells.
- The bound hormone can enter the cell after it is released from the protein whenever biologically active testosterone is needed more than the less active free form.
- The androgens bind to the cell's cytoplasmic receptors and the hormone-receptor complex allows it to penetrate the target cell nucleus to induce a biological response.

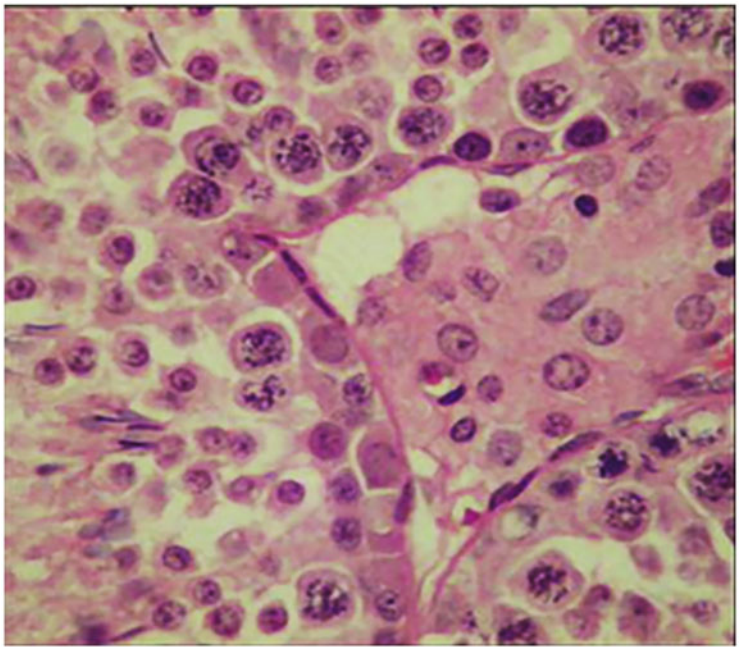

Fig. 9.11 Cross-section of the testis showing a reduction in the secretory activity of the interstitial endocrine cells, indicated by the dark-colored cytoplasm due to the presence of unreleased secretory vesicles (H&E magnification 200×)

- The androgens have a long half-life as they are bound to proteins. They have rapid clearance in the first hour with a half-life of 10 min, thereafter; they have a very slower decline in plasma level (100 min) (Sèdes et al. 2018; Guyton 1986; Guyton and Hall 2006, 2016; Bentley 1980; Bullock et al. 1991, 2001; Yeh et al. 2002).

9.2.4.4 Sexual and Reproductive Functions of the Androgens

The three steroids of main important in male reproductive functions are: Testosterone, dihydrotestosterone, and estradiol.

Sexual and Reproductive Functions

(a) **In the fetal phase**: This is essential for proper differentiation of the male reproductive system. Fetal Leydig cells are responsible for releasing the first peak of testosterone, the highest level required to masculinize the organs of the urogenital tract, like differentiation of vas deferens, seminal vesicles, and the Wolffian duct into the epididymis.

(b) **At puberty**: The hormone is involved in the growth and secretory activity of the reproductive tract such as the scrotum, epididymis, prostate, vas deferens, seminal vesicles, etc. Androgens are necessary for functional complementarity between these organs. At puberty, Leydig cells are also responsible for another secretory peak of testosterone to allow the development of secondary sexual characteristics and the initiation of spermatogenesis by promoting the physiological maturity of Sertoli cells.

(c) **Post-puberty**:

- The androgens are essential for the regulation of spermatogenesis. The androgens and their signals are essential for maintaining the survival and differentiation of the germ cell lineage. Thus, changes in androgenic signaling arrest the process of spermatogenesis.
- Although androgens are mainly expressed in somatic testicular cell types (Leydig, Sertoli, and peritubular myoid cells) in humans and rodents, its expression in germ cells is still debatable (Yeh et al. 2002). Androgens are also necessary for spermiogenesis phase, during which spermatids are transformed into mature sperms.
- After puberty they are necessary for preserving the differentiation and functions of the additional organs of the reproductive system needed for the production, storage, and secretion of sperms, such as the prostate, epididymis, and seminal vesicles, as well as to preserve male secondary sexual characteristics.
- The androgens respond to sexual appetite, and bring about hair growth of the pubis, underarm, face, chest, and areas of the body other than the scalp. They are also important for laryngeal development and increased vocal cord thickness in men. They are also involved in leadership characteristics and influence the social behavior of males.
- Androgens are key compounds for estrogen synthesis as well as for the bioavailability of free estrogen in peripheral tissues.
- Androgens directly affect the central nervous system to modulate other endocrine signals associated with hot flushes (Notelovitz 2004).

9.2.4.5 Anabolic Functions of Androgens

- Testosterone has an anabolic function and supports the development of muscle and bone. The androgens promote cell division, tissue growth and the extraction of nitrogen and certain salts needed for growth.
- The androgens are therefore anabolic hormones as they stimulate the synthesis of proteins in the skeletal muscles.
- In the same way as other sex hormones, the androgens promote the process of calcium deposition in the bone and epiphyseal fusion in the long bones. They do this efficiently but more slowly than estrogens (female hormone) which give males the opportunity for more bone growth, especially in the chest and shoulders.

- They increase weight and are involved in metabolism which is why removal of the testes leads to a lower metabolic rate.
- They stimulate red blood cell production; therefore, men have more red blood cells count than women (Guyton and Hall 2016; Bullock et al. 1991).

9.2.4.6 Recent Roles of Androgens in Female

Androgens have been found in recent years to be significant for regulation of female reproduction. The functioning of androgens is mediated through androgen receptor (AR). It has been proven that female fertility and follicle health, development, and ovulation is regulated by androgen functioning mediated by AR as suggested by global and cell-specific *AR*-knockout mouse models (Walters et al. 2019).

Numerous IVF clinics across the globe have implemented this concept on the basis of this information and the information obtained from clinics that depicted that androgens or androgen-modulating agents contribute in the enhancement of in vitro fertilization (IVF) stimulation in poor female responders. Moreover, it was also found from various human and animal researches that the onset of polycystic ovary syndrome (PCOS) may be attributed to the AR-mediated additional androgens. This implies that significant progress can be made in devising new therapies and treatments for PCOS by understanding the molecular processes behind the onset and advancement of PCOS as well as determining the target sites where AR is active (Azarchi et al. 2019).

The steroid-producing organs within human body including the adrenal glands and ovaries and tissues like skin are responsible for generation of androgens. The androgens commonly present in females are dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone, dihydrotestosterone, and androstenedione. Many cutaneous conditions can arise as a consequence of such androgens in women. For instance, women may experience androgen-mediated cutaneous disorders like acne, hirsutism, and female pattern hair loss (FPHL) (Reisch et al. 2019). But the pathophysiology of the mentioned conditions does not render complete understanding and clarity of the contribution of androgens in this regard.

9.2.4.7 Regulation of Testicular Function

The pituitary gonadotropin hormones LH and FSH are heterodimeric glycoprotein circulating hormones play a key role in reproductive processes. Further paracrine modulation by local factors like activins, and follistatin released within the pituitary gland itself. The integration of the entire these mechanisms and signals lead to the coordinated control of several responses such as expression of the subunit gene, protein production, and gonadotropin release to boost sexual maturation and regulate normal reproduction functions. GnRH is defined as the gatekeeper of reproduction's development and functions. GnRH stimulates specific, high affinity external cell receptors on gonadotropes triggers signal transduction cascades to activate the coordinated synthesis and release of the pituitary FSH and LH (Stamatiades et al. 2019).

Hypothalamic–Pituitary–Seminiferous Tubule Axis

- The hypothalamus secretes GnRH in a pulsatile manner into the portal veins leading to the anterior pituitary and this stimulates the pituitary to secrete LH (interstitial cell–stimulating hormone [ICSH]) and, to a lesser extent, FSH into the circulation (Fig. 9.12). Conversely, gonadotropin-releasing inhibitory hormone (GnIH) influences GnRH neurons, and inhibits the release of gonadotropins from the pituitary.
- FSH and testosterone act directly on the Sertoli "nurse" cells which facilitate the process of gamete production.
- FSH and androgens regulate the tight junctions between Sertoli cells and their proteins.
- FSH acts on the Sertoli cells which then secrete testosterone-binding protein which makes it possible to maintain a high level of bound testosterone in the tubule.
- FSH is needed to initiate spermatogenesis, whereas full maturation of the spermatozoa requires not only FSH, but also testosterone.
- Sertoli cells secrete an inhibitory hormone called inhibin which inhibits FSH secretion by the pituitary gland (Guyton and Hall 2016; Bullock et al. 1991, 2001).

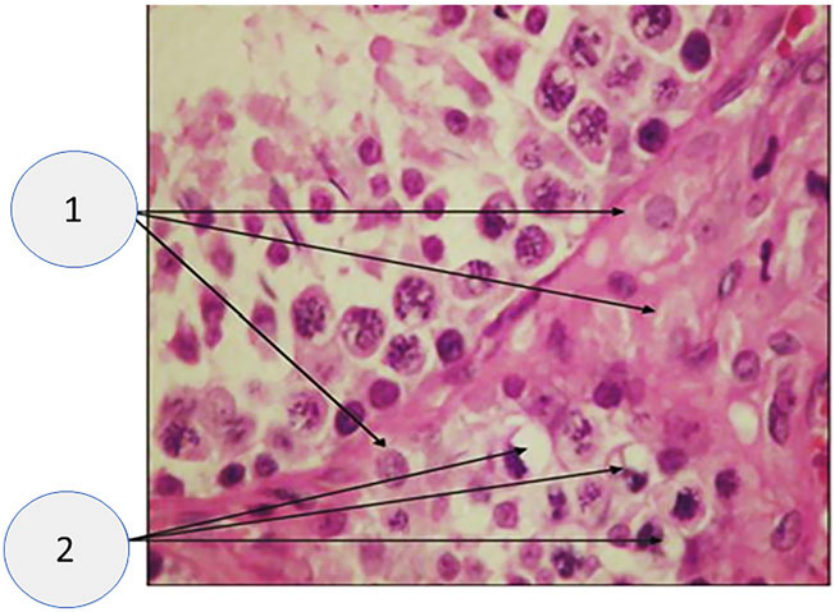

Fig. 9.12 Cross-section of the testis showing endocrine Leydig cells (testosterone secreting-cells) (1) with pale cytoplasm containing some spaces indicating secretory activity. It can also be seen that some of the other interstitial cells (2) contain cytoplasmic vacuoles due to fact collections (cholesterol as hormone's precursor pointing to lesser hormone production in them) (H&E magnification 200×)

The Domination Roles of Hypothalamic–Pituitary–Leydig Cell Axis

- The hypothalamus secretes pituitary-stimulating GnRH; these are hormones that stimulate the basal cells of the anterior pituitary to secrete the hormones ICSH (LH) and FSH.
- LH binds to its receptors on the Leydig cells. LH links with its G protein-coupled membrane receptors on Leydig cells and exerts its action through the protein kinase A signaling pathway.
- LH plays a key regulatory role in the steroidogenesis process at two levels:
  - By supporting cholesterol transfer into the mitochondria from the outer membrane to the inner membrane.
  - By activating the enzymatic pathways required for converting cholesterol to pregnenolone and then local testosterone production in enough amounts to meet the requirements for spermatogenesis, and to produce the hormone in the circulation.
- Increased testosterone levels in the blood inhibit LH secretion directly via the pituitary or the hypothalamus because both organs have androgen receptors which work by negative feedback mechanisms (Fig. 9.13).
- Many cytokines act at the hypothalamic level to inhibit significantly the release of LH but not FSH. Hypothalamic control of FSH and LH is influenced by cytokines, leptin, and nitric oxide. The adipocyte hormone, leptin, acts as a cytokine related to tumor necrosis factor (TNFα). In male rats, leptin shows a high tendency for the release of FSH and LH from the hemipituitaries in vitro. LHRH and leptin promote LH secretion by activation of neural nitric oxide synthase (nNOS) in the gonadotropes. The released nitric oxide induces guanylate cyclase that releases cyclic GMP leading to LH release (McCann et al. 1998).
- In addition to leptin, primate pituitaries express other adipokines such as adiponectin and resistin. It is thought that local production of adipokines/receptors integrates with circulating adipokine levels comprising of a relevant regulatory loop that participate to the precise regulation of pituitary functions (Sarmento-Cabral et al. 2017).
- The Leydig cells secrete peptide substances as paracrine signals which regulate testicular function.
- Prostaglandin acts as an autocrine signal. Dysfunction of its testicular synthesis may lead to idiopathic infertility in males (Rudolph et al. 2016a, b).
- Activins and inhibins are glycoprotein hormones that regulate the physiological function of the male and female reproductive systems. Inhibins antagonize activin and follistatin signaling in many aspects.
- Melatonin and serotonin from the pineal gland play physiological roles during puberty and the growth of the gonads. As described in Chap. 7, melatonin has important function on testis physiology, steroidogenesis and spermatogenesis in both somatic cells:
  - In Leydig cells, melatonin functions as a local endocrine modulator.
  - In Sertoli cells, melatonin affects cells growth, proliferation, energy metabolism and the oxidation state (Frungieri et al. 2017).

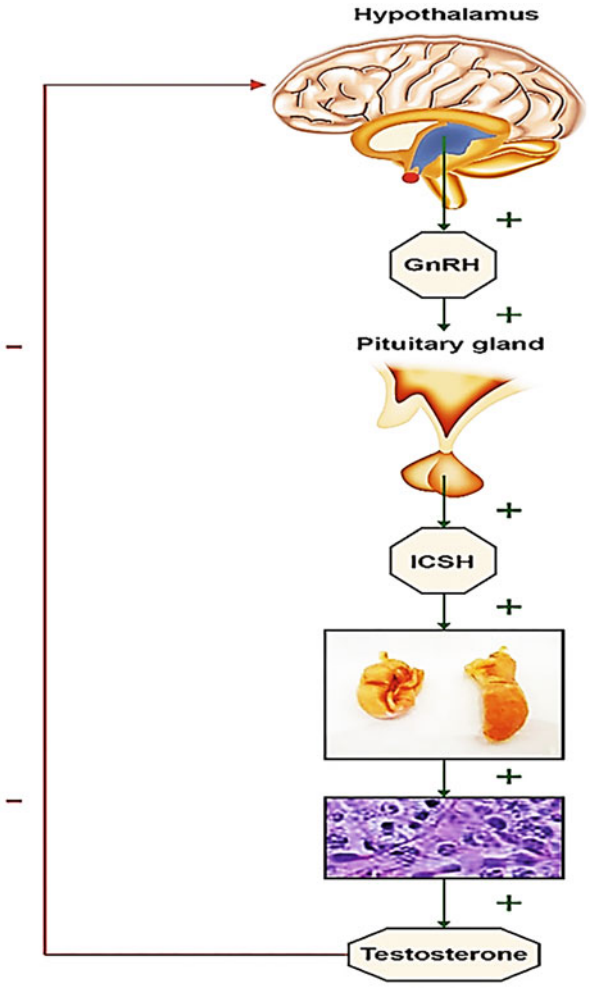

Fig. 9.13 Mechanism of testosterone secretion

  - Melatonin and corticotropin-releasing hormone (CRH) produced locally affect spermatogenesis through immune mechanisms in the testis (Rudolph et al. 2016a, b).
- **Calcium (Ca^{2+})** plays significant role in FSH & LH release. Calmodulin is calcium-modulated protein (CaM) which has four Ca^{2+} binding sites. Calcium influx plays a crucial function in GnRH regulation of rat LH DNA subunit gene transcription, Ca/CaMK II activation performs a significant role in the transit of GnRH signals from the plasma membrane to the LH subunit genes (Haisenleder et al. 2003). GnRH spends further effects on some gonadotroph functions, which clearly happen by CaM such as the proliferation of immature gonadotrophs, which is dependent on the enzyme called calcium and calmodulin-dependent

serine/threonine protein phosphatase (calcineurin) (Melamed et al. 2012). The Ca^{2+} molecular signal is essential pathway for testis steroidogenesis in Leydig cells (Abdou et al. 2013).
- Reproductive functions in male depend on cholesterol homeostasis, Sèdes et al. (2018) demonstrated cholesterol is a gatekeeper of fertility in male.
- There is an effect of bile acids on testis physiology and male reproduction, harmful impacts of bile acids on testis pathophysiology and fertility disturbances (Sèdes et al. 2017).

9.3 Ovarian Hormones and Reproduction

9.3.1 Ovaries: Tissue Zones of the Ovaries

These are the female reproductive glands and consist of a pair of endocrine and exocrine glands, whitish in color, each weighing up to 10 g. Their volume is about $4 \times 3 \times 2$ cm during the reproductive years. They are located in a low area called the ovarian fossa, on the anterolateral aspects of either side of the uterine wall and suspended super-posteriorly by the ovarian ligaments.

Tissue Zones of the Ovaries
- **Germline stem cell precursors** (ovarian surface epithelial cells).
- **Ovarian cortex** which is the part surrounding the medulla and is a connective tissue. The ovarian cortex contains ovarian follicles inside the stroma. It includes all follicular development stages: the oophorus pool, granulosa membrane with its cells, corona radiata, zona pellucida, primary oocyte, theca of follicle, antrum and follicular liquid, and the corpus luteum.
- **The inner layer is the ovarian medulla** which is in the center of the ovary and is devoid of follicles. It is made up of fibrous tissue, blood vessels and nerves.
- **Hilum**: This is the point of attachment of the ovary to the mesovarium (Gardner and Shoback 2007).

9.3.2 Puberty in Females

Puberty in females occurs when all the internal female organs are fully developed. This is clearly indicated by the start of menstruation (menarche) between the ages of 10 and 16 years. Puberty is basically regulated by the hypothalamus and pituitary glands. The hormones of the thymus gland, leptin, and pineal gland hormones are also involved. There is also a physiological relationship between melatonin levels and puberty in females. The decline in melatonin levels during puberty is not entirely accounted for by body mass or age (Crowley et al. 2012). The onset of puberty also varies according to geographical location, the environment, diet, and other regulatory hormones, in addition to psychological and other factors.

The period of minipuberty of infancy is characterized with greater activity of reproductive axis. The period is also characterized with variation in concentrations of reproductive hormone as well as variation in organ size; however, this period is not characterized with clear description of longitudinal changes. In short, the ovarian size of infant was at its peak at 16 weeks depending on the developed follicles' quantity and size. Hence, the current research may prove helpful in future to determine the reference range of postnatal development of ovary size in healthy term infants (Chin et al. 2021).

Puberty is unique in the sense that there has been continues changes may occur due to environmental influences and interaction with genetic determinants. These changes are suggested evolving pattern of the pubertal process. For example, some trends of early breast development have been observed during the two past decades in some countries (Bourguignon and Juul 2012).

9.3.3 Ovaries Functions

9.3.3.1 Exocrine Function

Production of mature ova during reproductive period from ovary epithelium stem cells. It has been reported that expression of pluripotent and oocyte-related genes in single putative stem cells obtained from human adult ovarian surface epithelium (Virant-Klun et al. 2013). In another study, differential expression of stem cell markers specific for pluripotent such as (nuclear OCT-4A, SSEA-4, CD133, cytoplasmic OCT-4 were reported in ovarian stem cells in vitro (Parte et al. 2014).

Oogenesis The embryo is initially developed on the basis of the genetic material supplied by female oocyte. Thousands of such oocytes are developed and incubated within the ovary. The first phase of ovary development or oogenesis involves the production of oogonia from the mitotic division of primordial germ cell. Consequently, oogonia act as primary oocytes that perform the first meiosis. This is followed by second meiotic division of the secondary oocyte which yields a haploid ovum as well as a second polar body (Rodrigues et al. 2008).

Folliculogenesis The main site of the onset of this process is core of ovarian cortex. There is a variation in the shape of membrane granulosa from flat to cuboidal shape with the development of primordial follicle inside the primary follicle. Moreover, the theca layer is developed inside the primary follicle; this layer contains the granulosa membrane. Due to mitotic division of Granulosa cells, there are 2–6 layers in secondary follicles. Follicular fluid is released by the granulosa cells when Graffian follicle is being developed; the form of this fluid and its constituents resemble those of blood. All the follicles found in a female are present in her body at the time of birth. The follicles do not develop afterwards. About 70–99% of these follicles are lost prior to ovulation age; this is because of atresia or apoptosis (Johnson and Everitt 2000).

9.3.3.2 Endocrine Function

- Production of most of the steroid sex hormones circulating in the blood.
- Production of local regulatory hormones.

The ovaries contain the following basic components (Fig. 9.14) which play a coordinated and regulated functional role under the control of the hypothalamus and pituitary:

- **Surface epithelium mesenchymal stem cells: Oogenic cells**.
- **Follicl**e: It performs both endocrine and exocrine functions simultaneously (synthesizes and releases the ovum, and releases estradiol). This is the functional unit in the pre-ovulatory phase and consists of theca cells and granulosa cells.
- **Ovum** which is surrounded by the same two layers.
- **Corpus luteum:** It functions as a temporary endocrine gland due its limited lifespan, releases progesterone. This is the main functional unit in the post-ovulatory phase.
- **The corpus albicans** is a white structure that results from luteolysis of the corpus luteum. The corpus albicans is the last component of the ovulatory cycle as it is absorbed completely.

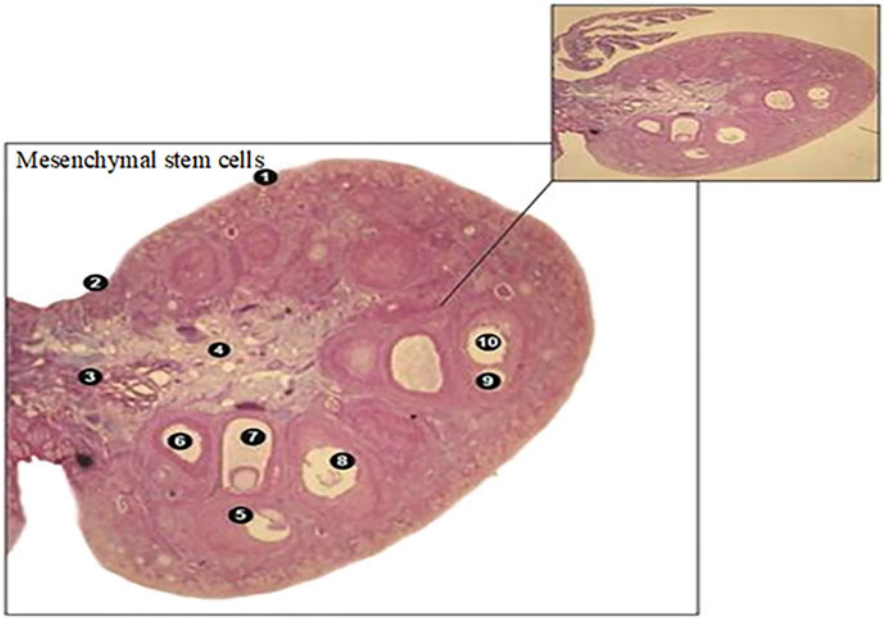

Fig. 9.14 Cross-section of ovarian tissue (H&E magnification 100×). Numbers (3–10) indicate the ten different stages of developing oocytes arising from mesenchymal/germline stem-cell precursors (oogenic-stem cells (1–2))

9.3.3.3 Main Sex Hormones and Sources

Sources of Androgens in the Male

- The Adrenal cortical layers of zona reticulata and zona fasciculata produce androgens namely the dehydroepiandrosterone (DHEA) and androstenedione.
- Leydig cells located near the seminiferous tubules in testes synthesize Testosterone which is acted upon by the 5α-reductase in target tissues to convert into dihydrotestosterone (DHT). Despite being about ten times scarce as compared to Testosterone, DHT performs almost all biological actions of testosterone.

