Mechanism of Hormones Secretion and Action

3

Ebtesam A. Al-Suhaimi, Meneerah A. Aljfary, Hanan Aldossary, Thamer Alshammari, Ayman AL-Qaaneh, Razan Aldahhan, and Zahra Alkhalifah

Contents

E. A. Al-Suhaimi (✉)
Biology Department, College of Science and Institute for Research and Medical Consultations, Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia
e-mail: ealsuhaimi@iau.edu.sa

M. A. Aljfary
Biology Department, College of Science, Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia

H. Aldossary · T. Alshammari · Z. Alkhalifah
Institute for Research and Medical Consultations, Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia

A. AL-Qaaneh
Institute for Research and Medical Consultations, Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia

John Hopkins Aramco Health Care Centre, Dharan, Saudi Arabia

R. Aldahhan
Biology Department, College of Science, Institute for Research and Medical Consultations, Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia

E. A. Al-Suhaimi (ed.), *Emerging Concepts in Endocrine Structure and Functions*,
https://doi.org/10.1007/978-981-16-9016-7_3

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

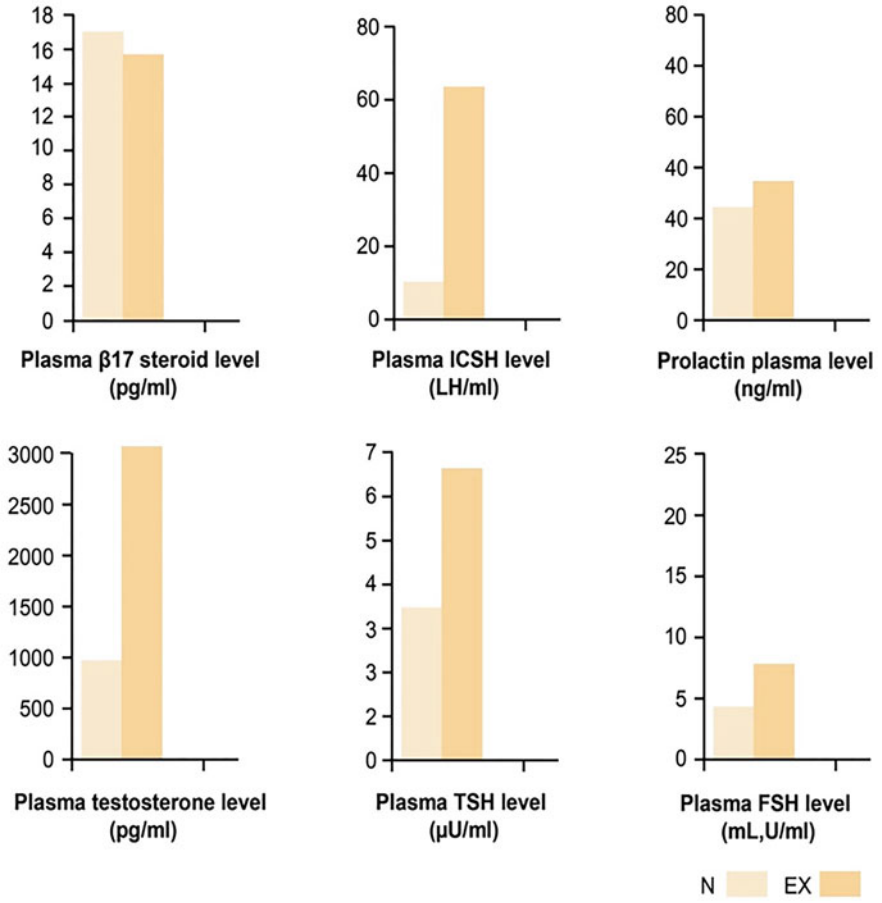

Fig. 3.1 The levels of some regulatory and sex hormones in adult male animals before (N) and after injection with calcium (E)

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

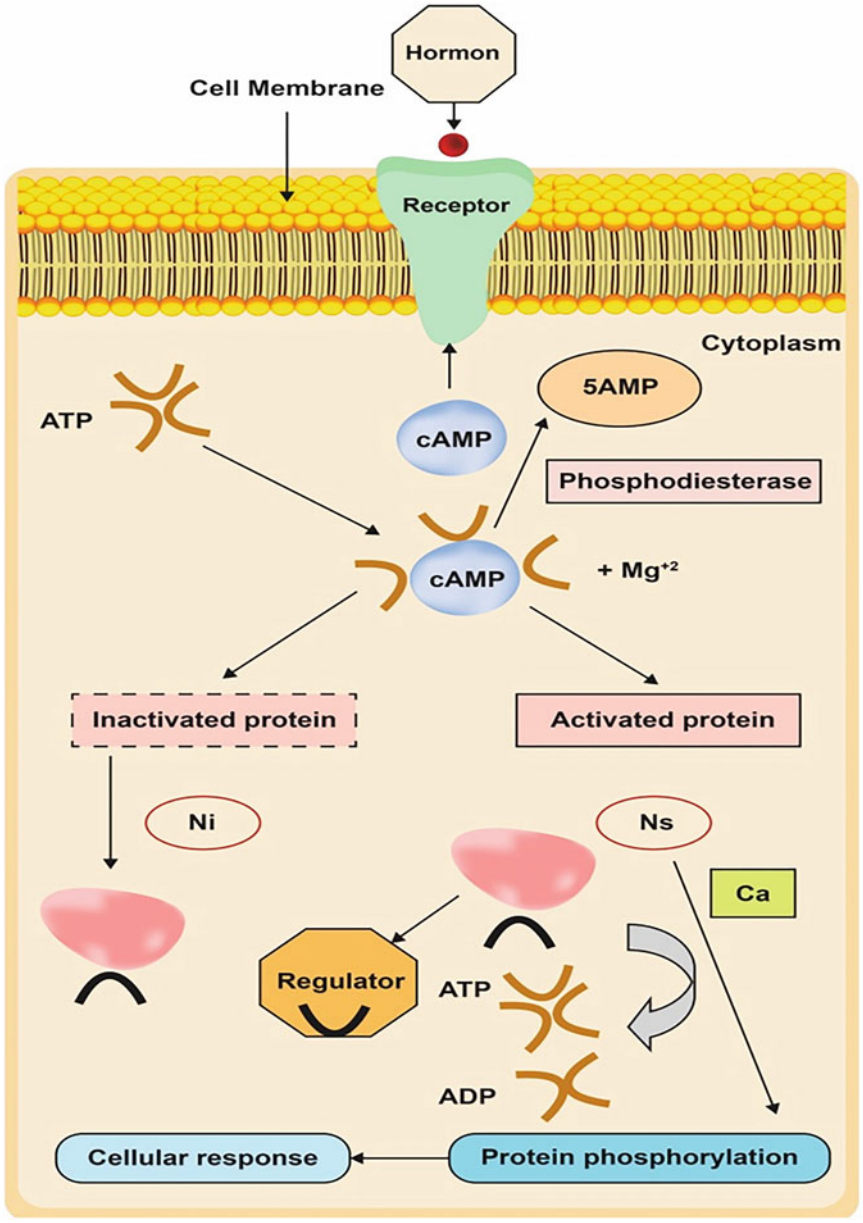

Fig. 3.2 The mechanism of action of hormones in the cell. The first messenger (hormone) binds to the receptor on the cell membrane which stimulates adenyl cyclase to form hormone–receptor complex, this triggers the release of cAMP; the secondary messenger cAMP in the presence of Mg^{2+}. cAMP acts on 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