Sources of Androgens in the Females

- The precursors circulating within the target tissues produce active androgens; these androgens act locally and are metabolized in the target tissues.
- In females, the following androgen precursors can be found (Burger 2002).
- DHEA sulfate (DHEAS) which is synthesized by zona reticularis within adrenal glands;
- DHEA which is synthesized by zona reticularis, theca cells in ovaries, and circulating DHEAS;
- Androstenedione which is synthesized by zona fasiculata within adrenal glands, ovarian stroma, and circulating DHEA.
- Circulating precursor molecules account for nearly 50% of testosterone production in females while the rest of the testosterone is produced in zona reticularis and ovarian stroma.
- Peripheral target tissues in females synthesize DHT but it has lower concentration within serum.
- Estrogens may be synthesized in postmenopausal women by conversion of Testosterone (not DHT) into estradiol in specific peripheral tissues in the presence of aromatase (P450aro).

Sources of Estrogen Synthesis

In the Females

- Estrogen is produced within the ovaries in granulosa and theca cells; it is also produced in corpus luteum.
- Considering the production of estrogen in extra-gonadal sites, it is produced by the conversion of androgens to estrone through peripheral aromatization in presence of aromatase.
- Fat cells: the conversion of androgen to estrone leads to rise in serum estrogens.
- Bone: estrogen is produced by the conversion of testosterone into local estrogen for assisting the development of epiphyses.

In the Males

- Aromatase is expressed in specific peripheral target tissues; it is an enzyme that plays a vital role in converting androstenedione to estrone and converting circulating testosterone into estradiol.

- It is believed that estrogens produced by the action of aromatase act locally and have limited systemic impact as they are metabolized in target tissues.
- Main expression of aromatase in males can be seen in bones (specifically osteoblasts and chondrocytes); in adipose tissues and in reproductive tract specifically in Leydig cells, Sertoli cells, and mature spermatocytes.

Sources of Progestin

- When 3β-HSD acts on pregnenolone in the corpus luteum, the progesterone is produced. It is also produced by the placenta during pregnancy. Adrenals also produce progesterone during the synthesis of androgen and mineralocorticoid.
- Two types of products are obtained during hormone synthesis depending on the menstrual cycle; one of these products is estradiol which is produced during follicular maturation, while the other is progesterone produced during the luteal phase after ovulation.
- The ovaries are not only the place where oocytes are produced and stored. It is also an endocrine gland that secretes, along with other tissues, several sex hormones essential for reproduction, the most important of which are:

  Pre-puberty: Estrogen is produced by peripheral and limited conversion of androgen to estrogen.

  Post-puberty: The ovary secretes estradiol, estrone, progesterone, and inhibin which circulate in the bloodstream. The ovary also secretes local hormones such as activin; the latter is a member of the TGF family (Burger 2002; Miller et al. 2006; Stocco 2001; Miller and Auchus 2011).

Steroidal Sex Hormones

The ovarian follicle and corpus luteum are the main units that secrete steroidal sex hormones.

- Follicle: This contains androgen-producing theca cells while the granulosa cells produce estrogen as well as inhibin A, B, and activin.
- The dominant follicle produces multiple intra-ovarian hormones and growth factors in its dominant follicular fluid (DFF) to serve as effective paracrine functions in both normal young and older ovulatory women (20–45 years) but in different concentrations. Several hormones are identified in DFF such as estradiol, progesterone, androstenedione, testosterone, inhibin A and B, activin A, and follistatin. DFF also, contains growth factors like Vascular Endothelial Growth Factor, Insulin-Like Growth Factor I (IGF-I), IGF-II, IGF-Binding Protein-2 (IGFBP-2), and IGFBP-3 (Klein et al. 2000).
- Corpus luteum which synthesizes progesterone.
- The zona reticularis of the adrenal cortex which produces androgens.
- Other tissues such as the liver, hair follicles and adipose tissue convert and produce estrone from precursor compounds (androgens).

- The placenta produces hormones such as estriol which is believed not produced by the ovary.
- The most important estrogens in the circulation are estrone, estrone sulfate, estradiol, and estriol, whose strengths of activity decrease from estradiol to the weakest, estriol.
- Woman produces greater amount of androgen than estrogen. The main blood steroids mostly categorized as androgens, comprise of the following compounds in ascending order of serum levels:
- Dihydrotestosterone, testosterone, androstenedione, dehydroepiandrosterone and dehydroepiandrosterone sulfate. Only the first two androgens bind their receptors, while the remaining steroids are working as pro-androgens.
- Dehydroepiandrosterone is mostly produced by adrenal, controlled by ACTH and acts as a precursor for the peripheral synthesis of effective androgens. The ovary is also synthesized dehydroepiandrosterone (Burger 2002).
- The most important androgens in the blood are dehydroepiandrosterone sulfate and testosterone.
- Steroids circulate in the blood in both free and bound forms. Most of steroids bind to sex-hormone binding globulin. A quarter is bound to albumin, apart from progesterone which binds to transcortin and albumin.

Chemical Structure of the Steroid Hormones

The estrogens and progesterone consist chemically of steroids synthesized by the cells from cholesterol, especially lipoproteins in the plasma, or from the small amount of cholesterol acetate produced in the cell (Fig. 2.4 in Chap. 2). After the synthesis of androgens, they are converted to estrogens by the process of "aromatization," during which androgens are converted to their corresponding estrogens by aromatases. The aromatase, estrogen synthetase, represents a key enzyme responsible for the biosynthesis of estrogens (Simpson et al. 1997).

9.3.4 Role of the Endometrium

During the reproductive period, the lining the uterus (endometrium) acts in synchrony with the ovulatory cycle functionally and periodically, but loses its regularity and continuity at the start of puberty and before the onset of menopause. The cycle is characterized by wide variability in its length, and normally ranges from 26 to 35 days, starting from the first day of the menses which takes about 5 days, followed by a fertile phase from 5 days before ovulation, and a lower fertility phase which depends on age and cycle length. The menstruation, endometrium phases and ovarian cycle with its hormonal regulation will be fully described in the following sections.

Proliferative Phase The endometrium becomes thicker, more vascular and richer in mucus-secreting glands. This phase coincides with the follicular phase in the ovary. It begins with menstruation and ends at ovulation.

Secretory Phase The uterine glands are characterized by aqueous mucous secretions. This coincides with the corpus luteum (luteal) phase in the ovary. It begins at ovulation and ends before menstruation.

Degenerative Phase and Menstruation The menstrual cycle in women is a physiological event and initiates between the ages of 12–16 years and continues throughout the reproductive period. It is an indication of puberty.

If the released ovum is not fertilized in the uterus, it is degraded and the endometrium—the continued existence of which is dependent on high progesterone and estrogen concentrations—begins to disintegrate and is eliminated with the blood. This is called **menstruation** and results from a decrease in these two hormones and other factors, after which the uterine cycle begins again.

Composition of the Menstruum This consists of secretions from the endometrial glands, uterine lining cells, blood from lysed capillaries and the unfertilized ovum.

Pregnancy When the ovum is fertilized during the ovulation phase, the hormones progesterone and estrogen continue to rise which maintains the corpus luteum throughout the pregnancy period and prevents the formation of an ovulatory follicle or new ovum. They also inhibit the pituitary from secreting FSH and LH. So long as the corpus luteum is present, the endometrium is not degraded, which means that menstruation does not take place.

9.3.5 Regulation of Ovarian Function

- The production of oogenic-stem cells is controlled by the endocrine and immune systems (Fig. 9.15).
- The main regulator of ovarian function is the hypothalamic–pituitary–ovarian axis. The arcuate nucleus of the hypothalamus contributes to reproductive function in females, so changes in its morphology influence female sexual receptivity in rats (Rudolph et al. 2016a, b). Ovarian function is linked to that of the hypothalamus which secretes GnRH (LHRH/FSHRH) in a repetitive and pulsatile manner, as the hypothalamus is the initiator of reproduction process.
- In contrast, Gonadotropin-Inhibiting hormone (GnIH) acts as an influential regulator of reproduction in human, mammalian, and birds. GnIH modulates the activity of GnRH neurons. GnIH inhibits the synthesis and release of pituitary gonadotropins by two pathways: decreasing the activity of GnRH neurons or/and directly by inhibiting the gonadotrophs (Ubuka et al. 2012; Aliaga-Guerrero et al. 2018).
- The hypothalamic hormones regulate the pituitary FSH and LH to synthesize and produce their gonad-regulating hormones which in turn regulate ovarian secretion.
- Kisspeptin (formerly known as metastin) in humans and non-human animal models was proven to be both vital and sufficient for activation of the

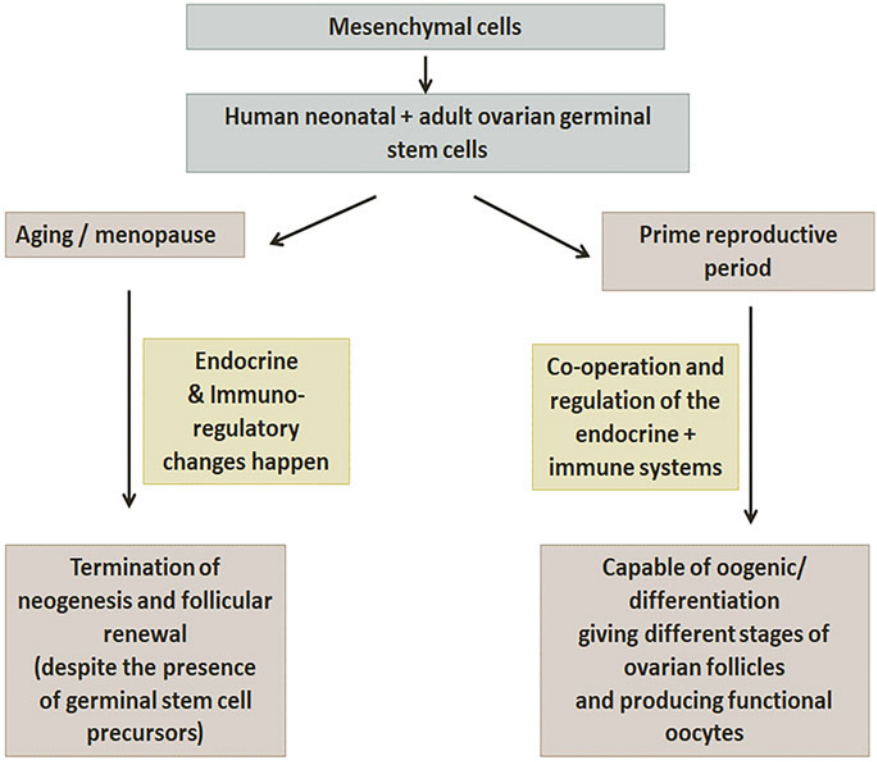

Fig. 9.15 Stem cell's role in oogenesis in ovary (Al-Suhaimi and Aljafary 2019)

reproductive system, during puberty and in adulthood, it is an essential component in the reproductive axis. Kisspeptin is the most potent activator of GnRH neurons. Importantly, kisspeptin neurons intermediate many of the regulatory actions of other signals such as metabolic, circadian, hormonal, or stress signals. This makes kisspeptin neurons as unique key and nodular points and ducts for transmitting many endogenous and exogenous signals to the reproductive axis (Kauffman and Smith 2013). Kisspeptin encoded by the *KISS-1* gene in humans acts as a modulator of puberty and fertility because of its stimulatory effect on hypothalamic GnRH. *KISS-1* transcripts are markedly elevated in both sexes 8 weeks after birth, and also maintains elevated levels in adults, indicating its reproductive functions at both the onset of puberty and maintenance of reproductive function (Chen et al. 2017a, b).

- The steroid hormones produced by the ovaries, especially estradiol and progesterone, are affected by negative and positive feedback, depending on the ovulation phase in question, and regulate the secretion of FSH with LH from the pituitary or through hypothalamus.
- Circadian rhythm cycles and photoperiod have a clear physiological effect on reproductive functions and regulation. Neuroendocrine hormones such as

gonadotropin-releasing hormones and gonadotropin-inhibitory hormones are influenced by melatonin in human and animals such as mammals, birds, and fishes.

- Important regulation is exerted by the hormones produced by the pineal gland, including melatonin and serotonin. During the prepubertal stage in females, melatonin and serotonin released from the pineal gland play modulatory roles in female puberty. Serotonin suppresses the hypothalamic signals to the gonads. In females, either intermediate decreases in hormone levels, or the decrease in melatonin peak may be considered as an indicator of pubertal progression (Crowley et al. 2012).
- In addition to the regulatory effect of GnRH on gonadotropins, there are important regulatory neurotransmitters, including acetylcholine, noradrenaline, dopamine, serotonin, melatonin, glutamic acid, oxytocin, and nitric oxide (NO). Neuropeptides such as noradrenaline, glutamic acid and oxytocin stimulate LHRH release through stimulation of nNOS, which follows the pathway described by McCann et al. (1998). Oxytocin and/or glutamic acid stimulate noradrenaline neurocytes in the hypothalamus that induces NOergic neurons by alpha-1 receptors. The secreted nitric oxide spreads into LHRH nerve terminals and stimulates LHRH secretion by activating guanylate cyclase and cyclooxygenase. Nitric oxide doesn't only regulate the secretion of LHRH to be directed to the pituitary, but also to stimulate mating by actions at the level of brain stem (McCann et al. 1998) (Fig. 9.16).
- Leptin. In females, leptin accelerates the onset of puberty. It also regulates LHRH secretion from the hypothalamus in adults. The leptin receptor gene is expressed in the hypothalamus and ovary. Leptin decreases estradiol production from the granulosa in vitro. Leptin as nutritional/ metabolic hormone gives rise a new tool on the tight correlation between leptin and reproductive functions. Its nutritional mechanisms are considered in several ovulatory disorders (Bringer et al. 1999).
- Other local or systemic ovarian hormones such as inhibin, activin, and follistatin have physiological effects will be fully described at the end of this chapter.
- Ovarian hormones such as activin and prostaglandin as well as oxytocin have a paracrine or autocrine action.
- The sympathetic innervation is required for the ovary as it influences the ovarian morphology, physiology and steroid synthesis. In contrast, prolonged post-natal denervation with an adrenergic blocking agent reduces more than 40% of the volume of ovarian follicles, granulosa cells and theca-interstitial cells. Also, denervation decreases the ovarian concentrations of pregnenolone and progesterone, leading to delayed puberty. The main cause of these disturbances is a blockade of the first steps of steroidogenesis, like levels of the cholesterol side chain cleavage enzyme P450, leading to reduction in pregnenolone levels (Rosa e Silva et al. 1997).
- The duration and intensity of regulatory hormones vary according to the phase of the ovarian cycle.
- Regulation varies depending on the life stage of the female: pre-puberty, reproductive age, and menopause.

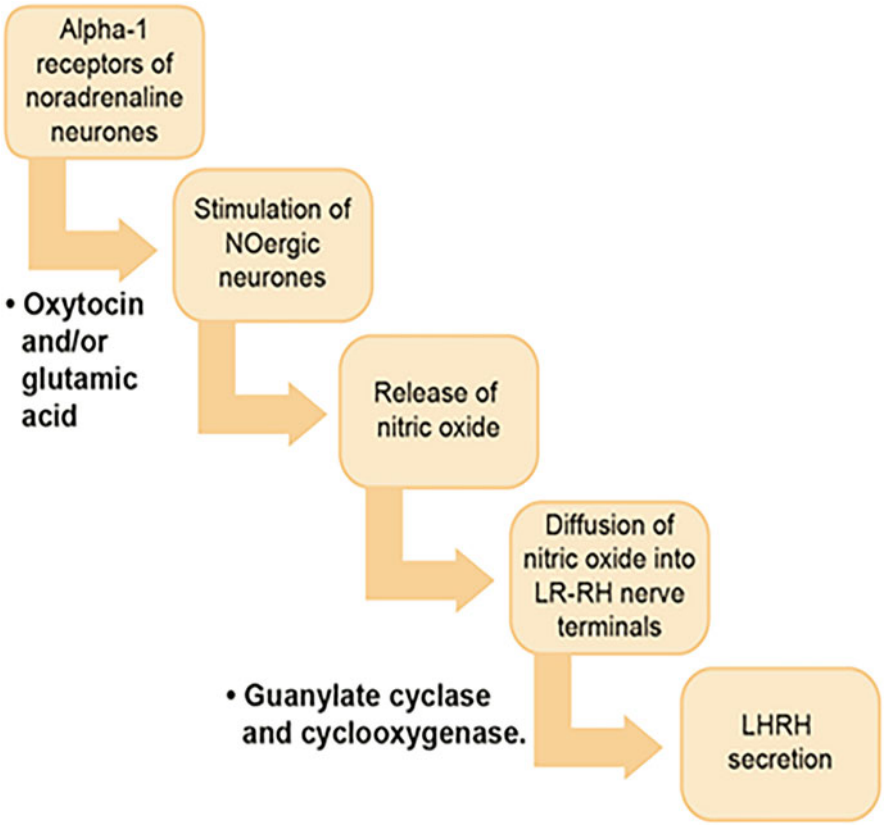

Fig. 9.16 Illustration of the pathway of the neurotransmitters on LHRH release

- During menopause, ovarian stem cells fail to maintain their oogenic property because of the changes in the endocrine and immunoregulation alteration (Fig. 9.15).
- Calcium (Ca^{2+})/ calmodulin plays significant roles in FSH & LH release in female.

9.3.6 Phases of the Ovarian Cycle

The ovary contains a network of blood vessels (for the endocrine functions) and local systems (for the paracrine and autocrine roles) to adjust the activity of gonadotropins FSH/LH and to coordinate follicular growth, steroid formation, and ovulation.

9.3.6.1 Pre-ovulatory Phase (Follicular Phase)

Gradual follicle growth takes place in the ovary until the follicle and ovum are fully mature. The beginning of follicular growth coincides with the release of menstrual blood from the uterus while the proliferative phase of the endometrium starts with the end of menstrual flow.

Duration The follicular phase takes about 10–16 days, its duration is variable, and it is therefore responsible for variations in the length of the ovarian cycle in women (Reed and Carr 2015), but the follicular phase can extend to 25 days.

A dominant follicle is selected in the mid period of this phase. By the end of this phase, only the dominant follicle generally reaches the final growth stage to be eligible for ovulation, after going through the following phases:

New concept on oogenesis

"Stem cells in the ovary and new concept on oocytes presence during the women life. In human and mammalian ovaries, surface epithelium mesenchymal stem cells are present not only in the fetal period but also in adulthood and old age".

New oocytes (with zona pellucida and granulosa cells) originate from the surface epithelium (somatic cells) arising from mesenchymal stem cells in the tunica albuginea. The ovary can form primary follicles during the reproductive period, so it was revealed that the term "germinal epithelium" could be reinstated (Nishida and Nishida 2006). It has become clear that both human neonatal and adult ovarian germline stem-cell precursors (ovarian surface cells) have the capability for oogenic/differentiating and producing functional oocytes, so it renews the oocyte pool (neo-oogenesis) and ensure follicular renewal during the prime reproductive period, with the co-operation and regulation of the endocrine and immune systems, and cellular support. After the prime reproductive period, aging starts, and menopause occurs because of the immunoregulatory changes that causes cessation and terminate neo-oogenesis and follicular renewal in vivo despite the existence of germline stem cell precursors. The rest of oocytes in the primordial follicles retain ovarian function but advancing age (aging oocytes) correlates positively with the occurrence of fetal chromosomal abnormality. Applications of ovarian stem cells can lead to a promising and advanced therapeutic approach to premature ovarian failure. For crossing over of chromosomes, new germ cells divide symmetrically, enter the cortical vasculature, and form new primordial follicles by connecting with cell nests of the granulosa deeply in the ovary cortex (Bukovsky 2011).

Primordial Follicles These are the essential reproductive units, composed of primary ovarian cells (oocytes) surrounded by a single layer of granulosa squamous cells and a basal membrane (Fig. 9.17). They haven't blood supply. The oocyte influences its own fate by releasing several factors include two specific growth factors related to Transforming growth factor (TGF-β); they are: Bone Morphogenic Protein (BMP)-15 and Growth Differentiation Factor (GDF)-9 that stimulate granulosa cell proliferation.

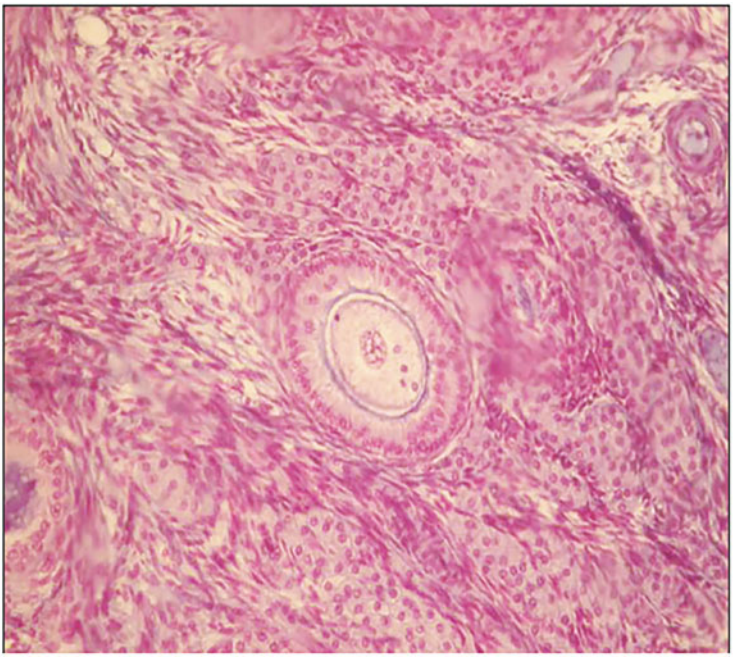

Fig. 9.17 Cross-section of ovarian tissue showing a primordial follicle (immature follicle) containing the oocyte (H&E magnification 100×)

The granulosa responds with local hormones such as follistatin, to decrease the inhibitory effects such as (activin A, Mullerian-inhibiting factor) and support stimulators of oocyte growth (Gardner and Shoback 2007).

Duration Develops from the sixth month of gestation.

Primary Follicle Its development indicates the beginning of follicular growth. Primary follicles differ from primordial follicles in multiple aspects. Primary follicle growth greatly leading to larger follicles called vesicular follicles. The oocyte begins to grow, the zona pellucida is formed, which is a thick glycoprotein layer synthesized by the oocyte and separates it from the granulosa layer, forming a barrier surrounds and protects the oocyte and the conception (Fig. 9.18). Finally, the granulosa transforms from squamous cells into cuboid cells.