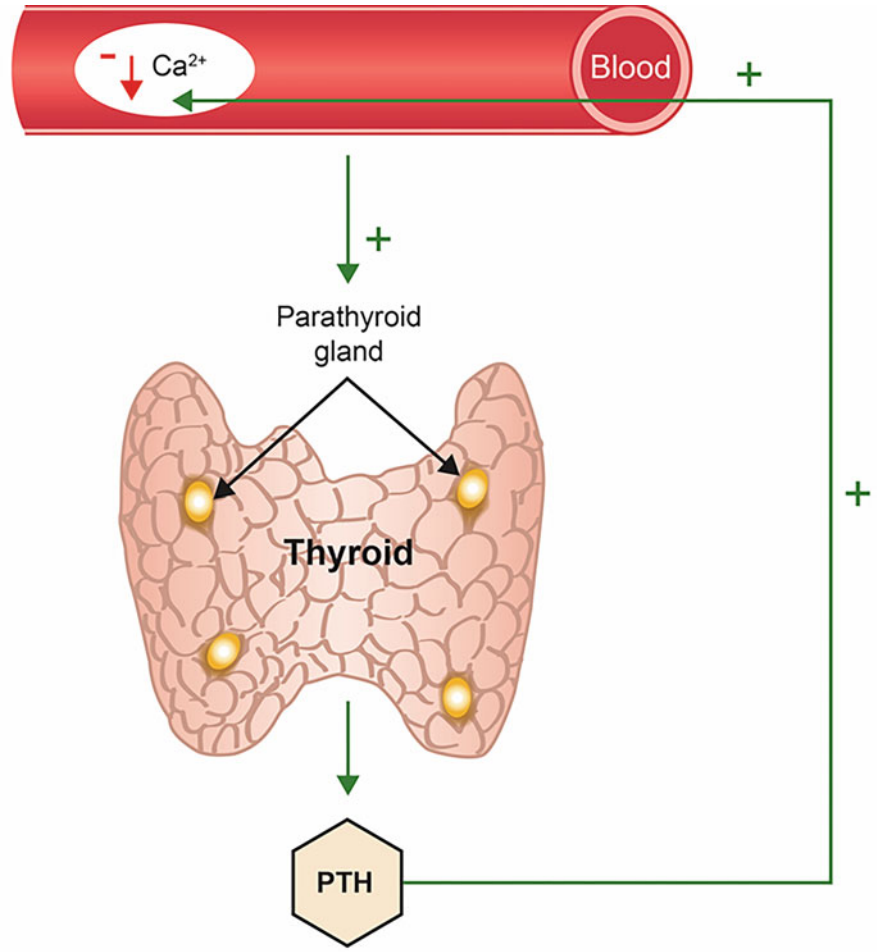

Fig. 3.3 Regulation of free calcium levels in the blood by parathyroid glands in negative back mechanism manner. PTH increases free calcium in the circulation to the normal physiological limit. To avoid higher levels, high level of calcium inhibits the secretion of PTH from parathyroid. In case calcium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

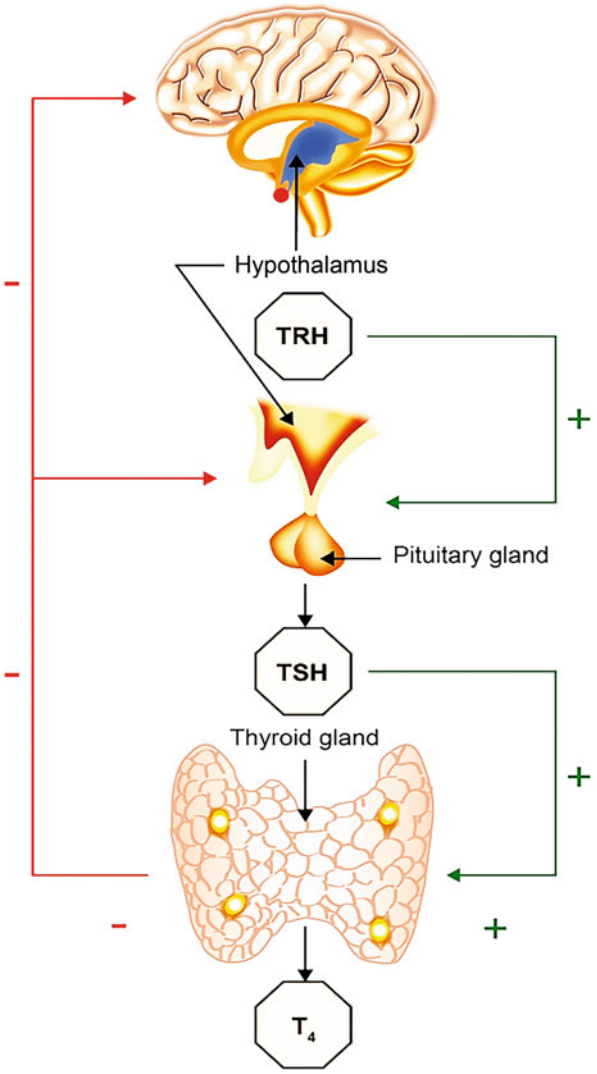

Fig. 3.4 Regulation of thyroid hormones secretion (T_4–T_3–Negative feedback mechanism). TSH increases T3 and T4 in the circulation to the normal physiological limit. To avoid higher levels, high level of T3 and T4 inhibits the secretion of TSH from pituitary as short loop or inhibits production of TRH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

References

Abbink MR, Schipper L, Naninck EFG, de Vos CMH, Meier R, van der Beek EM et al (2020) The effects of early life stress, postnatal diet modulation, and long-term western-style diet on later-life metabolic and cognitive outcomes. Nutrients 12:pii: E570. https://doi.org/10.3390/nu12020570

Abramicheva PA, Smirnova OV (2019) Prolactin receptor isoforms as the basis of tissue-specific action of prolactin in the norm and pathology. Biochemistry (Mosc) 84(4):329–345. https://doi.org/10.1134/S0006297919040011. PMID: 31228925

Al-Makawi SM (2000) Physiology of endocrine glands and hormones, 1st edn. Monshaat Almaaref/Arabic book

Anne B, Carré N, Mialon O, Matelot M, Servel N, Monget P et al (2013) The permissive role of prolactin as a regulator of luteinizing hormone action in the female mouse ovary and extragonadal tumorigenesis. Am J Physiol Endocrinol Metab 305:E845–E852. https://doi.org/10.1152/ajpendo.00243.2013

Bick RJ, Poindexter BJ, Davis RA, Schiess MC (2005) Determination of the site of action of calcitonin gene-related peptide in the alteration of intracellular calcium levels in adult and neonatal rodent myocytes. Peptides 26:2231–2238. https://doi.org/10.1016/j.peptides.2005.04.021

Bole-Feysot C, Goffin V, Edery M, Binart N, Kelly PA (1998) Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. Endocr Rev 19(3):225–268. https://doi.org/10.1210/edrv.19.3.0334. PMID: 9626554

Brück K (1983) Functions of the endocrine system. In: Schmidt RF, Thews G (eds) Human physiology. Springer, Berlin

Bullock D, Grossberg S (1991) Adaptive neural networks for control of movement trajectories invariant under speed and force rescaling. Hum Mov Sci 10:3–53. https://doi.org/10.1016/0167-9457(91)90029-w

Bullock J, Boyle J, Wang MB (1991) Physiology, 2nd edn. Williams and Wilkins, London

Bullock J, Boyle J, Wang MB (2001) Physiology, 4th edn. Williams and Wilkins, London

Burkitt HG, Young B, Heath JW (1996) Wheater's functional histology. A text and colour atlas, 3rd edn. Churchill Livingstone, London

Carlson ME, Conboy MJ, Hsu M, Barchas L, Jeong J, Agrawal A et al (2009) Relative roles of TGF-beta1 and Wnt in the systemic regulation and aging of satellite cell responses. Aging Cell 8:676–689. https://doi.org/10.1111/j.1474-9726.2009.00517.x

Chrousos GP (2007) Organization and integration of the endocrine system. Sleep Med Clin 2:125–145

Clevenger CV, Kline JB (2001) Prolactin receptor signal transduction. Lupus 10(10):706–718. https://doi.org/10.1191/096120301717164949. PMID: 11721697

Edgerton DS, Lautz M, Scott M, Everett CA, Stettler KM, Nealet DW et al (2006) Insulin's direct effects on the liver dominate the control of hepatic glucose production. J Clin Invest 116:521–527. https://doi.org/10.1172/jci27073

Feillet CA (2010) Food for thoughts: feeding time and hormonal secretion. J Neuroendocrinol 22:620–628

Focke CMB, Iremonger KJ (2020) Rhythmicity matters: circadian and ultradian patterns of HPA axis activity. Mol Cell Endocrinol 501:110652. https://doi.org/10.1016/j.mce.2019.110652

Friebe A, Sandner P, Seifert R (2015) From bedside to bench—meeting report of the 7th international conference on cGMP "cGMP: generators, effectors and therapeutic implications" in Trier, Germany, from June 19th to 21st 2015. Naunyn Schmiedeberg's Arch Pharmacol 388:1237–1246. https://doi.org/10.1007/s00210-015-1176-4

Gancz D, Lilach G (2013) Hormonal control of stem cell systems. Ann Rev Cell Dev Biol 29:137–162. https://doi.org/10.1146/annurev-cellbio-101512-122331

Gardner D, Shoback D (2007) Greenspan's basic and clinical endocrinology, 8th edn. McGraw-Hill Education, New York

Gardner D, Shoback D (2011) Greenspan's basic and clinical endocrinology, 9th edn. McGraw-Hill Education, New York

Ghorbani A, Naderi-Meshkin H (2016) The endocrine regulation of stem cells: physiological importance and pharmacological potentials for cell-based therapy. Curr Stem Cell Res Ther 11:19–34. https://doi.org/10.2174/1574888x10666150904113625

Greenspan FS, Forsham PH (1986) Basic and clinical endocrinology, 2nd edn. Lang Medical Publication/Los Atlas, California

Gribble FM, Reimann F (2017) Signalling in the gut endocrine axis. Physiol Behav 176:183–188. https://doi.org/10.1016/j.physbeh.2017.02.039