Duration This stage mostly lasts for 150 days because of the doubling time (more than 250 h) of granulosa cells.

Secondary Follicle The developing follicle. The ovum develops inside the follicle to a maximal oocyte growth (120 μm in diameter), proliferation and increase in number of the granulosa cells and acquisition of theca cells (Fig. 9.19). During this phase, receptors of FSH, estrogen, and androgen develop.

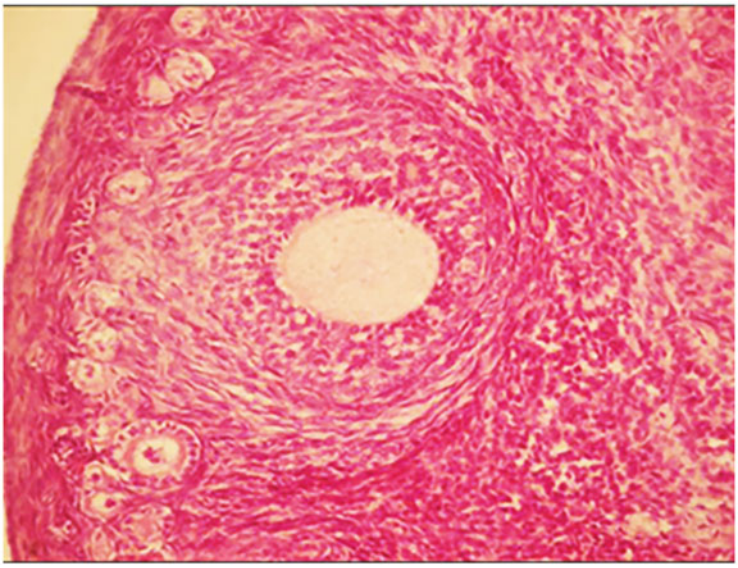

Fig. 9.18 Cross-section of ovarian tissue showing a primary follicle (immature follicle) containing the oocyte (H&E magnification 400×)

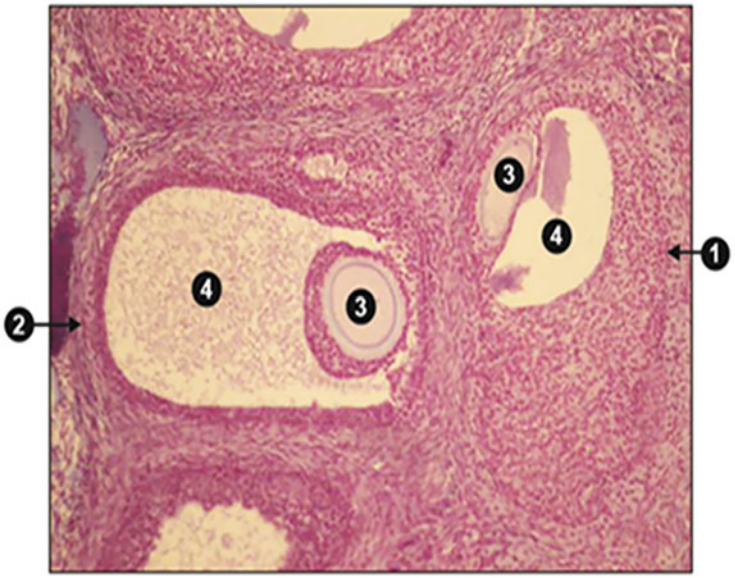

Fig. 9.19 Cross-section of ovarian tissue showing a secondary follicle (1) and mature follicle (2) containing the oocyte in a peripheral position (3) Note the difference in the amount of follicular fluid (4) Note the corona radiate surrounding the oocyte and the cellular connections with the granulosa zone (H&E magnification 400×)

Duration This stage takes about 120 days for the doubling time of granulosa cells.

Tertiary Follicle The follicle develops further (called the early antral phase). This is characterized by the formation of an antrum/ cavity containing a fluid made up of proteins, minerals, progesterone, steroid hormones and other permeable substances. During this phase the granulosa cells differentiate into several distinct layers by the control of FSH, the oocyte derived growth factor GDF-9 is an important in this process. The thecal cells become more differentiated and some of its subpopulations acquire LH receptors and are eligible for steroidogenesis, theca cells act as templates for the secretion of pre-estrogens as well as other hormones. The follicles develop receptors for FSH and can also secrete **activins** which generally function in an autocrine manner; there is negligible level in the blood and doesn't change throughout the menstrual cycle, but it acts in the ovary to stimulate FSH receptors expression in the granulosa to accelerate the folliculogenesis and forms the follicle with diameter of up to 400 μm. In addition to activin that regulates folliculogenesis, the granulosa cells synthesize inhibin A and inhibin B which have indirect roles in folliculogenesis and steroidogenesis.

In this stage, the ovum grows to its maximum size and is surrounded by cellular cumulus oophorus. In the cases of prepubertal females and those taking oral contraceptives, the follicles may arrest at different stages up until this point as in this phase of follicular development, FSH is critical for growth and survival, so if FSH doesn't rescue these follicles, they undergo atresia.

Mature Follicle It was called formerly a Graafian follicle. When the follicle nears maturation, additional follicles stop developing and the antrum filled with the follicular fluid increases in size. Highly differentiated granulosa cell layers begin to surround it. These can secrete steroids, particularly estrogen, at a maximum activity as can the inner thecal layer consisting of large clusters of steroid-producing cells. Immediately before ovulation, the cumulus oophorus surrounding the ovum ruptures, leaving the ovum surrounded by the corona radiata which are attached to the granulosa by cell connections which break before ovulation to allow the ovum surrounded by the corona radiata to float freely inside the follicle. At this point, the follicular diameter is 1.5–2.5 cm (Fig. 9.19) and can be seen below the surface of the ovary so that these cells no longer appear at the surface and become avascular and lysed (Al-Motabagani 2008; Burkitt et al. 1996; Young and Heath 2000; Bullock et al. 1991; Gardner and Shoback 2007; Greenspan and Forsham 1986). The ovarian follicle includes oocyte, cumulus oophorus, membrana granulosa & granulosa cell, and theca of follicle.

9.3.6.2 Ovulation Phase

The ovulation occurs 14 days after the onset of menstruation. Immediately before ovulation, the protruding outer wall of the follicle swells speedily, the *stigma*

(a small area in the center of the follicle) protrudes forming like a nipple, in about 30 min fluid oozes through the stigma, 2 subsequent minutes, the stigma ruptures allowing moving of viscous fluid carrying with it the ovum surrounded with a mass of thousands of granulosa cells called *corona radiata* to be released into the peritoneal cavity near the uterine opening.

Duration The ovulation period lasts for only 1 day, and the ovum survives for a short time after ovulation, usually 8 h. Sperms only have fertilization capability for 24 h even though they can survive for several days.

9.3.6.3 Post-ovulatory Phase

Corpus Luteum Phase

This begins after ovulation phase when the ovary secretes the basic hormones needed for implantation of the ovum. The mature follicle which secreted the ovum collapses and fills up with clotted blood. The cells re-regulate themselves with a well-developed blood supply to allow the follicle to form another, temporary yellow endocrine structure called the *corpus luteum*, which is similar in size to the follicle (Fig. 9.20). Vascular endothelial growth factor-A is involved in the angiogenesis for developing the corpus luteum (Rudolph et al. 2016a, b).

The theca cells continue to grow and secrete estrogen along with the zona reticularis cells which grow considerably more and start to secrete progesterone in addition to estrogen; their cytoplasm is distinguished by a bright yellow color due to its concentration of carotenoids pigments particularly (*lutein*), led to the name of

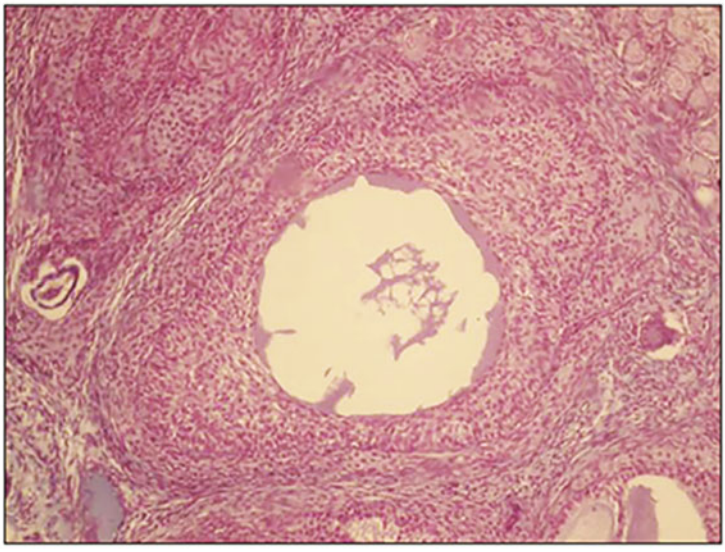

Fig. 9.20 Cross-section of ovarian tissue showing a corpus luteum (H&E magnification 400×)

granulosa lutein cells. The name of *corpus luteum* also came from a similar origin. (Czeczuga-Semeniuk and Wolczynski 2005, 2008) analyzed ovarian tissue of both normal and pathological lesions groups for identifying 14 carotenoids and revealed the presence of provitamin A carotenoids; beta-carotene, beta-cryptoxanthin, echinenone, and hydroxyechinenone but alpha-carotene was not detected. The results were similar in both groups; the overall carotenoid content was relatively low, while the mean content of provitamin A carotenoids was 17.28%. In 2008, the same authors analyzed physiological and pathological tissues of ovary, uterus and breast for identifying 16 carotenoids including the carotenoids belong to provitamin A group, the common carotenoids are: beta-carotene, beta-cryptoxanthin, lutein, mutatoxanthin, violaxanthin, lutein epoxide, and zeaxanthin. The corpus luteum relatively produce high levels of progesterone, moderate levels of estradiol and inhibin A, and small to moderate levels of estrogen inhibin B (Yamoto et al. 1997).

Duration The post-ovulatory phase has a set relatively length of time 12–15 mostly 14 days following ovulation in all women, the lifespan of the corpus luteum.

9.3.6.4 Corpus Albicans

If the ovum is not fertilized and implanted, the corpus luteum atrophies and turns into a non-functional **corpus albicans**. This means that the hormones responsible for continued growth of the endometrium disappear, leading to the appearance of menstruation signs. On the other hand, if fertilization happened, the role of the corpus luteum continues, and occupies a large space in the ovary, and estradiol and progesterone continue to be secreted gradually, especially at the beginning of pregnancy.

Additional Notes

- The ovulatory cycle can be counted by many ways: (a) Taking the first day of menstruation as day zero and the last day as 28 days after that, (b). A menstruation cycle duration is the count of days from the first day of menstruation (bleeding) of one cycle to the starting of menstruation of the next cycle, and (c) The occurrence of the peak LH level can be taken as day zero and the premenstrual period is indicated with a negative sign and the period after ovulation with a positive sign.
- The average length of the menstrual cycle is 28 days with common cycle durations of 25–30 days.
- The ideal volume of blood missing during menstruation is approximately 30 mL, any amount greater than 80 mL is believed abnormal.
- The menstruation cycle is most irregular and unequal at parties of the reproductive age (menarche and menopause) because of anovulation and inappropriate follicle growth.
- Carotenoids act as chemoprotective structures, irrespective of whether they are converted finally into vitamin A, and act a potential potent alternative to current chemotherapeutic methods to treating the ovarian cancer (Reed and Carr 2015; Czeczuga-Semeniuk and Wołczyński 2008; Yamoto et al. 1997).

9.3.7 Regulation of the Ovulatory Cycle (Figs. 9.21 and 9.22)

1. **Pre-ovulatory phase:**
   A stage of the primary follicle growth up to the antral stage is mainly stimulated by FSH alone. Then several mechanisms follow lead to significant accelerated growth to give rise larger follicular. Varying degrees of frequency for the synthesis and secretion of FSH which acts in harmony with a lower LH concentration to synthesize and secrete estrogens (for example, slow pulsed secretion stimulates activin which in turn stimulates FSH production). FSH is the main gonadotropic stimulating hormone secreted by the pituitary during this phase which leads to a slight increase followed by a gradual rise in the level of the main estrogen in the blood (estradiol) secreted by the ovary. Therefore, it is called the *follicular phase or the estrogenic phase*.

   Also, inhibin B is released in the early follicular phase. In the mid-follicular phase, one of the ovulatory follicles will be defined as a dominant follicle which grows and increasingly releases estradiol and inhibin A for 1-week prior to ovulation. Related actions are also identified for the dominant follicle which progresses to be the only follicle able to respond to the reduced levels of FSH, actions such as gonadotrophin responsiveness, vascularization, insulin-like growth factor binding protein expression and degradation.

   During the follicular phase, estrogen has a positive feedback effect on GnRH which increases its repeated pulsatile secretion from slow (every 1.5–2 h) to fast (every hour). Estrogen also acts directly on the pituitary to stimulate LH as well as FSH secretion to stimulate more estradiol production. This is further boosted by the local hormone activin, which encourages the expression of FSH receptors in the granulosa cells of the follicle. During this phase, estradiol increases positively with FSH. The estradiol concentration increases and peaks on day 13 as a function of the increase in inhibin A, which induces the pituitary-hypothalamus to secrete GnRH. This leads to an LH surge which peaks, if there is a sufficient level of FSH, 24 h after the estradiol peak on day 14 of the ovulation cycle.

   This is accompanied by negative feedback leading to a gradual decrease in FSH from the pituitary or indirectly from the hypothalamus (via the gamma-aminobutyric acid-containing neurons). In addition, inhibin B, whose levels align to those of FSH, has a negative feedback effect so that its concentration in the blood also rises in the pre-ovulatory phase to inhibit the secretion of FSH from the pituitary; progesterone on the other hand is at its lowest level during this pre-ovulatory phase.

   Per cycle, two-thirds of women show two follicular waves while one-third shows three follicular waves and have longer cycles, and a later estradiol increase and LH surge (Guyton and Hall 2016; Bullock et al. 1991, 2001; Mihm et al. 2011; Ursula 2017).
2. **Ovulation phase**
   Progesterone, LH, and FSH act in synchrony to stimulate the expression of lytic enzymes which degrade collagen in the follicular wall in preparation for its rupture. Prostaglandin production also increases as it is needed for contraction

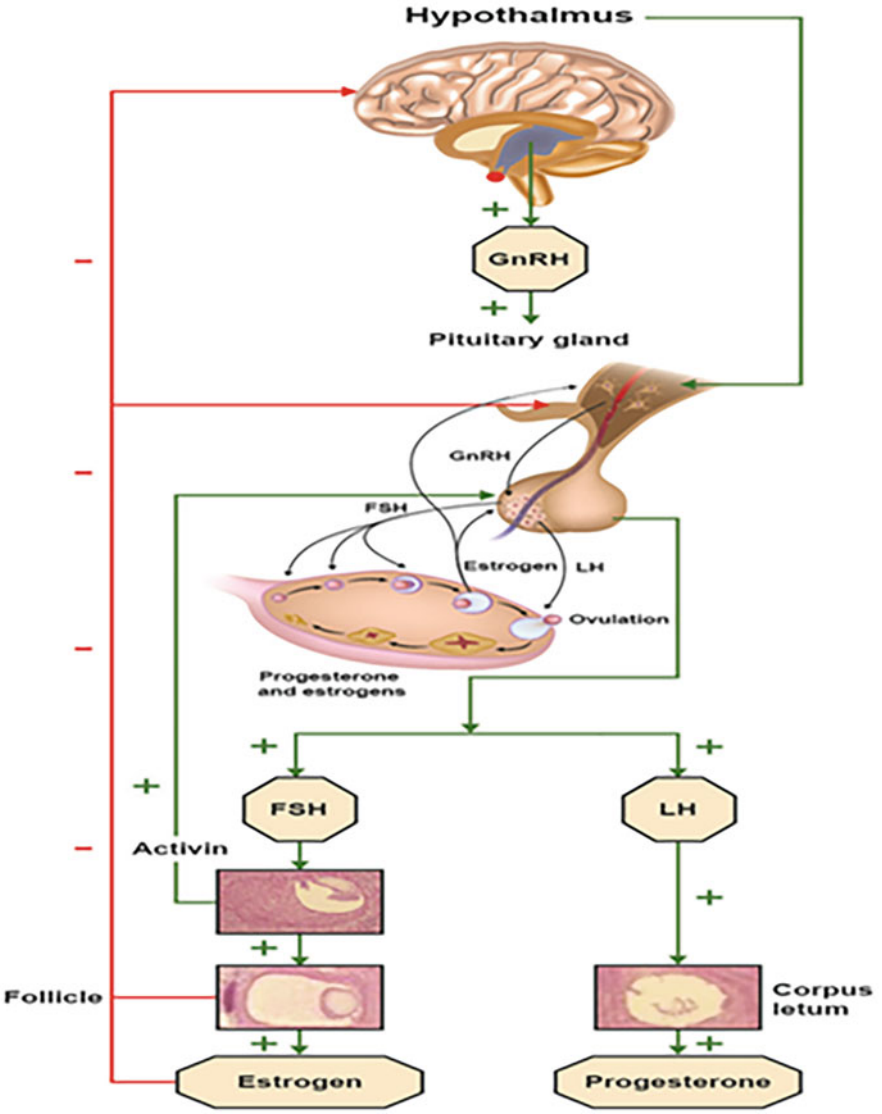

Fig. 9.21 Shows the hypothalamic and pituitary regulation of the ovarian cycle phases and the role of activin which is secreted by the granulosa cells of the ovary with a negative feedback effect on FSH secretion. Estrogen has a positive feedback effect on FSH during the follicular phase and at the end of this phase (on ovulation) estrogen has a negative feedback effect on FSH

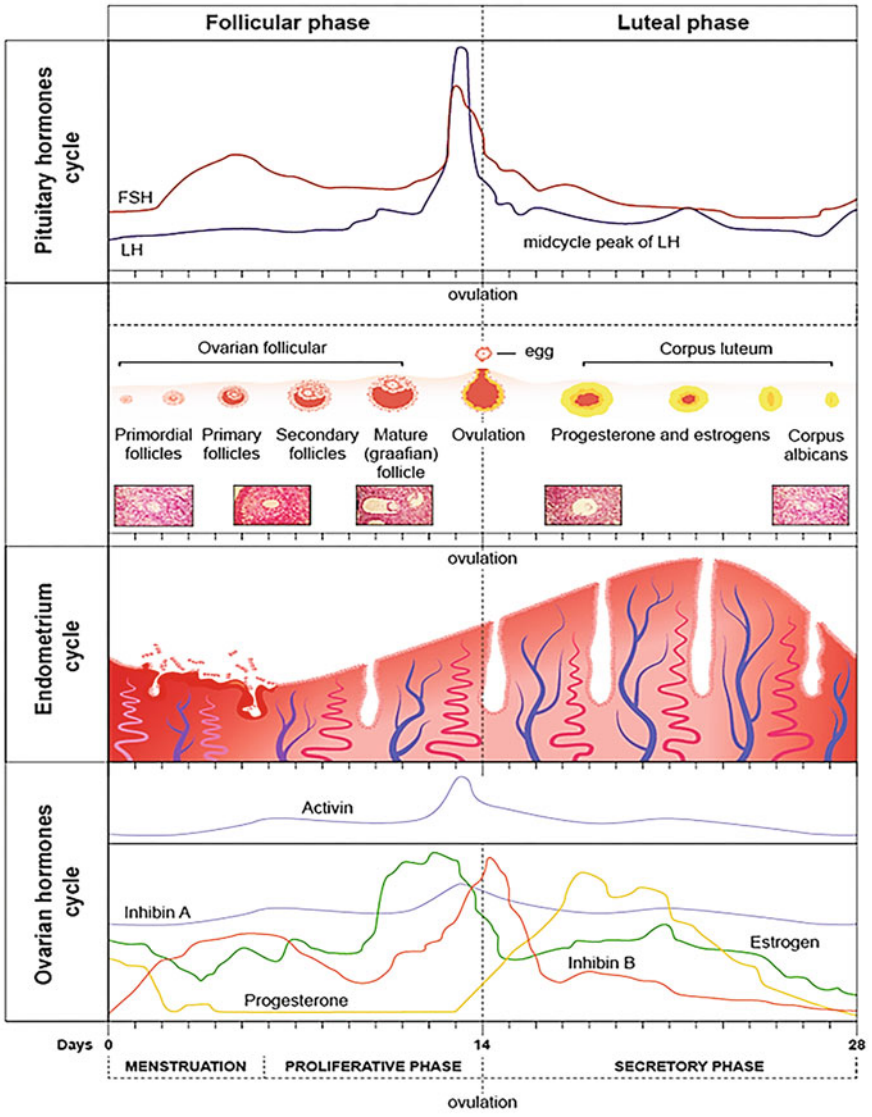

Fig. 9.22 Shows complementarity between the pituitary and ovarian hormones and the ovary and uterus during a single ovarian cycle. (1) Pituitary hormone cycle: FSH and LH levels. (2) Ovarian cycle: follicular maturation, ovulation, and corpus luteum growth. (3) Endometrial cycle: menstruation, reproductive phase, secretion phase. (4) Ovarian hormone cycle: estrange, progesterone, inhibin, and activin levels. All these events take place in the pituitary, ovary, endometrium, and the ovarian circulatory hormones simultaneously

of the smooth muscles in the ovary to release the ovum. The ovum is released 36 h after the LH surge, high levels of which continue for 48–50 h and this usually occurs on day 15 of the cycle (mid-cycle) just after LH peaks on day 14 in the presence of a significant lower FSH peak, a specific concentration of which is needed for LH to be effective. The increase in progesterone leads to sensitization of GnRH to lower the LH level.

3. **Post-ovulatory phase**
   After ovulation, the hypothalamus continues its pulsatile secretion of GnRH to stimulate the pituitary to secrete LH in sufficient quantities to maintain the function of the corpus luteum during this phase so, it secretes more progesterone, estradiol, and inhibin A as a response to LH pulses, and achieves its top size, secretions, and vascularization 6–7 days post-ovulation. Therefore, this phase is called ***the luteal phase or progesterone phase***. It has also been shown that inhibin A starts to increase at the end of the pre-ovulatory phase and remains high in the post-ovulatory phase.

During the **interim phase** from follicle to corpus luteum, progesterone acts via negative feedback on the hypothalamus to slow down pulsatile secretion of GnRH to once every 3–5 h. Luteal degradation is independent of the endometrium, but it is blocked by gestation as the placenta releases hCG (it has an effect similar to that of LH on maintaining the corpus luteum), the luteotropic signal from the trophoblasts from 8 days after conception.

The endometrial functional layer (proliferation, differentiation) has a steroid hormone-dependent effect. Thus, once steroids are reduced, or in the absence of trophoblasts, shedding occurs. With the degradation of the corpus luteum, progesterone levels begin to fall, and GnRH secretion increases to stimulate FSH to restart the cycle (Bullock et al. 1991, 2001; Mihm et al. 2011; Ursula 2017).