Guyton AC (1986) Textbook of medical physiology. In: Greenspan FS, Forsham PH (eds) Basic and clinical endocrinology, 2nd edn. Elsevier Saunders

Guyton AC, Hall JE (2006) Textbook of medical physiology, 11th edn. Elsevier Saunders

Guyton AC, Hall JE (2016) Textbook of medical physiology, 13th edn. Elsevier Saunders, Philadelphia, PA

Jahng JW, Song E, Sweeney G (2016) Crosstalk between the heart and peripheral organs in heart failure. Exp Mol Med 48:e217. https://doi.org/10.1038/emm.2016.20

Kauffman AS, Hoffmann HM (2020) Editorial: hormone release patterns in mammals. Mol Cell Endocrinol 507:110781. https://doi.org/10.1016/j.mce.2020.110781

Ketchesin KD, Becker-Krail D, McClung CA (2020) Mood-related central and peripheral clocks. Eur J Neurosci 51:326–345. https://doi.org/10.1111/ejn.14253

Kim JS, Han SY, Iremonger KJ (2019) Stress experience and hormone feedback tune distinct components of hypothalamic CRH neuron activity. Nat Commun 10:5696. https://doi.org/10.1038/s41467-019-13639-8

Lager I (1991) The insulin-antagonistic effect of the counterregulatory hormones. J Intern Med Suppl 735:41–47. PMID: 2043222

Lee JH, Miele ME, Hicks DJ, Phillips KK, Trent JM, Weissman BE et al (1986) KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. J Natl Cancer Inst 88:1731–1737. https://doi.org/10.1093/jnci/88.23.1731

Lin XW, Blum ID, Storch KF (2015) Clocks within the master gland: hypophyseal rhythms and their physiological significance. J Biol Rhythm 30:263–276. https://doi.org/10.1177/0748730415580881

Lockley SW, Arendt J, Skene DJ (2007) Visual impairment and circadian rhythm disorders. Dialogues Clin Neurosci 9(3):301–314

London RD, Berson L, Lipkowitz MS (1993) Hormonal modulation of ionic permeability in human red blood cells. J Am Soc Nephrol 3:1607–1612

Mariniello K, Ruiz-Babot G, McGaugh EC, Nicholson JG, Gualtieri A, Gaston-Massuet C et al (2019) Stem cells, self-renewal, and lineage commitment in the endocrine system. Front Endocrinol (Lausanne) 10:772. https://doi.org/10.3389/fendo.2019.00772

Mochida T, Ueno H, Tsubooka-Yamazoe N, Hiyoshi H, Ito R, Matsumoto H, Toyoda T (2020) Insulin-deficient diabetic condition upregulates the insulin-secreting capacity of human induced pluripotent stem cell-derived pancreatic endocrine progenitor cells after implantation in mice. Diabetes 69(4):634–646. https://doi.org/10.2337/db19-0728. Epub 2020 Jan 31. PMID: 32005704

Molina-Salinas G, Rivero-Segura NA, Cabrera-Reyes EA, Rodríguez-Chávez V, Langley E, Cerbon M (2021) Decoding signaling pathways involved in prolactin-induced neuroprotection: a review. Front Neuroendocrinol 61:100913. https://doi.org/10.1016/j.yfrne.2021.100913. Epub 2021 Mar 22. PMID: 33766566

Molnar C, Gair J (2019) Concepts of biology, 1st Canadian edition. B. C. Open Textbook Project

Nakhla AM, Bardin CW, Salomon Y, Mather JP, Jänne OA (1989) The actions of calcitonin on the TM3 Leydig cell line and on rat Leydig cell-enriched cultures. J Androl 10:311–320. https://doi.org/10.1002/j.1939-4640.1989.tb00110.x

Nussey S, Whitehead S (2001) Endocrinology: an integrated approach. BIOS Scientific Publishers, Oxford

O'Brien EM, Gomes DA, Sehgal S, Nathanson MH (2007) Hormonal regulation of nuclear permeability. J Biol Chem 282:4210–4217. https://doi.org/10.1074/jbc.m606300200

Odle AK, Noor A, Syed MM, Allensworth-James ML, Beneš H, Castillo AIM et al (2018) Leptin regulation of gonadotrope gonadotropin-releasing hormone receptors as a metabolic checkpoint and gateway to reproductive competence. Front Endocrinol (Lausanne) 8:367. https://doi.org/10.3389/fendo.2017.00367