9.3.8 Reasons for Corpus Luteum Degradation and Reduced Progesterone

Endocrine, paracrine/autocrine molecular signals are significantly involved with progesterone release during the luteal phase for endometrial receptivity, corpus luteum formation, maintenance, and regression.

Menstruation is initiated by reduction in progesterone-responsive decidual cells. Several factors result in menstruation, including:

- Estradiol metabolites: The human corpus luteum produces many estradiol metabolites which have a significant physiological role through autocrine/paracrine signals, and influence angiogenesis or LH-mediated mechanisms on corpus luteum functions and regression in non-conception ovarian cycles. One of these metabolites is 2-methoxyestradiol (2-ME2), which plays a role in corpus luteolysis through its anti-angiogenic and anti-proliferative effects, while

4-hydroxyestrone (4-OHE1) and 16-keto-E_2 promote angiogenesis in the early and midluteal phases of the normal ovarian cycles (Devoto et al. 2017).

- Increasing the activity of the enzyme aromatase: Rapid actions of estradiol are mediated through changes in aromatase activity, which accurately regulates the temporal and spatial availability of estrogene (Rudolph et al. 2016b).
- Local hormones, such as oxytocin which is secreted from the luteal cells and reduces the secretion of progesterone (Salonia et al. 2005). Also, autocrine signals like prostaglandins released from uterus or ovary during the post-ovulatory phase (such as prostaglandin E2 and prostaglandin F2-alpha.
- Matrix metalloprotease released from leukocytes (Mihm et al. 2011).
- Cytokines which cause necrosis and apoptosis.
- Vasoconstriction.

9.3.9 Functions of the Ovarian Hormones After Puberty

9.3.9.1 Functions of Estrogens

- There are only three estrogens are present in significant amounts in the plasma of nonpregnant human female: **β-esradiol, estrone, and *estriol***.
- **The ovarian cycle is regulated by estrogen feedback** with the help of the pituitary and hypothalamic hormones in general and the pre-ovulatory phase in particular.
- **In the hypothalamus of rats, estradiol and neuroprogesterone interact to stimulate kisspeptin** release in the rostral periventricular nucleus of the third ventricle to exert the LH surge; this is the most critical event in the reproduction cycle. In female rats, morphological alterations in the hypothalamic arcuate nucleus affects sexual receptivity. This is mediated by the rapid control exerted by estradiol-2 on synaptogenesis in that nucleus (Rudolph et al. 2016b).
- **Estrogens activate the cellular response**. Steroid hormones do not only act by binding to their classic mobile/nuclear receptors, but also bind to the target cell membrane. Thus, steroid hormones can initiate cascades of intracellular signaling which in turn elicit rapid actions such as releasing internal calcium ions from stores and the activation of kinases (Mittelman-Smith et al. 2017).
- **Effect of estrogen deficiency**. Several mutations in the aromatase gene (estrogen synthetase gene) lead to complete estrogen deficiency. Thus;
  - **In women**, at the time of puberty, this case leads to virilization of the uterus, primary amenorrhea, hypergonadotropic hypogonadism.
  - **In men**, the most notable characteristic is continued longitudinal bone growth after puberty phase, delayed bone age, and failure of epiphyseal closure; this clearly indicates the significant role of estrogens in bone metabolism in men.
  - **In both sexes**, these symptoms can be treated by estrogen administration (Simpson et al. 1997).
- **In normal humans, estrogen is involved in numerous post-pubertal functions**. Its concentration increases by about 20 times or more from its pre-puberty limited level.

- **Estrogens increase total proteins** slightly in the body and this is seen by a positive nitrogen balance, this is due to the growth promoting action of estrogen on the gonads, the bones and other tissues, but this effect is lesser than the powerful effect caused by testosterone.
- **The metabolic rate** slightly increases equivalent to one-third of what obtained by the effect of testosterone.
- **Effect on body weight and fat deposition**. Total weight of women is less than that of men who have more protein and less fat which can be seen by men floating less than women in water. Women mostly have a larger ratio of body mass as fat, and are more likely to deposit fat subcutaneously, in the breasts, buttocks, thighs (lower extremities) while men are more likely to deposit fat in the abdominal area. Estrogen seems to underlie many of these differences as women tolerate higher nutrient cost during reproductive period. Fat is linked with fertility in women via leptin, low leptin concentrations reduce fertility. Ovarian functions of adult women are associated with their fatness at childbirth. Women have benefited from an increased ability to store fat in easily metabolizable depots, while the style of trunk obesity, more usually seen in men, is not adaptive, but to some extent reflects the genetic trend hypothesis of human susceptibility to obesity. Female obesity, with extreme adiposity in the lower extremities reflects an excess of an adaptation for female reproductive success (Power and Schulkin 2008).
- **Effect on skin**. Estrogens result in skin softness and vascular which associates with elevated warmth and boost greater bleeding of injured surfaces than is seen in men. Estrogens have slight effect on hair distribution.
- Estrogen-like aldosterone and some adrenal cortex hormones **cause sodium** and water retention.
- **They have an anabolic effect on the organs of the female reproductive system**. Estrogens increase the glandular tissue of the fallopian tube, triple uterine size compared to its prepubertal size, changes the vaginal epithelial layer from cuboid to stratified cells, and boosts the proliferation of the mucous cells lining these organs.
- Under the influence of estrogens, the **cervix** secretes a water-based mucous substance.
- Estrogens stimulate proliferation of the **endometrial layer of the uterus** by increasing the flow of water and blood to it and this rapidly increases blood flow to the spiral arteries which become sensitive to estrogen and the subsequent processes needed to feed the implanted ovum.
- Estrogens increase the amount of contractile proteins in the **myometrium** and this effect is very evident during birth which makes this layer contracts by itself with the increase in estrogen. It also increases the sensitivity and number of oxytocin receptors in the area as this helps to expel the fetus, and this is accompanied by a decrease in progesterone and an increase in oxytocin.
- Estrogens stimulate the synthesis of **thyroxine-binding globulins**.
- **Effect on breasts**. Estrogens have receptors on breast tissues, they increase breast connective and develop stromal tissues, as well as growth of the mammary ducts, and deposit fat in the breasts. Estrogen alone develops the lobules and alveoli of

the breast to a little extent lesser than progesterone and prolactin that exert the typical growth and functions of these structures.

- **Estrogens initiate the milk-producing apparatus** and are responsible for the distinctive growth and external look of breasts in the mature female. But they don't complete the task of converting the breasts to complete milk-producing glands.
- **Effect on bones**. In the bones, estrogens act similarly to the androgens
  - Increase bone growth activity.
  - Estrogen plays critical functional function in the development, maturation of bones and in the bone turnover regulation in adult bone. During bones growth, estrogen is required for timely and adequate closing of epiphyseal growth plates. The sex steroids exert this effect in both sexes, but the bone epiphysis closures earlier in female due to the faster and intensive action of estrogen on skeletal growth leading to smaller skeleton volume in female than male that affected by slower action of androgens.
  - To a lesser degree than androgens, estrogens are involved in matrix deposition process in the bones and in calcium and phosphate retention.
  - **In young bone**, estrogen deficiency leads to increased osteoclasts synthesis and stimulated reabsorption of the bone.
  - **In menopause and old age**, estrogen deficiency stimulates osteoporosis and cortical bone derivation.
  - Estrogen is responsible for the distinctive oval shape of the pelvic area in women.
  - (Guyton 1986; Guyton and Hall 2006, 2016; Bullock et al. 1991, 2001; Gardner and Shoback 2007; Greenspan and Forsham 1986; Väänänen and Härkönen 1996).

9.3.9.2 Functions of Progesterone

The most important progestins is progesterone, some amounts of another progestin, 17-α-hydroxyprogesterone is released along with progesterone and have the same actions.

- Progesterone regulates the ovarian cycle in general and the post-ovulatory phase in particular by feedback mechanism with the pituitary and hypothalamus hormones.
- Like estradiol, progesterone can initiate signaling cascades at the cell membrane through classic and non-classic progesterone receptors (progesterone membrane receptors). Progesterone can then also elicit target cellular actions (Mittelman-Smith et al. 2017).
- Progesterone supports the secretory glands in the mucosa lining the fallopian tube.
- Under the effect of progesterone, mucous secretions of the cervix decrease and become thicker. These signs indicate that ovulation has done.

- Estrogen helps proliferation of the uterine endometrium (Fig. 9.18) whereas progesterone supports its secretory glands so that during the post-ovulatory phase, the glands increase in length and secrete a glycogen-rich fluid that encourages implantation of the ovum.
- Progesterone reduces the intensity and sequential contractions in the myometrium. So, it protects the fetus inside the uterus and is therefore the dominant hormone during pregnancy up until birth.
- Progesterone boosts the growth and development of the mammary lobules and alveoli, increasing the alveoli cellular proliferation, enlarge volume and become secretory. Progesterone doesn't cause milk secretion from the alveoli without further preparation of the breasts by the stimulatory effect of prolactin.
- It increases body temperature by 0.2–0.5 °C during most of the luteal phase; this serves as an indicator of ovulation.
- It has a moderate effect on protein catabolism in the body, similar to adrenal cortex hormones which regulate sugar levels especially during pregnancy.
- Similar to estrogen, testosterone, and adrenal cortex hormones, progesterone in large quantities increases the reabsorption of chloride and water from the distal kidney tubules and increase ionic sodium excretion (Guyton 1986; Guyton and Hall 2006, 2016; Bullock et al. 1991, 2001; Gardner and Shoback 2007).

New Novel Functions of Progesterone

Over the years, an interesting observation was made: the rapid effect of the non-genomic progesterone-R interaction in various tissues activates a wide variety of secondary messengers. These include Immunoregulatory function in Human T-lymphocytes via G-protein activation (Sartor and Cutler Jr 1996), platelet aggregation in human T-lymphocytes via Ca^{2+} influx (Scarpin et al. 2009), anti-apoptotic effects in rat (granulosa cells via Ca^{2+} homeostasis (Schlehofer et al. 1999), human intestinal smooth muscle cells contraction via Ca^{2+} currents reduction (Shao 2013) and vasoreactivity in rat vascular smooth muscle cells via Ca^{2+} influx regulation (Shinomiya et al. 1986). In addition progesterone has multiple functions on osteoporosis (Sica et al. 1989) and calcitonin secretion (Silvera et al. 2006). It increases insulin release resulting in promotion of metabolism (Sitruk-Ware 2006). It also reduces brain edema and restores the blood brain barrier (Snow et al. 2011).

Reproductive epidemiology of glial tumors may reveal novel treatments: high-dose progestins or progesterone antagonists as endocrino-immune modifiers against glioma. Progesterone receptor (PR) expression and mifepristone treatment was highly discussed for meningiomas. However, much less is known in regard to progesterone actions in gliomas despite PR expression strongly correlates with their grade (Altinoz et al. 2019). It has been found that systemic treatment of progesterone is neuroprotective as shown in multiple animal models of brain injury including traumatic brain injury. Moreover, progesterone has poor aqueous solubility which has limits its potential for use as a therapeutic agent (Sayeed et al. 2019). It has been reported that treatment with *Coriandrum sativum* has no negative impact on endocrine and reproductive organ structure and function (Al-Suhaimi 2008).

9.3.9.3 Extra-Regulating Roles of Local Hormones Inhibin, Activin, and Follistatin on the Physiology of the Gonads

The gonadotrophs and other cells types within the pituitary gland, produce both inhibin α- and β-subunits as well as follistatin. Activin B is also synthesized locally and promotes FSH release from the pituitary, as proven by a reduction in FSH release following treating cultures of pituitary with an activin-inhibiting antibody (Gregory et al. 2005). In addition to their production from the gonads.

Inhibin Inhibin is a dimeric glycoprotein hormone. It has two biologically active structures; inhibin A and B. Inhibin B is the circulating form. Inhibin is produced mainly by the Sertoli cells and Leydig cells in the testis and, granulosa and theca cells of the ovary.

Activins They are glycoproteins and members of the pleiotropic family of the TGF-beta superfamily of cytokines. They are isolated from pituitary extracts as activin acts as a stimulating factor for FSH.

Follistatin It is also a monomeric glycoprotein, and has multiple biological functions and pathological processes. It plays a key role in reproduction and adipocyte differentiation in vertebrates. It has muscle stimulatory, anti-inflammatory and energy homeostatic effects. Mostly, activin antagonizes the physiological functions of both inhibin and follistatin on the reproductive system.

9.3.9.4 Physiological Functions and Regulation

- In adults, serum inhibin B concentration is positively correlated with Sertoli cell physiological function, testicular volume and number of sperms, and spermatogenesis phase, while it is negatively correlated with FSH level. Thus, inhibin suppresses FSH secretion from the pituitary and regulates steroidogenesis through a negative feedback mechanism.
- Inhibin B aligns FSH levels patterns during the ovulatory cycle.
- Inhibins, which are produced mainly by Leydig cells, support testosterone release.
- The production of inhibin B is regulated by an interaction between FSH, Sertoli cells, germ cells, and Leydig cells.
- It acts as an autocrine or paracrine signal to modulate the activin activity.
- Inhibin A and activin A act inversely. Inhibin A has a perinatal peak in rats, while activin A reaches its peak level in the immediate post-natal duration as it is essential for the growth and regulation of both Sertoli cells and germ cells to be modulated by follistatin.
- The inhibin A concentrations in serum increase toward the late follicular stage. The levels reach a peak during the midluteal stage, followed by a decrease during the late luteal stage. The inhibin B levels in serum are high during the follicular stages and the early luteal stage. Then, decrease during the midluteal and late luteal stages (Yamoto et al. 1997).

- Follistatin suppresses FSH which is responsible for ovarian follicle and oocyte growth, while it has no significant effect on testicular growth,
- Follistatin is a key regulator of activin's biological action, and should be evaluated as a therapeutic polypeptide agent in conditions where activin A overexpression is known essentially as a contributing factor.
- Hypergravity influences follistatin concentration in muscle through the vestibular system in mice. Follistatin plays roles in the metabolic interactions between muscle and bone as response to gravity change.
- Follistatin acts as a stress responsive protein plays a protective function under a several stresses.
- Follistatin like-1 (FSTL1) inhibits proliferation of tumor cell, invasion and survival in non-small cell lung cancer, the overexpression of FSTL1 in the cell line (H446) with low endogenous levels of FSTL1 suppresses cell proliferation, migration, and invasion lead to increase cell apoptosis.
- Activin, is a well-known cytokine belonging to a transforming growth factor (TGF) class, and regulates many reproductive biological functions, inflammation and immunological pathways.
- Activin is a major regulator of testicular and ovarian development. In canines, both glycoproteins activin and inhibin are expressed by developing follicles and corpora lutea in the ovary.
- Activin group is a powerful morphogenetic factor in the fetal testis. While in the adult, it exerts a modulatory effect on Sertoli cell function and spermatogenesis.
- Activins have a promoting role on FSH and ovarian follicular development through the function of aromatase; in contrast, inhibin suppresses hyperplastic/ neoplastic activity.
- Activins are involved in both phases of ovulation and corpus luteum development, but inhibin A is elevated at the end of the follicular phase and continue during the luteal phase to stimulate progesterone production.
- Activin A is increased in both the circulation as well as locally in most reproductive disorders, which makes it an important biomarker. Thus, activin A has a role both as a pro-inflammatory and pro-fibrotic factor.
- Activin A concentrations are much lower in the testis of adult, but Sertoli cell production is activated by interleukin-1 and suppressed by FSH.
- There is limited information on the production of activin B, as a suitable assay method has not yet been identified. However, inhibin beta B-subunit mRNA is expressed in testicular Sertoli and germ cells and is phase-dependent; this expression indicates its importance as an autocrine/ paracrine factor in the seminiferous epithelium.

Understanding the physiological and pathological functions of inhibins, follistatin, and activins in humans make them of significance as biomarkers for conditions of infertility in men, and as prognostic markers in diseases of the reproductive system, or in women undergoing ovulation induction therapy (de Kretser et al. 2004; O'Connor and De Kretser 2004; Kumanov et al. 2005; Marino and Zanghì 2013;

Wen et al. 2015a, b; Tseng et al. 2016; Wijayarathna and de Kretser 2016; Kawao et al. 2018; Ni et al. 2018; Zhang et al. 2018).

9.3.10 Update on Minipuberty: The Fetal Hypothalamus–Pituitary Gonadal Axis

The period of minipuberty of infancy is characterized with greater activity of hypothalamic–pituitary–reproductive axis (Becker and Hesse 2020). The period is also characterized with variation in concentrations of reproductive hormone as well as variation in organ size; however, this period is not characterized with clear description of longitudinal changes. In short, the ovarian size of infant was at its peak at 16 weeks depending on the developed follicles' quantity and size. Hence, the current research may prove helpful in future to determine the reference range of postnatal development of ovary size in healthy term infants (Lanciotti et al. 2018).

The adrenal sex steroid precursor dehydroepiandrosterone initiates the biosynthesis of androgens within the human fetus. The testosterone is produced in the gonads by the conversion of dehydroepiandrosterone. Moreover, the dehydroepiandrosterone in genital skin is stimulated to 5α-dihydrotestosterone which allows external genital differentiation in males. The condition of under-virilization in males is caused by the disruption in dehydroepiandrosterone biosynthesis caused by congenital adrenal hyperplasia because of deficiency of P450 oxidoreductase. Moreover, females may suffer from virilization at the time of birth even in the presence of limited circulating agents. It is postulated that the prenatally active androgen biosynthesis pathway from 17α-hydroxyprogesterone to 5α-dihydrotestosterone may cause virilization in females and it also outperforms the dehydroepiandrosterone and testosterone due to its greater activity in congenital adrenal hyperplasia variants linked with accumulation of 17α-hydroxyprogesterone. The study was performed to investigate the explant cultures of human adrenals, gonads, and genital skin during sexual differentiation. The study analyzed cultures with the help of the liquid chromatography-tandem mass spectrometry which showed the activity of alternative pathway androgen biosynthesis in the fetus. The androgen receptor expression in male and female genital skin were observed in the study with the help of immunohistochemistry which revealed that nuclear translocation of the androgen receptor was stimulated by 5α-dihydrotestosterone as well as adrenal explant culture supernatant in primary cultures of female genital skin. The urinary steroid excretion was evaluated with the help of gas chromatography-mass spectrometry which revealed that androgens are synthesized in the first month of life in P450 oxidoreductase-deficient neonates with the help of alternative androgen pathway (Bizzarri and Cappa 2020).

9.3.11 New Concepts in Gametogenesis

9.3.11.1 Update on Spermatogenesis: Quantitative and Qualitative Factors

Temperature

The spermatogenesis may be adversely affected due to rise in scrotal temperature. It may also result in male infertility. The rise in scrotal temperature causes a sharp decline in the quantity and motility of spermatozoa besides affecting the capability of the sperm to undergo fertilization and it may also lead to poor fertilization-embryo. Mice subjected to 43 °C of scrotal temperature depicted changes in the structure of seminiferous tubule and spermatogenesis. The group of mice subjected to high temperature showed decline in their high Johnsen scores. On the other hand, there was a rise in their ratio of low Johnsen score points. This shows that a scrotal temperature of 433 °C disturbed the Spermatogenesis in male mice. From this experiment, it is also evident that histopathological alterations and spermatogenesis arrest are adversely affected by chronic scrotal heat stress (Thanh et al. 2020).

Obesity

Obesity is the key factor that affects the semen parameters and leads to poor fertility in males. But, there is still some uncertainty regarding the causal association of obesity with infertility in males. This uncertainty is specifically prevalent on a molecular level. This showed that reproductive system dysfunction in males with obesity is closely linked with oxidative stress and inflammation which ultimately affect their sperm function and may cause subfertility due to the negative impact of these processes on spermatogenesis specifically during the protein translation and folding phases (Pini et al. 2020).

The Role of Retinoid-Related Orphan Receptor (ROR)

Morphological testicular defects were detected in retinoid-related orphan nuclear receptor alpha-deficient (ROR) mice (Sayed et al. 2019). Irregular Sertoli cells and hypertrophied spermatogonia were observed during the Transmission electron microscopy examination conducted on mutant mice. The examination also showed spermatocytes with degenerated mitochondria along with partially developed sperms. This implies the significance of ROR alpha protein for regulating the functioning of testicles (Sayed et al. 2019).

9.3.11.2 Emerging Concept of Oogenesis

It was believed for long time that all ova were formed during the fetal period and remained inactive till the female matures. However, this belief has been debunked, as all mammalian ova are continuously formed, produced, and degraded during the reproductive phase and ovaries contain stem cells during the fetal and reproductive periods in human females.

Lately, there has been a development that suggested the presence of mitotically active germ cells in the ovaries of young and adult mice which challenged the earlier

belief regarding the loss of oocyte production ability in majority of female mammals at the time of birth. Consequently, it is confirmed that immunomagnetic separation and consequently culture for at least 15 months may help the neonatal mouse female germline stem cells (FGSCs) line to depict normal karyotype and high telomerase activity. The separation and the consequent culture were performed for FGSCs of adult mice for over 6 months. The process of oogenesis took place within the transplanted cells producing mice with GFP transgene. These outcomes support the performance of fundamental research besides providing foundations for further research in oogenesis as well as stem cell self-renewal; it also allows exploration of new prospects for effective application of FGSCs in the field of biotechnology and medicine (Zou et al. 2009).

In light of the existing evidence, it is clear that mitotically active germ cells are present in postnatal ovaries of various mammals specifically humans. As a result, there are high prospects of making the best use of germline stem cells in adults for generating female gametes externally. Extensive experimentation has been conducted to study the functional attributes of germline stem cells in women ovaries; (these stem cells are also called female germline or oogonial stem cells (OSCs)). One of these experiments includes the study about differentiation capacity of OSCs in humans at cellular level (Virant-Klun 2015). It has become possible to conduct further discussion on this novel concept and study the significance of these cells and management of female fertility in humans by considering the data obtained from these experiments and other data obtained from analysis of intra-ovarian transplantation and genetic tracing through animal models; the models indicated that OSCs are able to produce healthy eggs, embryos and offspring.

Different hormonal signals can critically impact stem cells functions and utilities in different stages of human life; fetal, postnatal, and adult tissues (Ghorbani and Naderi-Meshkin 2016). Growth hormone, insulin, thyroid hormone, parathormone, adrenocorticotropin, glucocorticoids, erythropoietin, and gastrointestinal hormones control stem cells behavior through influencing survival, proliferation, migration, homing, and differentiation of these cells (Fig. 9.23).

9.3.12 Physiology of Menopause and Andropause

Dehydroepiandrosterone (DHEA) is an important source for steroid sex hormone synthesis in men, as well as in women. A high secretion rate of DHEA by the human adrenal glands is associated with the premenopausal age, which suppresses ovarian estrogen release. Cessation of estrogen release at menopause abolishes risks of endometrial hyperplasia and cancer which could result from the non-negative back mechanism of estrogen release during the postmenopausal age. At the start of menopause and with the aging process, DHEA is the only, exclusive and particular sex steroid received by all tissues, except the uterus (Labrie 2010).

Dihydrotestosterone (DHT) is mostly a peripheral production of testosterone metabolism. The postmenopausal ovary is an androgen-releasing endocrine organ, the testosterone concentrations are not straightly influenced by the menopausal

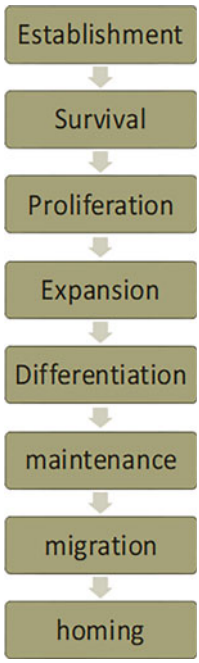

Fig. 9.23 Hormones control Stem cell stages and activities (Al-Suhaimi and Aljafary 2019)

transmission or the happening of menopause (Burger 2002). DHEA, the sex steroid is involved in the improvement of postmenopausal symptoms which appear in women at menopause, including some/most of the following: osteoporosis, muscle weakness, hot flushes, skin and vaginal atrophy, depression, impaired memory and cognition, and some metabolic issues like fat accumulation, type 2 diabetes, and reproductive dysfunction, and other changes. Similar symptoms are associated with aging in men: impaired concentration, insomnia, easy fatigability, nervousness, impatience, depression, impaired memory, hot flushes, periodic sweating, skin atrophy, reduction in muscle mass and strength, bone pain, and sexual dysfunction. Medically, DHEA could be administered without systemic exposure to estrogens for improving the life. In men, adrenal DHEA also contributes to the total androgen. Blocking both testicular and adrenal androgen sources is required for in the typical prostate cancer therapy (Labrie 2010; Tenover 1992).

Reductions in systemic steroid hormones levels may be responsible for the characteristic FSH increase in the premenopausal period in women (Mihm et al. 2011). Menopause starts around the age of 45–50 years in women and andropause at the age of 75 years or more in men due to lack of steroid hormone secretion owing to diminishing gonadotropic function of the testis/ovary and their non-responsiveness to the pituitary hormones' LH and FSH. Menstruation stops suddenly over a short period of time or after a gradual decrease in the number of cycles or irregular ovulation and menstruation. This can take up to 10 years.

As mentioned earlier, although ovarian stem cells are available during the aging period, stem cells cannot prevent menopause because with advancing age, there is a

regression in the contribution of the immune system to the process of neo-oogenesis and follicular renewal in vivo from germline stem-cell precursors. The reduction in fertility induced by advanced age involves ovarian kisspeptin regulation for the sympathetic innervation (Rudolph et al. 2016b). It has been reported that treatment of cerium oxide nanoparticles caused amelioration of diabetes-induced testicular and sperm in rats (Artimani et al. 2018).

9.3.13 Stem Cells and Bi-Potential Progenitor Structure Genital Ridge

The significance of sex determination in context of sexual reproduction cannot be denied for reproductive functions since it develops functional male or female reproductive cells or gametes essential for the reproduction. The sex is initially determined in mammals depending on whether the Y-chromosome is present or not; the Y-chromosome regulates gonadal ridges or primordium. The reproductive organs that distinguish between male and female reproductive systems (i.e., ovary or testis) are developed at the mid-gestation stage by the genital ridges which are somatic precursor of gonads (Burkitt et al. 1996). An individual's gender and his germ cells are identified on the basis of genital ridge which in turn is dependent on somatic cell differentiation; in case of testes, the somatic cells differentiate into Sertoli cells while in case of ovary, there is differentiation of somatic cells into granulosa cells. Various factors that help in the determination of sex in mammals were identified in mouse models and human mutation studies performed on individuals with disorders of sex development. The testicular differentiation in majority of mammals is regulated by the genetic indicator of the gene Sry present in Y-chromosome (Tanaka and Nishinakamura 2014).

Anatomy, physiology, genetics, bio and regenerative medicine, should be integrated to know a comprehensive knowledge of the later stages of development of the reproductive system in human and animal models. The ovary and testis arise from bi-potential progenitor structure called as the genital ridge (GR). This structure forms in a late stage in embryonic growth to potential formation either the ovary or testis, and then their hormones required for the growth of the reproductive system. Studying the genetic networks for GR formation leads not only to understand of the genetic regulation of reproductive development but gives new approaches for managing reproductive abnormalities and infertility (Yang et al. 2018).

Oncostatin M (OSM) acts as an inhibitory factor of rat stem Leydig cell growth. In vivo seminiferous tubule culture system, stem Leydig cell growth was reduced along with the differentiation due to action of inhibitor Oncostatin M (OSM) (Wang et al. 2019). Mainly the testosterone level and downstream effect of the Leydig cell-specific genes expression and their proteins (Lhcgr, Star, Hsd3b1, Cyp17a1 Cyp11a1, and Hsd11b1). OSM related function was downregulated due to the influence of S3I-201 (a STAT3 antagonist) or filgotinib (a JAK1 inhibitor). Clinically, exogenous testosterone could be administrated for treating testosterone deficiency; but it has several contrary effects include infertility because of negative

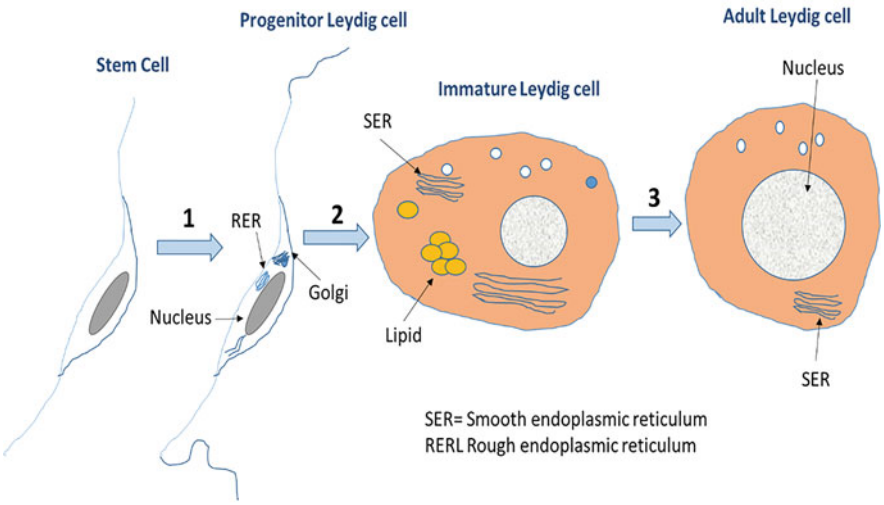

Fig. 9.24 Differentiation of stem cells into Leydig cell (1) stem cell differentiates into progenitor cell (2) progenitor cell differentiates into immature Leydig cell and (3) immature Leydig cell grows into adult Leydig cell

feedback on the hypothalamus-pituitary-gonads (HPG) axis. Arora et al. (2019) for the first time demonstrated that autografting of Leydig stem cell (LSC) subcutaneously together with Sertoli cells and myoid cells, stimulate testosterone synthesis. Therefore, autograft of LSC may provide a new strategy for treating testosterone deficiency while simultaneously stabilizing HPG. The differentiation of stem cells into Leydig cell with three stages is shown in Fig. 9.24.

Presently, the effective de novo synthesis of testicular tissues and consequently the complete spermatogenesis in vitro has been observed only in rodents. It is also indicated in some outcomes that human testicular organoids (TOs) or multi-cellular tissue surrogates may be produced as primary human testicular cells undergo self-organization both in the presence and absence of biological support (Baert et al. 2017). Although these mini-tissues thus produced do not have the testis-specific topography, they are successful in facilitating spermatogonia. Moreover, in long-term culture, the niche cells inside these tissues maintained their particular functionalities. Hence, it is evident that in vitro re-engineering of human testicular microenvironment can be done from primary cells. It is possible to develop a biomimetic testicular model from human TOs; such a model would facilitate research and development in this field as well as clinical treatment and screening of infertility; it also supports drug discovery and toxicology (Baert et al. 2017). Functional assessment of spermatogonial stem cell has been done and this technique will not only be useful to link functional relevance to novel markers that will be identified in the future, but also for providing validation of purity for marker-selected populations of spermatogonia that are commonly considered to be spermatogonial stem cell by many researchers (Lord and Oatley 2018).

9.4 Conclusion

Pituitary gland in endocrine system in coordination with hypothalamus plays a vital role in reproductive system, differentiation and different physiological functions in the entire stages of life and its circadian rhythm in both male and female. Description about male gonads, location, physiological functions of testicles, interstitial tissue (Leydig cells) and peritubular myoid cells. The Sertoli cells act as "nurse & stem" cells, spermatogenesis, spermiogenesis. Gonad's steroid hormones such as androgens are involved in male reproductive activity. Ovaries are female reproductive glands and there are two main functions (exocrine and endocrine) controlled and coordinated by the hypothalamus and the pituitary. Female sex hormones in pre-puberty (Estrogen) and post-puberty (estradiol, estrone, progesterone, and inhibin), and sources (ovarian follicle and corpus luteum) were discussed in detail. Structure of steroid hormones discussed with role of endometrium, regulation of ovarian functions, and puberty by endocrine and immune system. The different phases of ovarian cycle explained to regulate gonadotropins, follicular growth, steroid synthesis, non-functional corpus albicans (infertile ovum), and regulation of ovarian cycle (pre-ovulatory phase, ovulation phase, and post-ovulatory phase). The involvement of estradiol metabolites, enzyme aromatase, hormone oxytocin, matrix metalloprotease, cytokines and vasoconstriction in corpus luteum formation related along with maintenance and regression. Synthesis of ovarian hormones (β-esradiol, estrone, and estriol) after puberty discussed with important functions of progesterone, regulatory roles of inhibin, activin, and follistatin in physiology of testis and ovary. Dehydroepiandrosterone (DHEA) involvement discussed for menopause in elderly women and andropause in men. The chapter declares that the classic theory of cessation of oocytes production after birth was cancelled. Both human neonatal and adult ovarian germline stem-cell precursors (ovarian surface cells) have the capability for oogenic or differentiating and producing functional oocytes, so it renews the oocyte pool (neo-oogenesis) and ensure renewal during the prime reproductive period, with follicular co-operation under regulation of the endocrine, immune systems, and cellular support. After the prime reproductive period, aging starts, and menopause occurs because of the immunoregulatory changes that causes cessation and terminate neo-oogenesis and follicular renewal in vivo despite the existence of germline stem cell precursors. The rest of oocytes in the primordial follicles retain ovarian function but advancing age (aging oocytes) correlates positively with the occurrence of fetal chromosomal abnormality.

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Adipose Tissue as an Endocrine Organ and a Glance on Local Hormones

10

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Abstract

The role of adipose issue for fat storage and energy production is well known, but this classic function doesn't reflect its significant effects as an endocrine tissue as well as immune mediator. Adipose tissue secretes soluble peptides like adipocytokines, adipokines, cytokines, chemokines expressed in coordination with central nervous system (CNS) and pituitary gland. Adipose tissue reacts differentially to physiological or metabolic stress by secreting aforementioned endocrine factors to cope with metabolic and immune processes including, appetite control, energy expenditure, insulin sensitivity glucose homeostasis, tissue and skin repair, bone turnover and inflammation response. Adipose tissue-derived adipocytes produce adipokines such as leptin, adiponectin, visfatin, resistin, apelin, chemerin, adipsin, kisspeptin, interleukin 6, tumor necrosis factor α (TNF-α) which act as local (paracrine) and systemic (endocrine) signals on the organs expresses their receptors on the hypothalamus, pituitary gland, β-cells of pancreas, the liver, muscle skeletal, muscle systems. Under stress and metabolic syndrome, immune cells of adipose tissue accelerate a proinflammatory response with perturbed the release of adipokines, thereby activating innate and adaptive response. In this chapter, we underpin the secretion and physiological functions of adipose tissue-derived adipokines for metabolic adapting to the environmental factor as well as their effect on reproduction, immune system, heart protection, tissue remodeling and hematopoiesis by influencing hypothalamic/pituitary axis. Leptin's detection (obese (ob) gene), the obese mouse model led to using it continuously to present its oriental function to showing leptin as the missing regulator in the obese ob/ob mouse which provided high quality and quantity scientific information of leptin and adipose tissue as a novel endocrine tissue. A disturbed adipokine profile is contemporary

with many disorders such as obesity, type 1 and 2 diabetes mellitus (T1DM and T2DM). In common example, depravation of sleep affecting leptin and other factors roles lead to obesity which is mediated through increased appetite. We also discuss the production of these adipokines by other organs and tissues, which further highlighting the endocrine contribution in various physiological and pathophysiological conditions.

Keywords

Adopokines · Cytokines · Prostaglandins · Adrenomedullin · Vitamin D · Angiotensinogen · Local hormones

Abbreviations

AC/PKA	Adenylyl cyclase/protein kinase A
ACTH	Adrenocorticotropic hormone
AM	Adrenomedullin
AMP	Adenosine monophosphate
ASCs	Adipose-derived stem cells
BBB	Blood–brain barrier
CCK	Cholecystokinin
CD34+	Cluster of differentiation 34 positive cells
CNS	Central nervous system
DM	Diabetes mellitus
ESF	Erythropoietic stimulating factor
FSH	Follicle stimulating hormone
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
GHRHR	Growth hormone-releasing hormone receptor
GnRH	Gonadotropin releasing hormone
H&E	Hematoxylin and eosin stain
hCG	Human chorionic gonadotropin
HCl	Hydrochloric acid
HMSC	Human mesenchymal stem cell
hsCRP	High-sensitivity C-reactive protein
LH	Luteinizing hormone
MMP	Matrix metalloproteinases
PAMP	Proadrenomedullin N-terminal 20 peptide
PG	Prostaglandin
PGA	Prostaglandin A
PGD2	Prostaglandin D2
PGE	Prostaglandin E
PGE2	Prostaglandin E2
PGF2α	Prostaglandin F2 alpha
PGI2	Prostaglandin I2 (prostacyclin)

PI3K/Akt	Phosphatidylinositol 3-kinase/protein kinase B
PLC/PKC	Phospholipase C/protein kinase C
PRL	Prolactin
TIMP	Tissue inhibitors of metalloproteinases
TNF-α	Tumor necrosis factor alpha

10.1 Introduction

Since discovering leptin hormone in 1994 by Friedman and his team, the peptide hormone secreted by adipocytes, it allowed to know that adipose tissue has the ability to synthesize and release biologically effective secretions named "adipokines." Leptin is the hormone of obese (ob) gene, released by white adipocytes and acts as the peripheral signaling to CNS for nutritional notifications. Leptin's detection, the obese mouse model led to using it continuously to present its oriental function to showing leptin as the missing regulator in the obese ob/ob mouse which provided high quality and quantity scientific information of leptin and adipose tissue novel physiology (Castracane and Henson 2006; Korek and Krauss 2015). The dynamic role of adipose tissue in fat storage in form of glycerides and energy production is well-established, it has been evidenced that adipose tissue has a vital role as an endocrine tissue. Adipose tissue secretes more than 100 soluble substances, mainly peptides such as adipokines, cytokines, chemokines or hormones, along with fatty acids and prostaglandins (Kluzek et al. 2015). Additionally, adipokines play several physiological functions such as energy homeostasis, reproduction, hematogenesis, immune system, bone metabolism, cell proliferation and other functions. But in case of adipokine's disturbance, its regulatory role will be missing, then many pathologies and pathogenesis are caused by the altered adipokine.

Sources of Adipokines It evidenced that more than 90% of the adipokines are produced by fat tissue while leptin, adiponectin, and some adipokines can be also attributed to non-adipose tissue sources. Although white fat tissue is the main source of leptin, it can be released by brown adipose tissue, skeletal muscle, bone marrow, placenta, ovaries, stomach specifically by lower part of fundic glands), liver, mammery epithelial cells, as well as pituitary (Guerre-Millo 2004). Additionally, the brain is a possible source and net releaser for leptin (Wiesner et al. 1999), cells of human follicular papilla are source for leptin production (Iguchi et al. 2001). Viscerally adipose tissue produces high level of vascular endothelial growth factor, plasminogen activator inhibitor 1 and IL-6. Greater amount of adipocytokines like TNFalpha, IL-8, and IL-10 produced by non-adipose cells by obese (mass index of 45) than those of (32). Additionally, after digestion by collagenase, most of the

adipokines produced by the non-adipose cells in the cell matrix of adipose tissue (Fain et al. 2004). In addition to Kisspeptins are neuropeptides produced by hypothalamus (Abbara et al. 2021) in addition to its expression in adipose tissue (Brown 1974).

10.2 Adipose Tissue as an Endocrine Tissue

Adipose tissue is a metabolically dynamic organ that has also immune function in addition to its endocrine function. Adipose tissue secrets peptide hormones (adipokines) as autocrine, paracrine, and endocrine signaling factors, which have a variety of receptors, thus allowing it to respond to a variety of stimuli from other hormonal networks and also from central nervous system (CNS). Keeping in view multifactorial ability of adipose tissue, it can make cross-communication between numerous organs within the body (Zhang et al. 2017a; Tsai 2017). The adipokines regulate key physiological activities and functions. Moreover, adipokines and their receptors form a network which is expressed and regulated by the nervous system and other organs including the hypothalamus and pituitary gland (Odle et al. 2018). Among various adipokines, leptin was the first discovered polypeptide primarily expressed by white adipose tissue, which adjusts energy by controlling body weight and appetite through leptin-sensitive neurocytes in hypothalamus. Studies have shown that changes in the adipose tissue modulate the levels of adipokine, thereby causing metabolic and other inflammatory conditions including obesity, insulin resistance, disturbed lipid profile, and high risk of cardiovascular disorders (Kluzek et al. 2015; Zhang et al. 2017a; Tsai 2017; Odle et al. 2018). All these disorders are well known as endocrine disorders. Leptin receptors are distributed in the body and brain, including the hypothalamus and pituitary. Adiponectin also has a key role; it is an anti-inflammatory and anti-atherogenic adipokine. It has negative relation with body weight. Visceral fat is also linked to low levels of adiponectin (Mente et al. 2010; Indulekha et al. 2011). Adiponectin has also antidiabetic effect while visfatin may mimic the effect of insulin. Additionally, visfatin, provides a new plan for treating type 2 DM and insulin resistance (Yamauchi et al. 2001; Stofkova 2009; Al-Suhaimi and Shehzad 2013). This chapter aims to summarize the important adipokines including leptin, adiponectin, visfatin, resistin, apelin, chemerin, adipsin, kisspeptin, and other active molecules produced by adipose tissue. Also the chapter highlights the physiological endocrine functions of the adipokines in energy homeostasis, metabolism and immunity, circadian clocks and neuroendocrine functions showing involvement of these new adipokines in most of physio and pathophysiological status in human and different models of experimental animals (Estienne et al. 2019).

10.3 Adipose Tissue Hormones (Adipokines)

This section briefs the most known adipokines.

10.3.1 Leptin, Adiponectin, Visfatin, Resistin

Leptin It is a 16 kDa polypeptide, an adipokine which contains 167-amino acid residues and one of the highly critical adipose tissue hormones. Leptin is also produced and released by the brain as a non-adipose source of leptin. Additionally, the higher concentration of leptin secreted by brain in females may participate in gender's variances reported in plasma leptin concentrations (Wiesner et al. 1999). It has a crucial role in regulating energy, appetite, weight regulation, reproduction (Hall et al. 2015), since Leptin is a regulator for neuropeptides related with food intake and gonadotropin's release (Guzmán et al. 2019). In the hypothalamus particularly in the arcuate nucleus, both pro-opiomelanocortin (POMC) and neuropeptide Y neurons are essential locations for expression of leptin receptor and also the origin of effective neuropeptide modifiers (melanocortins and neuropeptide Y) that perform contrary functions on food intake as well as metabolism (Cowley et al. 2001). Leptin links between endocrine metabolic diseases and immunity (Al-Suhaimi and Shehzad 2013), it has an important function in many immune cells as they respond to leptin straightly *through* the leptin receptor leading to a significant proinflammatory reaction (Kiernan and MacIver 2021; Di Filippo et al. 2021). Additionally, it has many other physiological and metabolic disorders. It is a key adipokine hormone for the physiology of the cardiovascular system as it regulates its metabolism and functions. Although it its contribution in heart hypertrophy is still debated but leptin contributes in useful manner in fatty acid and glucose's metabolism of myocardium. It protects heart from unsuitable effectors such as obesity's lipid accumulation, transient ischemia (Hall et al. 2015). One of recessive genetic sign associated with an obesity syndrome exhibits hyperphagia, infertility, and disturbances in metabolic hormones. This relates to mutation on chromosome 6 identified, the sign named "obese" ob/ob (Flier and Maratos-Flier 2010). Additionally, another mutation "diabetes" was detected on chromosome 4, and the trait was named db/db. This ob gene encodes peptide of 167 amino acids has been designated as leptin in 1994 (Flier and Maratos-Flier 2010). There is high blood level of leptin in obese people that are resistant to the effects of leptin (Yonis and Al-Doski 2013; Ghanem et al. 2019).

Adiponectin This is a 244-amino acid long polypeptide hormone with a 180-kDa. Adiponectin was first characterized in 1995. It is required in adjusting glucose concentrations and fatty acid metabolism. It is encoded by the ADIPOQ gene in human. Leptin and adiponectin express also unique features: leptin, known as a signaling for metabolism, while adiponectin, is an effective anti-atherogenic hormone. In human, the anti-hyperglycemic agent (thiazolidinedione) boosts endogenous adiponectin release, promoting the concept that develop of adipokines—

targeting drugs may reveal a promising treating plan against insulin resistance and atherosclerosis in obesity (Guerre-Millo 2004). Recently, in Asian Indians, adiponectin may act as a mechanistic connection between omentin and high risk of cardiometabolic disorders regardless obesity status (Vimaleswaran et al. 2021). Additionally, adiponectin is the most effective biomarker for the early diagnosis of DM and other metabolic disorders (Goel et al. 2021). Adiponectin has an anti-inflammatory effect, while leptin as mentioned is a proinflammatory hormone). So, their ratio Adiponectin /Leptin is important since its high value (high adiponectin and low leptin), is compensative plan for inflammation (Di Filippo et al. 2021).

Visfatin Visfatin is 52 kDa adipokine. As its name indicates, it is essentially produced by the visceral adipose tissue, and also produced by nonfat cells such as macrophages from the adipose tissue as the main source of visfatin so, visfatin could be named as pre-B cell colony enhancing factor since it acts as a growth promoter for early stage of B cells. It is known (nicotinamide phosphoribosyl transferase), an enzyme encoded by the NAMPT gene in human. It presents in blood circulation (Para et al. 2021; Chen et al. 2021) and in great amounts in the perivascular adipose tissue. High production of visfatin—as inflammatory signal—in obese enhances expressing of some pro inflammatory substances such as cytokines of proliferation and migration, TNF and IL-6 that can contribute to vascular remodeling (Para et al. 2021). In human, visfatin relates with atherosclerosis as it is expressed in adipose tissue in periaortic and pericoronary artery and has inverse relationship with endothelial function. Visfatin may lead to systemic inflammation. Additionally, visfatin has potent proliferative, and angiogenesis effect. It supports migration and tube formation in chorioretinal retinal endothelial cells (RF/6A) of monkey treated with elevated glucose levels, that visfatin has an effective action on retinal neovascularization (Chen et al. 2021).