Parikh SS, Blackwell DJ, Gomez-Hurtado N, Frisk M, Wang L, Kim K et al (2017) Thyroid and glucocorticoid hormones promote functional T-tubule development in human-induced pluripotent stem cell-derived cardiomyocytes. Circ Res 121:1323–1330. https://doi.org/10.1161/circresaha.117.311920

Ponzi D, Flinn MV, Muehlenbein MP, Nepomnaschy PA (2020) Hormones and human developmental plasticity. Mol Cell Endocrinol 505:110721. https://doi.org/10.1016/j.mce.2020.110721

Radu A, Dahl G, Loewenstein WR (1982) Hormonal regulation of cell junction permeability: upregulation by catecholamine and prostaglandin E_1. J Membr Biol 70:239–251. https://doi.org/10.1007/bf01870566

Rubinek T, Rubinfeld H, Hadani M, Barkai G, Shimon I (2005) Nitric oxide stimulates growth hormone secretion from human fetal pituitaries and cultured pituitary adenomas. Endocrine 28:209–216. https://doi.org/10.1385/endo:28:2:209

Salonia A, Nappi RE, Pontillo M, Daverio R, Smeraldi A, Briganti A et al (2005) Menstrual cycle-related changes in plasma oxytocin are relevant to normal sexual function in healthy women. Horm Behav 47:164–169. https://doi.org/10.1016/j.yhbeh.2004.10.002

Salvatore D (2018) Deiodinases and stem cells: an intimate relationship. J Endocrinol Investig 41:59–66. https://doi.org/10.1007/s40618-017-0737-4

Schinner E, Wetzl V, Schlossmann J (2015) Cyclic nucleotide signalling in kidney fibrosis. Int J Mol Sci 16:2320–2351. https://doi.org/10.3390/ijms16022320

Schwartz GJ, Zeltser LM (2013) Functional organization of neuronal and humoral signals regulating feeding behaviour. Ann Rev Nutr 33:1–21. https://doi.org/10.1146/annurev-nutr-071812-161125

Shahjalal HM, Abdal Dayem A, Lim KM, Jeon TI, Cho SG (2018) Generation of pancreatic β cells for treatment of diabetes: advances and challenges. Stem Cell Res Ther 9(1):355. https://doi.org/10.1186/s13287-018-1099-3. PMID: 30594258; PMCID: PMC6310974

Skorupskaite K, George JT, Anderson RA (2014) The kisspeptin-GnRH pathway in human reproductive health and disease. Hum Reprod Update 20:485–500. https://doi.org/10.1093/humupd/dmu009

Sukkar MY, Hunter WM, Passmore R (1967) Plasma levels of insulin and growth-hormone levels after a protein meal. Lancet 2:1020–1022. https://doi.org/10.1016/S0140-6736(67)90291-7

Tremblay J, Hamet P (2019) Environmental and genetic contributions to diabetes. Metabolism 100S:153952. https://doi.org/10.1016/j.metabol.2019.153952. PMID: 31610851

Tsuruzoe K, Emkey R, Kriauciunas KM, Ueki K, Kahn CR (2001) Insulin receptor substrate 3 (IRS-3) and IRS-4 impair IRS-1- and IRS-2-mediated signaling. Mol Cell Biol 21(1):26–38. https://doi.org/10.1128/MCB.21.1.26-38.2001

van den Berg HA (2019) On a general theoretical foundation for endocrinology. Sci Prog 102:43–60

Vankelecom H (2007) Stem cells in the postnatal pituitary? Neuroendocrinology 85:110–130. https://doi.org/10.1159/000100278

Waugh A, Grant A (2006) Ross and Wilson anatomy and physiology in health and illness, 10th edn. Elsevier Health, United Kingdom

Whitaker-Azmitia PM (2020) Serotonin and development. In: Müller CP, Cunningham K (eds) Handbook of behavioral neuroscience, vol 31. Academic Press, London, pp 413–435. https://doi.org/10.1016/b978-0-444-64125-0.00023-2

Whitwam JG (1977) APUD cells and the apudomas. A concept relevant to anaesthesia and endocrinology. Anaesthesia 32(9):879–888. https://doi.org/10.1111/j.1365-2044.1977.tb10110.x

Wollheim CB, Sharp GW (1981) Regulation of insulin release by calcium. Physiol Rev 61:914–973. https://doi.org/10.1152/physrev.1981.61.4.914

Zbrojkiewicz M, Śliwiński L (2016) Cyclic guanosine monophosphate in the regulation of the cell function. Postepy Hig Med Dosw (Online) 70:1276–1285