Resistin It is a 12.5 kDa, cysteine-rich peptide adipokine produced mainly by adipose tissue, it includes 108 amino acid residues. It is encoded by the RETN gene. It is called resistin because of high insulin resistance noticed in mice after its administrated. It acts an endocrine function as it is required for insulin resistance so, its physiological function contribute to obesity and type 2 DM. Also it is needed physiologically in energy homeostasis and inflammation and in human liver (Steppan et al. 2001; Gabriely et al. 2002), it induces the synthesis of low-density lipoprotein (bad cholesterol) and also downregulates LDL receptors causing high concentrations of the LDL (bad cholesterol) in blood circulation and its accumulation in arteries prompting cardiovascular issues (Degawa-Yamauchi et al. 2003). Resistin is linked to chronic disorders such as cardiovascular diseases and cancers (Taouis and Benomar 2021).

10.3.2 Other Adipokines (Apelin, Chemerin, Adipsin, Kisspeptin)

Apelin Apelin is an endogenous adipokine it has been identified in 1998. Apelin is encoded by gene *apln*, it synthesizes from a larger peptide (77-amino acid)as a

prepropeptide precursor (Tatemoto et al. 1998) which splitted to a smaller active peptide (36 amino acid) recognized as a ligand of the G protein-coupled (APJ)) receptor in multiple tissues indicating its several physiological roles such as endocrine stress response, energy metabolism, blood pressure, homeostasis, cardiac pulse and angiogenesis. This peptide has also hypotensive and diuretic effects. In animal model, endogenous apelin through its receptors APJ, doesn't require in the hypertension's continuance. On other hand, apelin participates in pathological cases such as, diabetes, obesity, and cardiac diseases in addition to cancer. Interestingly, apelin has a crucial role in regulating response of myocardial response to infarction and ischem. Targeting this apelin's pathway therapeutically is possible (Wang et al. 2013; Griffiths et al. 2018; Wysocka et al. 2018; Shareef and Abduljalal 2020).

Chemerin The chemokine (retinoic acid receptor responder protein 2) is identified in 2003 as the adipokine chemerin produced by adipose tissue and encoded by the *RARRES2* gene on chromosome 7 in human. Chemerin has a significant role in modifying many physiological functions and pathophysiological events.

Physiologically, it plays role in lipid and glucose metabolism (Bozaoglu et al. 2007) and it is notably expressed placenta (Goralski et al. 2007). In the hypothalamus, there is expression for chemerin and its receptors in the ependymal and tanycytes cells, it plays a significant role as a neuroendocrine function in hypothalamic–pituitary remodeling, photoperioding, feeding behavior, and energy balance (Helfer et al. 2016). In immune system, it acts a key player as a chemoattractant agent, facilitator for both natural and acquired immune response, reacts with its receptor (chemR23) as a contributor in the acute inflammation in its early phase. Additionally, it is involved in signaling for pre-adipocyte's maturation, differentiation. While pathophysiologically, chemerin's concentrations elevated remarkedly in many diseases such as inflammation (Su et al. 2021a). In hepatic stellate cells, human chemerin variant (huChem-156) has a proinflammatory effect (Spirk et al. 2020), it is also a key biomarker either in benign or cancer tumors (Su et al. 2021b), as well as in carotid intima-media thickness, which indicates a connection links the chemerin with atherosclerotic ischemic cerebrovascular disease (Demir et al. 2021).

Adipsin Adipsin is one of the families of the serine protease; it is a 28-kDa protein. Adipsin is the adipokine that also known as the complement factor D which in the immunology view regulates the alternative pathway of the complement cascade and also produces C3a (the complement component of complement 3 which increases insulin from beta cell. Adipsin has a key role in the synthesis of other of complements C5–C9 that storms membrane of antigen and also in the production of multiple signals such as complement components such as C3a and C5a (Lo et al. 2014). Experimentally, the adipsin/C3a improves the hyperglycemia and boosts insulin concentrations while protects beta cells through the phosphatase. The higher level of blood adipsin accompanies with a remarkable minimal risk of possible diabetes medium old adults (Gómez-Banoy et al. 2019) and improves

hyperglycemia through saving β-cell survival and transcription of its identify (Tafere et al. 2020). Additionally, Adipsin is a new biomarker that detects causes of death in coronary artery patients, indicating the alternative complementary cascade in the pathogenesis of coronary artery ill (Ohtsuki et al. 2019).

Kisspeptin Kisspeptin 1 (kiss 1), is an adipokine encoded by *kiss1* gene. It is generated from preprokisspeptin 1 to putative mature bioactive peptide (kiss 1) which contains 16 amino acid produced by adipose tissue, it is a neuropeptide hormone of the RFamide family plays a regulatory function in the reproduction through to cover the pathway between the sex steroid concentrations and mechanisms of negative and positive feedback regulating the production of hypothalamic GnRH, that stimulates pituitary gonadotropin (FSH and LH) affecting gonads' steroid hormones to produce gametes in either in male or female. It also has a critical regulator role in the onset of puberty and regulation of fertility (Trevisan et al. 2018). So, the disturbance of its GPR54/kiss-1 receptor (kiss1R) causes idiopathic hypogonadotropic hypogonadism (de Roux et al. 2003). Mutations in both KISS 1 or GPR54 genes are related to hypogonadotropic hypogonadism and prepuberty. So, kisspeptin has to be considered to be promising in infertility therapy (Trevisan et al. 2018). In animal, kisspeptin modifies glucose-activated insulin production, appetite, expense of energy, reproductive behavior. In human, kisspeptin plays role in sexual and passionately brain handling. Kisspeptin has fear-inhibiting and antidepressive effects (Mills et al. 2021).

Understanding physiologic and pathologic underlying mechanisms of these adipokines actions is potential advancement for new therapeutic strategies for managing several of many diseases.

10.4 Functions of Adipokines

In addition to the well-established role of adipose tissue in energy production, storage and consumption, adipokines play roles in relation to neuroendocrine function, metabolism, immunity, and reproduction. In these contexts, adipokines have roles in processes such as angiogenesis, inflammation, hematopoiesis, and peripheral circadian functions.

10.4.1 Regulatory Role of Adipokines in Energy Homeostasis

Leptin and other essential hormones (e.g., insulin, thyroid hormones and cortisol) participate in energy homeostasis under normal conditions, as well as under normal physiological conditions such as pregnancy and lactation (Cardinali et al. 2017) and pathological conditions such as obesity and diabetes. Adipose tissue is mostly categorized into white tissue (WAT) and brown tissue (BAT) (Fig. 10.1). WAT is principally dependable to form and store triglycerides, while BAT is essential for producing and expending energy because of it has abundant amount of uncoupling

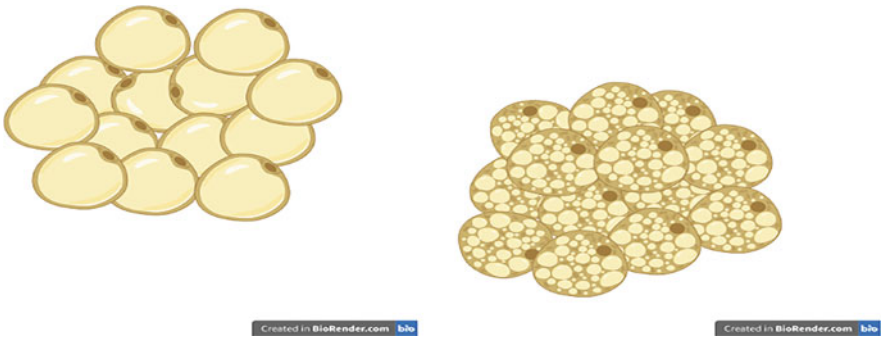

Fig. 10.1 Left part: White Adipose cells. Right part: Brown adipose cells

protein-1 (Musi and Guardado-Mendoza 2014) which required for transporting anionic fatty acids inside the mitochondria of BAT's cell (Hasan and Mahmood 2012). BAT scatters energy to yield heat. Then it regulates body temperature by thermogenesis. BAT is a potential thermogenic approach targeting metabolic diseases such as obesity and diabetes. BAT thermogenic system is influenced through different mechanism such as thyroid gland hormones, adrenergic stimulation, glucocorticoids, natriuretic peptides, retinoids, or capsinoids. In obesity, BAT's activity and abundance are reduced drastically as many pathological mechanisms are accompanied that may impact the proper differentiation of BAT, such as inflammation, adrenaline resistance, endoplasmic reticulum and oxidative stress (Alcalá et al. 2019).

10.4.2 Adipokines and Metabolic Disorders

Adipokines can be used as a sensitive measure of nutritional status, which reflects changes in fat levels in children and adolescents suffering from obesity and anorexia nervosa (Leoni et al. 2010; Pyrzak et al. 2010). In contrast, adiponectin is anti-inflammatory and anti-atherogenic. The adiponectin level is also low in obese individuals and increases after weight loss. Visceral fat is also linked to low levels of adiponectin (Indulekha et al. 2011; Mente et al. 2010), TNF-α, and visfatin. Adiponectin also boosts insulin levels; in other words, it has an antidiabetic effect while visfatin may mimic the effect of insulin. Adiponectin also protects against the destruction of pancreatic beta cells, and along with visfatin, may provide a new way for treating insulin resistance and type 2 DM (Yamauchi et al. 2001; Stofkova 2009; Al-Suhaimi and Shehzad 2013). There is compelling evidence that decreased expression of adiponectin from adipocytes and hepatocyte induced nonalcoholic fatty liver disease. In the patients with HCV infection, it is known that liver steatosis is related reversibly with adiponectin. Hepatocytes can be protected from accumulated triglycerides by elevation of β-oxidation of free fatty acid which in turn decreases formation of de novo free fatty acid (Baranova et al. 2011). Adipose

tissue has a role in cardiometabolic disorders related to obesity through enhancing the proinflammatory. So, cell signals and molecular mechanisms regulating adipocyte and its physiological functions, is a new strategy for protection and therapeutic plans of metabolic disorders by targeting adipose tissue and its hormones (Musi and Guardado-Mendoza 2014).

10.4.3 Adipokines Role in Appetite

Leptin plays a significant role in regulating appetite and energy balance. Mutations in the genes encoding leptin or leptin receptors lead to various pathological conditions including obesity and obesity-related metabolic disorder. Leptin controls appetite through communication with neuroendocrine signals in the hypothalamus, hindering orexigenic peptides (neuropeptide Y and orexin A), as well as activating anorexigenic peptides (pro-opiomelanocortin). In addition to leptin, white adipose tissue releases many other appetite-concerning adipokines including adiponectin, interleukin-6 which also take a role in regulating appetite and energy. It is clear that adipose tissue-derived adipokines communicate and interact with other organs through receptors and regulate metabolic homeostasis (Cardinali et al. 2017; Odle et al. 2018). Adiponectin receptors are present in hippocampus, hypothalamus, prefrontal cortex, and brainstem showing its contribution in the energy homeostasis and appetite in concordance with leptin (Yamauchi et al. 2001; Suyama et al. 2016).

10.4.4 Adipokines and Sleep Disorders

The relationship between sleep disorders such as obstructive sleep apnea (OSA) or obstructive sleep apnea and sleep apnea hypopnea syndrome (OSAHS) with multiple syndromes includes metabolic and cardiovascular disease has been evidenced (Lu et al. 2019). Individuals with OSA have shown decreased concentrations of omentin, which associated with sleep measurements include omentin concentrations, apnea hypopnea index, SpO_2, sleep phase of rapid eye movement %, hypersensitive C-reactive protein, high-density lipoprotein cholesterol. However, plasma levels of hormones including adiponectin, visfatin, and ghrelin in OSA remain similar to control group (Zhang et al. 2018). While plasma or serum concentrations of adiponectin are significantly decreased in OSAHS individuals in comparison with normal subjects, showing a potential effect of adiponectin in pathogenesis of such sleep disorders (Lu et al. 2019). Deficit in sleep that influences leptin functions, may induce obesity then develops T2DM via boosted appetite then increased and food intake (Mosavat et al. 2021) with low energy expenditure. Decreased sleep quality during pregnancy is related to newborn's leptin and lipid concentrations which may affect kid' health (Meng et al. 2021). During sleep, obesity leads to deterrent OSA in the upper airway which causes hypoventilation syndrome resulting hypercapnia (high level of CO_2) during day. Impairment signaling of leptin in the brain was implicated in these issues (Amorim et al. 2021; Moreira et al. 2021; Pho et al. 2021;

Salzano et al. 2021). Recent evidence reported in *db/db* mice that expression of leptin receptors in the dorsomedial hypothalamus improve breathing quality in NREM sleep (Pho et al. 2021). Leptin is an effective respiratory stimulant during sleep in *Lepr*^{b}-Cre-GFP mice experimentally induced obesity (Amorim et al. 2021). Diurnal cycles of sleep-wake are controlled strictly by circadian regulation with robust effect of rhythmic known hormones such as cortisol, melatonin. Contrastly, food intake, counters circadian modification via many metabolic hormones like leptin, orexin, insulin, and ghrelin (Koop and Oster 2021).

10.4.5 Adipose Tissues Is a Member in Immune System: Role of Leptin

Adipose tissue is generally distributed in various depots subcutaneously and internally, reflecting functional heterogeneity and involvement in metabolic syndrome and other inflammatory disorders. The adipokines exhibit immunodmodulatory actions; it has an important role in integrating metabolism with immune activities. There is modulation in the adipokines during stress, energy restriction, and starvation, which creates host of energy deficits environment and participates in suppressing immune response (Fernández-Riejos et al. 2010; Al-Suhaimi and Shehzad 2013). In normal and pathological metabolism and immune status, leptin and leptin receptors regulate the innate and adaptive immune response, as leptin expression has been modulated in metabolic disorders and immunity diseases. Leptin resistance is a risk factor for obesity and the related low grade of inflammation (Al-Suhaimi and Shehzad 2013). Adipokines are a substantial link links between metabolism and optimum roles of immune system. Thus, adipokines dysregulation as in obesity participates to chronic low-grade inflammation and pathological complications (Taylor 2021). The hormone leptin has been associated with neurohumoral and immune response. There is compelling evidence that low level of leptin is linked with increased infection susceptibility. On the other hand, leptin and proinflammatory cytokines increased acting as pathogenic for autoimmune disease. Hence, leptin mediates the inflammatory response (Busso et al. 2002).

Adipose tissues include immune cells and macrophages (Fig. 10.2). B and T lymphocytes express leptin receptor Ob-Rb showing the involvement of leptin in B and T cell responses (Busso et al. 2002). It is known that leptin has a proinflammatory effect, promotes proinflammatory cells, T-helper 1 and cytokines, such as IL-2, IL-6 or TNF-α, (Busso et al. 2002; Sánchez-Margalet et al. 2003). Gene mutation in leptin or leptin receptors lead to obesity characterized by deficiency in phagocytosis and expression of proinflammatory cytokines (Henriksson and Lamia 2015; Lekkas and Paschos 2019). In line with this, leptin deficiency leads to infectious and inflammatory stimuli, which induces dysregulation of cytokine production (Baranova et al. 2011). Moreover, leptin deficiency changes Kupffer cell-derived cytokines to regulate the innate immunity. Increased plasma concentration of leptin, apelin, and visfatin has been found in children with T1DM. T2DM in adults is linked to increased plasma levels of visfatin. Also, obese T2DM patients

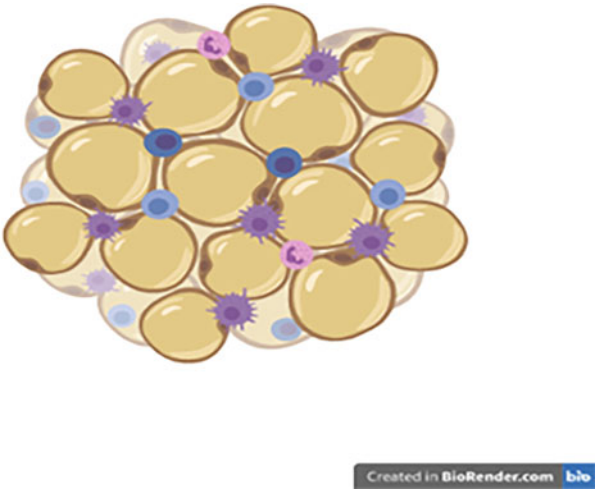

Fig. 10.2 Adipocytes showing immune cells and macrophages making cross talk between them

showed disturbance in adipokine levels including visfatin (Kocot et al. 2017). Additionally, leptin enhances proliferation and function of blood monocytes in vitro, as well as promotes expression of various Cluster Differentiation (CD). Additionally, increase the expression of surface markers on monocytes such as HLA-DR, some CDs (Santos-Alvarez et al. 1999). Leptin receptor is expressed on natural killer cells confirming the role of leptin in natural killer cell maturation, differentiation, cytotoxicity, and activation (Tian et al. 2002).

10.4.6 Role of Adipokines as a Part of Circadian Clocks

Many endogenous circadian clocks are located in the hypothalamus suprachiasmatic nuclei as well as in organs such as the intestine, liver, adipose tissue that responds to the environmental light–dark cycle (Ajabnoor et al. 2014). Circadian clocks optimize and adjust the timing of physiological processes including proliferation and differentiation of adipocyte, lipid metabolism and hormones under complex control of signaling to endocrine, neuronal, or behavioral rhythms. Changes in the circadian clocks associate with changes in adipocyte metabolism and hormone secretion to accomplish temporal coordination and whole-body homeostasis (Henriksson and Lamia 2015). Adipose tissue modulates behavior and organ physiology by adipokine hormones. The circadian clock coordinates the production of fatty acids from white adipose tissue through hydrolysis of triglycerides to free fatty acids and glycerol. It has been noted that PER2 suppresses the transcriptional activity of nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) and reduces the synthesis of saturated and monounsaturated fatty acids in white adipose tissue (Henriksson and Lamia 2015; Lekkas and Paschos 2019). While adiponectin

controls glucose and lipid metabolism, increases fatty acid oxidation, promote insulin sensitivity and inhibits hepatic gluconeogenesis. Expression of adiponectin is controlled by the clock by the circadian expression of its nuclear transcription factor PPARγ and its co-activator PPARγ co-activator 1α (PGC1α) in both white adipose tissue and differentiated adipocytes (Barnea et al. 2015). Because clock siRNA completely abolishes the adiponectin expression. There is compelling evidence that adipokines regulate cardiometabolic functions but hypercortisolism alters the adipokine release pattern and abolishes high-sensitivity C-reactive protein (hsCRP) circadian rhythm which may increase cardiometabolic risk (Ajabnoor et al. 2014; Schutte et al. 2010). The shifting in the circadian clock changed gene expression and dipocyte transformation with accumulation of lipids in brown adipose tissue (Herrero et al. 2015). In mice, continuous expose to light throughout the full day cycle elevated adiposity by lowering adrenergic signaling to brown adipose tissue which decrease metabolites (glucose and fatty acid) uptake in brown adipose tissue (Kooijman et al. 2015). It has been reported that β-oxidation of fatty acids promote thermogenesis, consequently, increases uptaking these metabolites by brown adipose tissue (Bilski et al. 2016)**.**

10.4.7 Effect of Adipokines on Neuroendocrine Functions

It is known that adipokines receptors are widely distributed in the brain, where it regulates eating behavior, neurotrophic, neuroplasticity, and neuroprotective factors in the brain. In the hypothalamus, leptin and adiponectin establish adipose-brain axis to regulate many physiological functions like energy homeostasis, appetite, satiety, metabolism, and weight. The adipokine's anti-inflammatory and neurotrophic effects make it potential neuroprotective molecule in neurodegenerative disorders (Parimisetty et al. 2016).

Leptin and **adiponectin** can cross the blood brain barrier and regulate cell proliferation, survival, and synaptic plasticity via modulation, cell metabolism and suppression of inflammation in the brain. As a result of energy accumulation, leptin responds by suppressing orexigenic neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP), it also stimulates the anorexigenic pro-opiomelanocortin (POMC) neurons in the hypothalamic arcuate nucleus (ARC). The comprehensive anorexigenic action dominates during energy accumulation post feeding-phase accompanying with an increased body fat oxidation, and hence reduced leptin levels in a negative feedback mechanism (Park and Ahima 2015). Leptin enhancing-GABA secretion from LH to VTA's dopaminergic neuron is correlated with low food take in leptin-deficient mice by modulating JAK/STAT/PI3K/Mtor pathway. Leptin-induced neuroprotection has indicated that it's beneficial in treating ischemic stroke (Zhang et al. 2013). Elevated leptin concentrations in human boost positive feelings while reduced leptin concentrations may lead to change toward motivation (Licinio et al. 2014).

Adiponectin administration in the cerebral ventricle leads to an orexigenic effect under high glucose levels but is anorexigenic at its low levels (Yamauchi et al. 2001;

Suyama et al. 2016). Decreased expression of adiponectin increases dopaminergic activity, cognitive dysfunction and anxiety behavior.

Chemerin In animals with hypoxic-ischemic encephalopathy, chemerin significantly improves cognitive and sensorimotor, decreases apoptosis and the expressions of pro-apoptotic markers, showing a neuroprotective effect. Chemerin is thought to play a mediator in neuro-inflammatory effect in the brain. Upregulated expression of chemokine-like receptor 1 is observed in AD patients, indicating the effect of central chemerin signaling in AD progression (Zhang et al. 2019).

Visfatin has a neuroprotective effect against ischemia-induced injury because NAMPT overexpression decreases infarct and improves long-term neurologic effect. Visfatin has also significant apoptotic and necrotic effects in the CA1 region of the hippocampus, with improved memory deficiency (Zhao et al. 2015).

The adipokine **adipsin** can be found in human cerebrospinal fluid in addition to its presence in the serum under certain pathophysiological conditions such as obesity, lipodystrophy or severe and recurrent meningococcal infections in human (Schmid et al. 2016).

10.4.8 Relation of Adipokines with the Hypothalamus Releasing and Pituitary Hormones

Pituitary gland has specific cell types produce various hormones into the hypophyseal portal system of the pituitary to regulate the target organs. Pituitary produces prolactin (PRL), growth hormone (GH), thyroid stimulating hormone (TSH), adrenocorticotropin (ACTH), and the gonadotropins, luteinizing (LH) and follicle stimulating (FSH) hormones (Davis et al. 2013). Adipokines are produced, expressed and regulated in the hypothalamic and pituitary indicating a regulatory circuit that modulates pituitary cell-function. Leptin, adiponectin and resistin regulate all hormonal cell types in primary anterior pituitary cell cultures in different manner (Sarmento-Cabral et al. 2017). Adiponectin mediate neuroendocrine effect in the control of both somatotrophs and gonadotrophs by inhibiting GH and LH release in pituitary cells. GnRH release is suppressed by adiponectin by activating AMP-activated protein kinase and extracellular signal-regulated kinase (Cheng et al. 2011). The effects of leptin to stimulate GH at the pituitary is mediated through activation of adenylyl cyclase/protein kinase A (AC/PKA), phospholipase C/protein kinase C (PLC/PKC), PI3K and extra-/intracellular Ca^{2+} mobilization, but does not require mTOR and MAPK activation. Leptin expression in the pituitary gland is regulated directly by various factors (Sarmento-Cabral et al. 2017). GHRH has a key role in growth hormone (GH) release from adipocytes under various conditions including obesity. Difference has been noted in the expression level of GHRH and GH-R in obese and nonobese subjects. Studies have shown that GHRH may exert an anti-obesity effect through inhibition of human adipocytes mesenchymal stem cells (HMSC) differentiation as well as increasing lipolysis of the adipocyte in an

autocrine or paracrine signal which are mediated through GH and GH receptors (Rodríguez-Pacheco et al. 2017).

10.4.9 Effects of Adipokines on Reproduction

Adipokines play a vital role in reproduction. In women, leptin levels are around three times that in men, its release reaches peak in the midnight, which is inverse of the highest level of cortisol (Guerre-Millo 2004). They influence the hypothalamic-pituitary-gonad axis both centrally at the hypothalamic/pituitary level, and peripherally in the gonads (Parimisetty et al. 2016; Sarmento-Cabral et al. 2017). Leptin, adiponectin, resistin, chemerin, and the peptide kisspeptin play various roles in the hypothalamic-pituitary-gonad axis, which affects male and female fertility. Moreover, adipokines and adipose tissue cytokines easily modulate the immune system response leading to inflammation, which in turn affects the hypothalamic-pituitary-gonad axis, thus proving a link between metabolic inflammation and fertility (Tsatsanis et al. 2015). Leptin plays a primary role in the normal reproductive system physiology in connection with various levels of the hypothalamic–pituitary–gonadal axis, since different states of leptin disturbance like decrease, increase or resistance can be correlated with disorders of reproduction functions (Pérez-Pérez et al. 2015; Azaïs et al. 2017). In addition to adipose tissue, leptin is also released by the placenta, and performs an autocrine function. There is compelling evidence that leptin dysregulation or resistance can disturb reproductive functions (Pérez-Pérez et al. 2015). Leptin has a boosting proliferative effect on stem/progenitor spermatogonia in neonatal mouse (Yersal et al. 2020) and a proliferative and anti-apoptotic action on granulosa cells in some birds via molecular signal of the PI3K/Akt/mTOR. This introduces a potential therapeutic plan for to proliferate the stem or progenitor spermatogonia or granulosa population in the neonatal gonads to achieve autotransplantion post tumor therapy (Wen et al. 2015). kisspeptin hormone plays a key function in the onset of human puberty (Messager 2005) and regulatory roles in reproduction include sex differentiation, physiology of gonadotropin production and fertility (Pinilla et al. 2012).

10.4.10 Adipokines Participate in Hematopoiesis and Cardiovascular System

The strong link between immunity and metabolism involves adipokines mediation plays a critical role in hematopoietic stem cells (Cousin et al. 2016)**.** Also, in pathological states, the link of immune -metabolism and inflammatory processes plays roles (Ketterl et al. 2018). Since fat tissue has been known as an endocrine and paracrine organ produced adipokines involved in metabolism and proinflammatory effects. Adult who had survived of cancer and subjected to hematopoietic cell transplantation in childhood—when compared with healthy control group—have higher rate more than expected of obesity risk for metabolic cardiovascular

disorders. Also, there is significant differences between the studied group and control population of relation in adipokines include (leptin and adiponectin) and cytokines/inflammatory factors include (IL-6 and TNF-α) and as well as obesity. So, LBM could introduce a tangible goal for relieving the high rate of cardiometabolic risk in survivors (Ketterl et al. 2018). Leptin receptors are expressed on hematopoietic CD34+ stem cells, erythrocytes, lymphocytes, and blast cells. Moreover, these receptors are also expressed in hemopathological cases such as leukemia and lymphoma cells. Adipokines activate cell proliferation, cytokine release and protect diseased cells from apoptosis through various signaling pathways (Han and Wang 2015). Adipokines play a role in angiogenesis. Apelin supports forming new blood vessels and hypotensive (angiogenesis) (Hashimoto et al. 2004; Cox et al. 2006). It also has a hypotensive effect because it contributes to release of nitrogen oxide which acts as an effective arterial vasodilator since it relaxes the smooth muscular layer of the artery's wall. Apelin has a diuretic action associated with its hypotensive effect (Tatemoto et al. 2001; Mesmin et al. 2010; Kechyn et al. 2015). In humans, leptin regulates the biological functions of adventitial pericyte (contractile muscle cell lines among the endothelial cells of the capillaries and some venules) functions by paracrine and autocrine signals (Riu et al. 2017). In rat model, leptin system (the hormone and receptors) is present in the in all areas of the heart which is an important target for leptin effects as it modifies cardiac functions either in an autocrine or paracrine- dependent signal (Purdham et al. 2004), as it has important functions in regulating cardiac metabolism and its protection from lipotoxicity (Hall et al. 2015). Additionally, adiponectin preserves cardiovascular cells via its vasodilator, anti-inflammatory and anti-oxidative and anti-apoptotic effects. Adiponectin-targeted drug is possible management for metabolic and cardiovascular diseases (Hui et al. 2012).

10.4.11 Adipokines Influence Bone Turnover

Adipokines influence bone turnover by both direct effects on bone cells and indirect signals mediated by the CNS (Naot and Cornish 2014). Age-associated bone lack is related with bone marrow adiposity. In osteoarthritis and osteoporosis, visfatin, leptin and resistin known are immune-modulators and affects differentiation of bone marrow-derived mesenchymal stem cells**.** It has been reported that visfatin mediated increase of matrix mineralization and reduced collagen type I expression could participate in bone fragility. Visfatin also is required in reduced bone remodeling at the adipose tissue/bone interface via stimulation of proinflammatory factors/cytokines and disturbed MMP/TIMP neutralize during mesenchymal stem cells differentiation (Tsiklauri et al. 2018). Chemerin and chemokine-like receptor 1 positively controls bone's metabolism by mediating testosterone synthesis and the stability between osteoblasts and osteoclasts formation. Moreover, the dipocytokine chemerin receptors have ability to regulate the bone remodeling through testosterone production and provide stable nature among osteoblasts and osteoclasts synthesis (Zhao et al. 2019). There is a remarkable physiological connection between vitamin

K-dependent-osteocalcin, metabolism, bone metabolism and cardiovascular diseases intermediated by certain molecular signaling regulated by adipokines (Al-Suhaimi and Al-Jafary 2020).

10.4.12 Adipokines and the Skin

Leptin has powerful improving, tropic and preservative effects and its mimetics may be used for skin protection, regeneration as well as improvement of hair cycle, and might restore some appearance aged skin. Moreover, it supports wound healing and hair growth. As leptin stimulates mitochondria and its dependent molecular signals in the target stimulating its metabolism and proliferation (Poeggeler et al. 2010). Leptin is involved in several dermatopathologies such as psoriasis, lupus erythematosus, hidradenitis suppurativa, and some skin tumors. Elevated serum leptin as in obesity and deterioration receptor and signals are implicated in skin pathogenesis of many skin disorders (Su et al. 2021c). Obesity is one of the risk elements of multiple cancers, melanoma, which represents most of skin tumor deaths. The molecular signaling of adipokines may modulate many phases such as proliferation, migration, angiogenesis, invasion, as well as apoptosis of melanoma cells. Adipokines could be used as biomarkers for skin pathologies (Olszańska et al. 2021). Additionally, adiponectin can participate in psoriasis (Ruiyang et al. 2021).

10.4.13 Adipokines Has Double Proliferative and Apoptotic Actions

Suppression of leptin signal is a key strategy for vitamin K apoptotic effect as a possible treatment against hepatic tumor's cells survival and proliferation (Al-Suhaimi 2014). Among the multiple adipokines, leptin and adiponectin have a direct regulatory proliferative effect on hepatic cells include (hepatocytes, hepatic stellate cells and Kupffer cells). Additionally, both these adipokines regulate cell cycle in hepatic cancer's cells in a complicated way. Adiponectin has both pro- and antiproliferative effects, while leptin seems to be as pro-proliferative adipokine. In liver physiology, adipokines are significant factors in regulating cell apoptosis and liver functions (Nepal and Park 2015). Additionally, adipokines activate cell proliferation, cytokine release and protect diseased cells from apoptosis through various signaling pathways (Han and Wang 2015). Also, adipokines play a role in angiogenesis. Leptin administration reveals a concentration–time-dependent proliferative action on stem/progenitor spermatogonia that connects with high expression of ERK1/2 and STAT3 pathways while preserving their undifferentiated status. Also has a similar proliferative effect on granulosa cells in some birds as well anti-apoptotic action via which made leptin a potential proliferative tool on the stem or progenitor of gonads cells (Wen et al. 2015; Yersal et al. 2020).

10.4.14 Novel Adipocytokines: Pathogenesis, Treatment, and as Biomarkers

Obesity is the most growing public health issue clinically, socially, and economically and it is the main cause for several diseases in the human. The knowledge of the functions of discovered adipokines from adipose tissue lead greatly to many strategies for diagnosis, disease biomarkers and managing many syndromes and diseases like metabolic, cardiovascular and bone, immune diseases, etc. Adipokines are shared diagnostic, prediction biomarkers as well as therapeutic targets are reported for both obesity and type 1 & 2 diabetes and its related pathogenesis (Kim et al. 2019). For example: There is a remarkable positive relation between serum insulin and a group of parameters include (HbA1c, glucose, leptin, apelin). High concentration of adipocytokines include serum (leptin, visfatin, and apelin) may relate to the increased HbA1c, glucose, and insulin. In human, treated T1DM children with regular insulin treatment failed to regulate adipocytokines (leptin, visfatin, apelin) as well as metabolic factors (HbA1c, fasting glucose) in serum. Leptin, visfatin, and apelin are playing critical part as biomarkers in T1DM (Al-Suhaimi et al. 2012a, b). In comparison with healthy individuals and normal BMI T2DM patients with those obese and treated T2DM, serum adipocytokines have disturbed in the form of a significant elevated leptin levels and decreased adiponectin level. Additionally, HA1c, visfatin were also the noticeable biomarkers in treated T2DM but serum leptin was the highest level in obese gro (BMI < 30) up (Al-Suhaimi and Shehzad 2013; Liu et al. 2020).

Even in animals such as dromedary camels, asynchronized rise in leptin and insulin concentrations during age progression in males and reduced their concentrations in females (Al-Suhaimi et al. 2009).

There is also a connection between low blood concentrations of (TNF-related apoptosis-inducing ligand) and the markers of obesity-stimulated diseases (resistin and lipocalin-2/ngal) (Tisato et al. 2017). The disturbance in adipokine concentrations include (leptin, adiponectin, and resistin) participates in increasing hypertension risk in metabolically healthy obese in both children and adolescents. Adipokines as non-classic factors must be considered in metabolically healthy obese children and adolescents in medical clinics and research clinical trials (Ding et al. 2018). The adipokine, chemerin, is possibly implicated in dysregulation of early glucose metabolism disorders (Sitar-Taut et al. 2020). Many adipokines contribute to regulating of insulin resistance, inflammatory and immune responses and vascular function. Also, adipokines are demonstrating potential part in managing obesity and obesity-related syndromes, such as metabolic and cardiovascular disorders. These adipokines include leptin, diponectin, visfatin, resistin, apelin, chemerin, vaspin, omentin, progranulin, lipocalin-2, follistatin-like 1, nesfatin-1, retinol binding protein 4, and plasminogen activator inhibitor-1, secreted protein acidic and rich in cysteine, C1q/TNF-related proteins, wingless-type inducible signaling pathway protein-1, family with sequence similarity to 19 member A5, secreted frizzled-related protein 5, (Recinella et al. 2020). But increased fat mass leads to changes in the regulations of adipose tissue physiology which leads to obesity and its

associated diseases, as there is epidemiological evidence that obesity associates with some cancer types. The regulation of adipokines has a key role affecting cancer pathophysiology. Adiponectin is significantly reduced in obese persons and which may play a role in growth of tumor, despite some studies are in debate on the role of adiponectin on tumorigenesis but mostly accredited hypothesis revealed that it a protective hormone, prohibiting cancer growth and advancement, but still, it needs more molecular and signaling studies to discover its role in managing cancer especially on endocrine malignans (Tumminia et al. 2019). As the obesity is the main reason of many pathologies in the human including cancer, adipokines distribution contributes to melanoma progression, metastasis, and its patient survival (Olszańska et al. 2021).

Diabetes and cancer show main challenging health problem since hyperglycemia, hyperinsulinemia, and disturbance of fats metabolism in T2DM rise the changed metabolism in tumor cells. This metabolic connection between cancer and diabetes complicates therapeutic management and decreases survival ratios (Talib et al. 2021). Transplantation of brown adipose tissue is a new alternative strategy for treating obesity (Payab et al. 2020). So, knowing how obesity can boost associated diseases and some types of cancers development may help in its therapeutics management and treatment.

In human, plasma resistin concentrations are related with inflammatory markers and are predictive of atherosclerosis. Resistin could act as a novel connection between metabolism, inflammatory cytokines, and atherosclerosis (Reilly et al. 2005), Resistin has been considered as biomarker (Taouis and Benomar 2021). Systemic sclerosis (SS) is an autoimmune multiorgans disorder featured by vasculopathy and tissue fibrosis without known etiology, adipokines have attracted the scientists in its participation in many pathologies of SS. Leptin, adiponectin, adipsin, resistin visfatin, or chemerin are heterogenic adipokines. Leptin boosts fibrosis and inflammation while diponectin shows anti-fibrotic brows and influences inflammatory processes. Resistin associates with vascular participation in SS. But in late-stage SS, visfatin associated with retrogression of skin lesions. Whether chemerin was a possible marker of elevated risk of decreased renal function and progression of skin sclerosis in the early stage of SS. Chemerin is also a key biomarker either in benign or cancer tumors (Su et al. 2021a). Vaspin has a preventive role in digital ulcers progression. New group of adipokines (adipsin, omentin, apelin, and C1q/TNFa-related protein are potentially required in SS pathogenesis. Thus, serum adipokines concentrations are possible predictive and diagnostic markers in SS (Żółkiewicz et al. 2019). Adipsin (complement C3a) and phosphatase DUSP26-oriented treatment may display a novel plan to obtain beta cell health to protect and treat type 2 DM (Gómez-Banoy et al. 2019; Tafere et al. 2020). As well as used as a biomarker in disease of coronary artery's patients (Ohtsuki et al. 2019). Kisspeptin has a possible role as a biomarker in infertility therapy and in regulation of ovarian hyperstimulation (Trevisan et al. 2018). Therapeutic strategy targeting kisspeptin mechanism may contribute to management of some disorders range obesity to mood (Mills et al. 2021). Adipokines contribute to critical illness and sepsis as blood biomarkers. In their circulating levels, there are

increased in C1q/tumor necrosis factor a-related protein 1, Leptin and Leptin Receptor, visfatin, resistin and decreased in C1q/ tumor necrosis factor a -related protein, adiponectin, and retinol binding protein 4 (Loosen et al. 2019). Adiponectin is key adipokine as metabolic biomarker (Otu and Otu 2021). Low concentrations of adiponectin in obese and other metabolic disorders are not promoting the dental implant (Goel et al. 2021). In worse cardiometabolic health such as diabetic, hypertensive patients, if Adiponectin/leptin ratio weakens, it may participate to mortality (Di Filippo et al. 2021). In diabetes, the adipocytokines profile in the form of proinflammatory and anti-inflammatory factors is a potential biomarker for heart failure risk stratification (Berezin et al. 2020).

10.5 A Glance on Adipose Tissue Stem Cells as New Therapeutics Techniques

Adipocytes and osteoblasts arise from the same mesenchymal stem cell progenitors. Leptin effectively regulates the differentiation of mesenchymal stem cells to adipocytes and osteoblasts through a phase that may be disturbed by the consumption of a high-fat diet (Lindenmaier et al. 2016). Adipose-derived stem cells (ASCs) contribute to tissue remodeling by releasing cytokines and growth factors. Hypoxia-conditioned ASCs help to maintain angiogenesis by secreting leptin (Delle Monache et al. 2016). In humans and mice, exposure to cold environment stimulates progenitor cells in white fat tissue to form beige adipocytes that generate energy. However, aging impairs this property. Therefore, enhanced age modulation may be a potential antidiabetic therapeutic strategy (Berry et al. 2017). Adipose-derived mesenchymal stem cells (ASCs) are growing field of regenerative medicine. This new generation therapeutics are promising for musculoskeletal diseases such as Achondroplasia, Duchenne muscular dystrophy, and osteogenesis imperfecta are the most frequent rare genetic defect that affect the musculoskeletal system in children. Administration of ASCs promotes fracture healing, joint healing, tendinopathy (tendon injury) and physiological changes in muscle. However, stem cell's safety and side effects are still unclear. ASCs technique are beneficial in controlling immune disorders (autoimmune reaction), high potential to transform into new identity of mesodermal cells, ex vivo expansion, and other effects such as release of neurotrophic and anti-inflammatory factors (Rivera-Izquierdo et al. 2019). ASCs display mesenchymal stem cell (MSC) features as they have demonstrated have differentiative properties into different lineages such as neurogenic, myogenic, chondrogenic, and osteogenic. There is a possibility to substitute bone marrow for source' availability of mesenchymal stem cells, and to recruit them in reconstructive medicine (Jankowski et al. 2020). Sex steroids function key roles not only in the adipose tissues/cell's distribution, but also, in its metabolism, proliferation, and functions. This role of sex steroids on adipocyte function is intermediated through adipose-derived stem cells of human (Fitzgerald et al. 2018).

Many challenges have been faced in that regard. So, to bridge some of these challenges, scientists settled many protocols to produce effective and high

functionality of ASCs such as preadapting ASCs that treated with several stimulating substances, manipulation of ASCs's genes and create alterations in culture environments using three-dimensional (3D) cell culture. Additionally, exosomes and extracellular vesicles by ASCs may be employed to improve ASCs's performance (Seo et al. 2019). Moreover, and to overcome the limitation of stem cell therapy, scientists have established the strategy called "The total secretome of adipose-derived stem cells includes ASC-derived exosomes" abbreviated as (ASC-exos) with its proangiogenic, immunomodulative, and neurotropic effects could be applied effectively in treating many diseases such as neurodegeneration, heart, respiratory system, inflammation and immunity. ASC-exos strategy have higher beneficial effects with lower risks such as (1) applying stem cell-free therapy, (2) higher effectiveness, less side effects, (3) safer alternative therapy than stem cell therapy, (4) possible biobanking of the ASCs secretome (Trzyna and Banaś-Ząbczyk 2021).

10.6 Local Hormones

Some organs and tissues, including the skin, heart, mucous membranes, stomach, intestines, kidneys, placenta, thymus, and hypothalamus, and other sites can produce hormones in addition to their primary functions. Each tissue in the body can secrete hormones to regulate different functions in autocrine/paracrine or throughout the body.

10.6.1 Prostaglandins

More than 20 types of prostaglandin (PG) have been identified. They are classified into four series, the A, B, E, and F alpha series. The four main bioactive prostaglandin compounds produced in vivo are prostaglandin (PGE2), prostacyclin (PGI2), prostaglandin (PGD2), and prostaglandin (PGF2α). Prostaglandins such as PGE 2 is produced de novo from arachidonic acid, a polyunsaturated fatty acid, by a stimulus. Cytosolic phospholipase A2 (cPLA2) group accurately regulates cellular arachidonic acid to be mobilized by both PGH synthase and PGH2 (Jones 1972). PGH synthase found in two isoforms, known as 2 (COX-1 and COX-2) and cyclooxygenase-1 (Greenspan and Forsham 1986). COX-1 is responsible for prostaglandin synthesis, whereas COX-2 is responsible for proinflammatory effects including cancer and metabolic diseases by binding with their prostanoid receptors (Jones 1972; Greenspan and Forsham 1986). PG receptors groups are classified based on the different presence of a divergent carboxy-terminus which provided nine group of receptors; four groups (EP1-EP4) bind to PGE2 (Ricciotti and FitzGerald 2011). In response to inflammation, both the production level and the performance of the prostaglandin changes significantly. PGE2 can influence development of adaptive immunity by promoting dendritic cell migration and upregulate costimulatory molecule expression to induced T cell activation (Jones 1972; Greenspan and

Forsham 1986; Ricciotti and FitzGerald 2011). PGE_2 plays important homeostatic functions by regulating multiple aspects of innate and adaptive immunity.

10.6.1.1 Main Functions of Prostaglandins

The prostaglandins have several regulatory functions in the body such as: Protect the cells in the body, secretion of the acid in the stomach, and regulation of temperature, regulation of blood pressure, it decreases blood pressure with essential hypertension in humans, PG plays a role in the metabolism of fatty acid including lipolysis, they also play a major role in reproduction; prostaglandins are involved in reproductive functions such as conception, luteolysis, menstruation, and parturition. PG also contributes to smooth muscle contraction in the ovaries needed for expulsion of the ovum. They also contribute to the degeneration of the corpus luteum, breakdown of collagen fiber in the cervix at birth and reinforcing uterine contraction during birth.

They play a prominent role in the inflammatory response, pain and fever production. PGE inhibits platelet aggregation and can contribute to preventing thrombosis. There are also other compounds such as leukotriene and thromboxanes like thromboxane A_2 which boost platelet aggregation; other substances are still active but occur in small quantities and degrade quickly. PGs are involved in muscle activity in organs such as the air bronchioles, intestines, and womb (Jones 1972; Greenspan and Forsham 1986; Ricciotti and FitzGerald 2011)

10.6.2 Gastrointestinal Mucosa Hormones

The regulation of metabolism is very complicated and requires several factors by both the nervous and endocrine systems, as well as local elements. Gastrointestinal hormones are peptides in nature generally produced by enteroendocrine cells that distributed widely throughout the length of the gut epithelium of intestine making the gastrointestinal duct the biggest endocrine organ. It produces over than 20 multiple hormones include the most functionally bioactive gastrointestinal hormones: Proadrenomedullin, adrenomedullin**,** gastrin, secretin, Cholecystokinin (CCK), serotonin, GLP-1, PYY, GIP (Ahlman and Nilsson 2001). Each hormone plays essential functions in regulating energy and glucose homeostasis in the whole body. Moreover, some gut hormones are applied to act the basis role of several therapeutic glucose-decreasing and weight loss drugs (Martin et al. 2019). The mucous membrane of the digestive tract secretes local hormones which regulate intestines peristalsis, enzymes secretion, food absorption and digestion, and gut motility (Ahlman and Nilsson 2001). The enteroendocrine cells are present and working in a complex environment, as they are subjected to various physiological influencers such as ingested foods, circulating elements and metabolites provided by surrounding gastrointestine microbiome. Gastrointestine-derived hormones exert their regulating action on digestion and metabolic via their interactions with various key organs involved in these processes include the digestive system-supplementing glands (liver and pancreas), adipose tissue as well as brain (Martin et al. 2019). Different

gastrointestinal hormones has been discussed below, which act through their specific receptors to produce any biological effects.

10.6.3 Digestive Tract Stimulating Hormones

10.6.3.1 Adrenomedullin (AM) and Proadrenomedullin

Both of adrenomedullin (AM) a 52-amino acid peptide and proadrenomedullin N-terminal 20 peptide (PAMP) are 2 biologically active hormones encoded by a single gene that are distributed ubiquitously and have many physiological functions. Both AM and PAMP are found throughout the gastrointestinal tract and are particularly rich in enterochromaffin-like and chief cells of the gastric fundus, neuroendocrine cells of the gastrointestinae mucosa, submucosa of the duodenum, ileum, and colon (Sackett et al. 2008; Martínez-Herrero and Martínez 2016). The distribution in the GI duct indicates that the hormones AM and PAMP act to regulate many physiological and pathologic conditions in the gut. AM and PAMP have been proven to act as autocrine, paracrine neuroendocrine growth factors in the GI epithelium. Both has potent inhibiting effect of gastric functions particularly enzyme production and evacuation. AM and PAMP regulate the active transport of sugars in small intestine, water and ion transport in the large intestine, improve endothelial barrier function, modify small intestine and colonic motility, and stabilize blood function during GI inflammation (Sackett et al. 2008; Martínez-Herrero and Martínez 2016). AM and PAMP are useful biomarkers for prediction of localized bacterial infection and differentiation of sepsis (Al Shuaibi et al. 2013; Li et al. 2018). In obesity, AM has an inhibiting effect on inflammation in white adipose tissue through activating its receptors and protein kinase A (Dai et al. 2021). AM and PAMP also has a protective function for the gastric mucosa against injuries and promote curing in pathologies such as stomach ulcers and inflammation of bowel disease (Sackett et al. 2008; Martínez-Herrero and Martínez 2016). In case of enterohemorrhagic *E. coli* infection, the expression of PAMP would be modulated either in vascular endothelium or intestine epithelium to perform its protective action as PAMP ruptures the cell membrane of enterohemorrhagic *E. coli* and reduces virulence of the bacteria and suppresses inflammatory reaction (Wang et al. 2020). Also, there was a perfect alleviation in patients with steroid-resistant ulcerative colitis treated for 8 weeks with a high dose of AM (Kita et al. 2021). Moreover, AM has cardioprotective actions against doxorubicin that has cardiotoxic side effects (Durdagi et al. 2021).

10.6.3.2 Gastrin

Gastrin is a peptide hormone that stimulates growth of gastric mucosa, movement, and release of HCL. It is known as the major biological regulator of gut physiology (Dimaline and Varro 2014). Gastrin is initially produced from the G cells in the antral area of the stomach and duodenum. Gastrin is also produced by other sources includes extraantral G cells, pituitary, pancreatic endocrine cells (Dockray 1999). Gastrin is released directly into the blood circulation to reach the fundus and cardiac

areas of the stomach in which most of HCl secreting parietal cells are present. Gastrin is regulated by some stimulator and inhibitors. Vagal and gastrin-releasing peptides are essential stimulators. Then it is secondary released as a response to amino acids and peptides containing meal, gastric distention, and an elevated stomach pH on the contrary gastrin secretion by paracrine inhibition of somatostatin and also reduces stomach pH (Schubert 2016; Xiaoli et al. 2017). Gastrin targets the HCL-producing parietal cells and histamine secreting enterochromaffin-like cells. Gastrin is also a critical growth regulator in mucosal layer of the gut and implicated in the growth of many GI cancers. Gastrin—as mentioned—secreted from antral G cells which is tightly controlled by different paracrine, endocrine, neural signals and (Schubert and Makhlouf 1993). Other factors also regulate gastrin such as somatostatin short peptides, calcium in a meal and aromatic amino acids. Additionally, gastrin release influenced by the lower pH (Schubert and Makhlouf 1993). Gastrin is clinically assayed to detect a gastrin-producing cancer (Prosapio et al. 2021).

10.6.3.3 Ghrelin

Ghrelin is orexigenic peptide hormone contains 28-amino acid, it acts as ligand for growth hormone secretagogue receptor (GHSR). The effective form of ghrelin is acyl ghrelin that binds to GHSR-1a, and transport via the blood–brain barrier. It is called hunger hormone as it is increased during fasting and in status of negative energy balance such as starvation or anorexia. Conversely, in ghrelin concentrations, ghrelin activates the resecretion of GH. It has a key function in the neurohormonal regulation of appetite, energy, stomach emptying, and HCL production. It has also been found that ghrelin influences the secretion of growth hormone and prolactin, and has an effect on carbohydrate metabolization (Al-Ayed et al. 2020; Rodger 2021) (Fig. 4.9). The gut microbiota can directly or indirectly affect oghrelin secretion, the microbiota-ghrelin axis has an effect on metabolism and CNS-regulated homeostatic and non-homeostatic regulation of food intake (Leeuwendaal et al. 2021).

10.6.3.4 Secretin

Secretin is a hormone peptide released by S cells in the duodenum and influences many other organs. Receptors of secretin are present in the basolateral domain of various cells. Secretin has been identified as a hormone-controlling pancreatic exocrine function, it regulates the growth and the secretion of epithelial cells of the pancreatic follicles as well as biliary in the liver. It regulates gastric acid release, and motility (Chey and Chang 2003). In the stomach, acidic chyme stimulates the duodenal cells to release secretin which stimulates the release of pancreatic and intestinal juices specifically fluid and bicarbonate. Secretin has also trophic regulating functions (Afroze et al. 2013; Chey and Chang 2014). Secretin is controlled by hormone–hormone or hormone–neuro signals. The vagus nerve has a key role in secretin release and functions. The physiological regulation of secretin hormone in secretions and motility of intestines, also it has actions on extragastrointestal sites. Secretin as a neuropeptide is present with its receptors in central nervous system (Chey and Chang 2003).

10.6.3.5 Cholecystokinin

Cholecystokinin (CCK) is one peptide of the gut–brain peptides, it is produced by endocrine cells found predominantly in duodenum and jejunum, it released by the neurons in the myenteric plexus as well as brain. CCK is important for contraction of the gallbladder, secretion of pancreatic enzymes, suppression of gastric emptying, bowel motility, and insulin release. **CCK** has growth effects on the pancreas and gut mucosa (Ma et al. 2013). Bile influxes via hepatic duct into the gallbladder, to be intensified and saved. Under physiological status, CCK is activated by reaching digested food to the intestine. Once acidic chyme goes out from stomach, it stimulates the duodenum to secrete CCK that stimulates the exocrine pancreas to release pancreatic juices and stimulates pushing bile via the gallbladder to contract and excrete bile into the common bile duct. CCK also relaxes the sphincter of Oddi, allowing bile to come in the duodenal lumen (Hundt et al. 2020; Coucke et al. 2021). Interestingly, CCK is the most plentiful neuropeptide in the brain. In chronic neuropathic pain, cholecystokinin B receptors and their peptide ligand are upregulated (Westlund et al. 2021). CCK is required in related behaviors actions such as reward, cognition and memory via its communications with the dopaminergic and opioid systems. CCK has a neuromodulatory role in mental disorders. To stimulate neurons, CCK binds with both CCK_1 and CCK_2 receptors that expressed with decreased and increased concentrations respectively in the brain. CCK_2 receptors relate to induction of human panic attacks. Also, CCK modifies the exciting effect of glutamate, the secretion of suppressor GABA, and the dopamine drainage (Ballaz and Bourin 2021).

10.6.4 Digestion-Inhibiting Hormones

10.6.4.1 Somatostatin

Somatostatin **(SST)** is a cyclic peptide/neuropeptide hormone, it has robust regulating effects in many functions in the body. It is also named (Growth hormone (GH) inhibiting hormone) as it inhibits GH. it is produced by various sources, include the gastrointestinal (GI) system and pancreas as well as in central nervous system and hypothalamus. SST represented in two active isoforms 14 and 28 amino acids show clear difference in sites and functions. The small isoform acts mainly in the brain, while the larger isoform works in the GI tract. SST has mainly neuroendocrine suppressing actions, it inhibits GI, endocrine, exocrine functions in many organs like pituitary and pancreas, as well as modulates neurotransmission and memory in CNS. SST also inhibits gastric acid release and motility, bicarbonate and enzyme release from pancreas, selective decreases of splanchnic, portal blood influx and intestine absorption. SST is produced by gastric fundic and antral D cells, enterochromaffin-like cells and gastrin G cells either directly via paracrine signal or indirectly via endocrine release. SST also has angiogenesis inhibiting and antiproliferative actions on normal and cancer cells. SST has short half-life (1–3) minutes while exogenously synthesized SST is more constant with prolonged half-life which permits its initially clinical application in treating neuroendocrine tumors

(Eigler and Ben-Shlomo 2014; O'Toole and Sharma 2021). SST analog drugs are used in medical managing and treating of acromegaly and gigantism (Bello and Garla 2021)

10.6.4.2 Glucagon

Glucagon is produced by stimulated pancreatic alpha cells. While glucagon-like peptide-1 (GLP-1), released by the GI tract, acts a key coordinating effect on homeostasis of postprandial glucose levels via its effect on insulin release, appetite and gut motility (Gribble and Reimann 2021). Intestine glucagon reduces gastrointestinal tract function by relaxing smooth muscle of the intestine and stomach as well as reduces gastrointestinal secretion (Greenspan and Forsham 1986; Ahlman and Nilsson 2001). GLP-1 is the base of many medications that treat type 2 DM and obesity as well as hypoglycemia (Gribble and Reimann 2021). GLP-1 works in the hypothalamus to stimulate the secretory terminals gonadotropin releasing hormone neurons. In female sheep, GLP-1 microadministration into the median eminence triggers a large capacity of luteinizing hormone pulse in plasma of jugular vein (Arbabi et al. 2021). It is known that glucagon-like peptide-1 (7–36) amide is one of the isoforms released in the brain from its prohormone (proglucagon). Proglucagon is expressed in many organs include alpha cell of pancreatic islets, intestine, and brain, and after translational step of the prohormone, it produces various compounds in these organs. GLP-1 receptors in brain are similar to those receptors present in pancreatic islets. GLP-1 (7–36) amide is one from those receptors from gut /brain sources stimulates its actions to release neurotransmitters from selective brain nuclei, inhibit gastric release and motility, regulate food and drink intake, as well as thermoregulation, and arterial blood pressure. GLP-1 (7–36) amide acts as a neurotransmitter as it is found in the synaptosome and K+ stimulates its Ca^{2+}-dependent release (Blázquez et al. 1998)

10.6.4.3 Enterogastrone

Enterogastrone was a name for the hormone released by the upper part of small intestinal mucosa in response to the presence of fat or its digestive metabolites (fatty acids/triglycerides) that suppresses secretion and motility of the stomach (Brown 1974). Enterogastrone is called a Gastric Inhibitory Polypeptide (GIP). In 1968, it has been reported that secretin hormone is the solely enterogastrone peptide stimulated by acidic element in the duodenum (Johnson and Grossman, 1968). It inhibits the secretory activity and motility in some parts of the digestive tract and particularly HCl secretion (Greenspan and Forsham 1986; Ahlman and Nilsson 2001). Enterogastrone treatment is potent not only for protecting from repetition within the duration of its administration but also to avoid recurrency of ulcer attacks after treatment is stopped (Sandweiss et al. 1948).

10.6.5 Kidneys Hormones

The kidneys act as endocrine glands which secrete and promote the synthesis of the following hormones:

10.6.5.1 Vitamin D Is a Steroid Hormone

The kidneys and liver secrete the enzyme 1-α hydroxylase, which converts vitamin D in the kidneys into one of its active forms *(refer to Chap. 6)*.

10.6.5.2 Stimulating Factor (ESF)

This factor is also known as erythropoietin (hemopiotein). Reduced blood oxygenation (i.e., hypoxemia) in response to a high altitude or suffocatingcondition triggers the kidney to secrete a substance known as kidney factor to produce red blood cells with globulin secreted by the liver to synthesize a hormone called erythropoietin, which bind to cells in the bone marrow to form more red blood cells in order to increase hemoglobin binding to oxygen (Aachmann-Andersen et al. 2018; Rudzitis-Auth et al. 2020).

10.6.5.3 Renin

Renin is secreted in response to a reduced circulating blood volume in the kidneys. This hormone stimulates the conversion of angiotensinogen to angiotensin in the liver, which increases thirst. Renin also stimulates the secretion of antidiuretic hormone from the pituitary and aldosterone from the adrenal cortex to enable the reabsorption of water from the renal tubules (Aachmann-Andersen et al. 2018).

10.6.6 Ovaries and Testes Local Hormones

These gonads secrete the hormones inhibin, activin, and follistatin, which are required for the regulation of follicle stimulating hormone. Sertoli cells in the testes also secrete inhibin, estradiol, and an insulin-like growth factor, whereas ovarian cells secrete prostaglandins (O'Connor and De Kretser 2004; Marino and Zanghì 2013; Wijayarathna and de Kretser 2016). They have been discussed in detail in Chap. 9.

10.6.7 Thymus Gland Hormones

The thymus is located near the heart in humans and mammals (Figs. 10.3 and 10.4) and along the length of the neck in birds. The thymus gland originates from an endocrine region of the foregut, and continues the original powerful of this region. While its population comes from bone marrow lymphatic cells and synthesizes the thymus gland, that plays a key role in the immunity in addition to its effective role in endocrine orchestra. This gland has several immune functions. Primarily, the thymus is the site of T-lymphocyte development and selection during childhood. Thymus

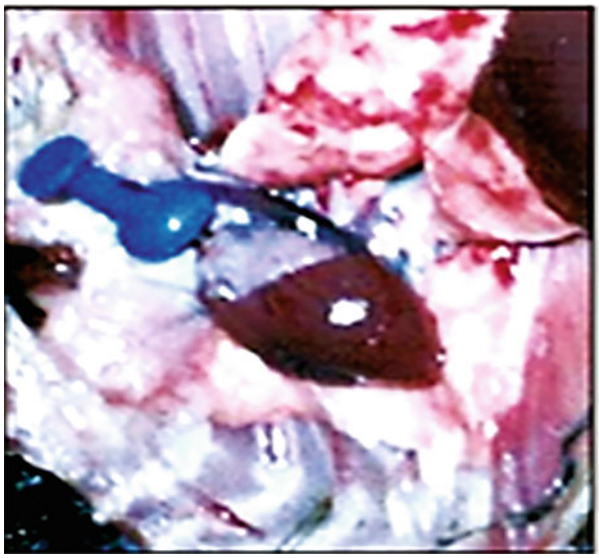

Fig. 10.3 The thymus gland located on the top of the heart; it is shown to adhere to the area (indicated in blue)

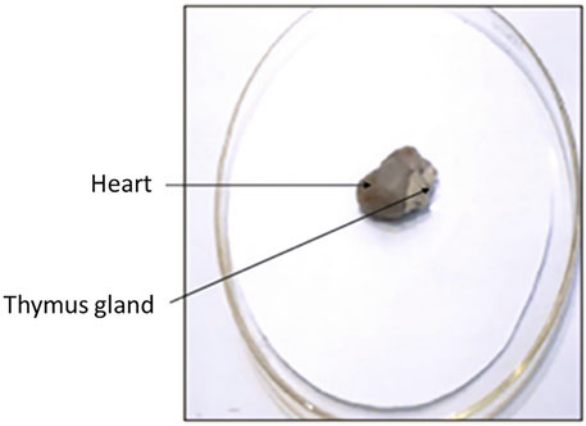

Fig. 10.4 Shows the thymus gland above the heart in mammals

produces many hormones include (Thymulin, Thymosin, Thymopoietin, Thymopentin, Thymus humoral factor, MB-35 and other peptides), which regulate immune cell transformation and selection. The thymus also contains Hassell's corpuscles which play a role in antibodies production (Fig. 10.5). Thymus also produces some hormones synthesized by other endocrine glands such as insulin, neuropeptides and melatonin which are transported by the immune cells to the target

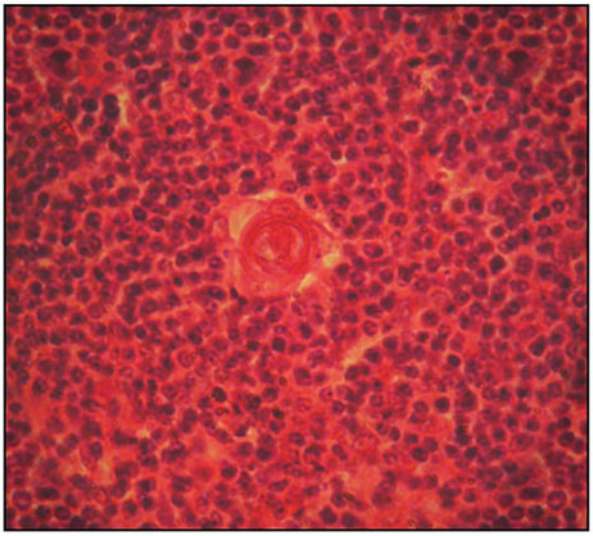

Fig. 10.5 Shows a cross-section of the thymus gland where Hassall's corpuscles can be seen (H&E ×40)

sites. Thymic (epithelial and immune) cells express receptors for hormones it regulates. Thymus regresses continuously throughout the age and acts as a pacemaker of life, the role is mainly controlled by some thymocytes since their full demolition aids the gland growth up to puberty and its progressive secretion for its regression post puberty leading to appearing of gland aging. Co-convolution between pineal and thymus functions can estimate the aging and death's time (Csaba 2016), as a similar, special involution approach found in thymus and Pineal gland. The immune system is functionally connected with the endocrine and nervous systems for their integrating dynamic network (Rezzani et al. 2020).

10.6.7.1 Thymosin

The thymus also contributes to puberty through the pentapeptide hormones thymosin and thymopoietin, which have immune regulatory functions (Burkitt et al. 1996). Thymopoietin is involved in physical and sexual maturation until puberty. Additionally, thymosin and thymopoietin on the interferon production in lymphocytes (Rentz 1984). The most forms of thymosin are thymosin alpha 1 (Tα1), and thymosin beta that includes thymosin β4 (Tβ 4), thymosin β10 (Tβ 10) and thymosin β10 (Tβ 15). Tβ 4 and Tβ 10 are the most abundant in beta thymosin family.

Thymosin Alpha 1

Thymosin alpha 1 (Tα1) is a peptide contains 28-amino acid. It enhances T cell, dendritic cell and antibodies production, intones cytokines production and suppresses steroid-induced apoptosis on thymocytes. Tα1 has pleiotropic

physiological effects, Tα1 is applied for treating many diseases which enforce its synthetic production (Li et al. 2010).

Thymosin β4

Thymosin β4 (Tβ 4) is a small natural peptide of 43-amino acid. It has a G actin-sequestering, angiogenesis, wound repair accelerating effect, hair growth, and elevated tumor cell metastatic ability (Aronson 2016). Tβ 4 has novel therapeutics effects like a speed corneal reepithelialization and a decrease in corneal inflammation and it is possible for some diseases such as ocular surface and neurotrophic keratopathy (Sosne et al. 2016).

Thymosin β10

Thymosin β10 (Tβ 10) is a 43-amino acid residue polypeptide. It speeds up apoptosis, it has a significant and potential mandatory function in regulating cell's apoptosis via its role as an actin-mediated tumor inhibitor, also may it act as a neo-apoptotic action in embryogenesis, and it can intermediate some of the pro-apoptotic antitumor effects of retinoids (Hall 1995). It has a role on action for cell motility. It is a promising biomarker and a potential facilitator for therapeutic strategy against breast cancer (Zhang et al. 2017b), Tβ 10 also can act as a biomarker and a potential therapy for cell renal cell carcinoma (Pan et al. 2020).

10.6.7.2 Thymopoietin

Thymopoietin is polypeptide hormone contains 49 amino acid synthesized by epithelial cells of the thymus. The pentapeptide (Arg-Lys-Asp-Val-Tyr) thymopentin (TP-5) is a region that includes the amino acids 32–36 in thymopoietin that represents the active region of thymopoietin, so it possesses the entire biological functions of thymopoietin (the native hormone). It has a pleiotropic effect includes neuromuscular transmission; it also induces T cell differentiation. The immunoregulatory effect of thymopentin on blood T cells is mediated by the high intracellular cGMP in comparison with the intracellular high cAMP to promote differentiation of precursor T cells to T cells. Both of thymopoietin and thymopentin have immunonormalizing effect in animal models with immune dysbalance such as thymectomy or the thymic involution in aging (Goldstein and Audhya 1985). Targeting the Toll-like receptor 2 with a new designed thymopentin-derived peptide can modulate immune response it significantly elevated TNF-α and IL-6, and the antibodies IgG, IgM, and IgA. The new derived peptide was a combination of the full-length TP-5 with the best active peptide fragments (CbTP) (Wei et al. 2021). In mice, thymopentin relieves the ageing of ovarian granulosa cells, it can achieve a therapeutic effect for premature ovarian failure (Liu et al. 2021).

10.6.8 Placenta Hormones

The placenta secretes **progesterone**, **estrogens** distinct from those secreted by the ovary (e.g., estriol) and human chorionic gonadotropin (**hCG**). Notably, hCG is 90%

similar in structure and function to luteinizing hormone (LH) which is secreted by the anterior pituitary (Marino and Zanghì 2013; Wijayarathna and de Kretser 2016). hCG is present in different glycoforms on the basis of its tissue source (Fournier 2016). This hormone preserves the corpus luteum which secretes progesterone during the postovulatory phase and pregnancy semesters. The placenta releases **growth hormones** at levels that can be detected in some women as early as the eighth week of gestation. These levels increase during gestation to a maximum of 5.9–24.4 ng/mL at 35–36 weeks of pregnancy and decline at parturition. The growth hormone level reflects fetal growth and placental activity during pregnancy (Lønberg et al. 2003). In addition to **placental growth hormone**, syncytiotrophoblasts produces placenta produces **human placental lactogens** for glucose metabolism and anabolic effects. **Ghrelin** is also significantly expressed in the human placenta mainly in cytotrophoblasts and in placental villi stroma (Armistead et al. 2020). Many adipokines are expressed in placenta as described by Brooke and his team such as: **Leptin** and **adiponectin** have been identified with autocrine and paracrine effects in placenta, leptin is expressed in placental trophoblasts and amnion cells. While adiponectin receptors 1 and 2 are found on placental trophoblasts. Additionally, **Irisin** is localized in cytotrophoblasts. Irisin is localized in cytotrophoblasts (Armistead et al. 2020).

Weak functional placenta or early loss associate with some neurodevelopmental disturbances. One of placenta hormone is called **Allopregnanolone (ALLO)**, a progesterone-derived GABA-A receptor (GABAAR) modifier, its decrease changes neurodevelopment in a sex-dependent manner. Experimentally deletion of ALLO's gene in trophoblasts, led to deficiency in placental ALLO which revealed cerebellum abnormalities in white matter appeared with autism-similar behavior in male only, which could be recovered by a single dose of ALLO during late phase of pregnancy. Novel function for a placental hormone in orchestrating brain behaviors in a sex-dependent way. Placental hormone rtherapy could present new therapeutic for managing neurobehavioral diseases (Vacher et al. 2021).

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