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

Ebtesam A. Al-Suhaimi and Firdos Alam Khan

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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

F. A. Khan
Department of Stem Cell Research, Institute for Research and Medical Consultations, Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia

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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)

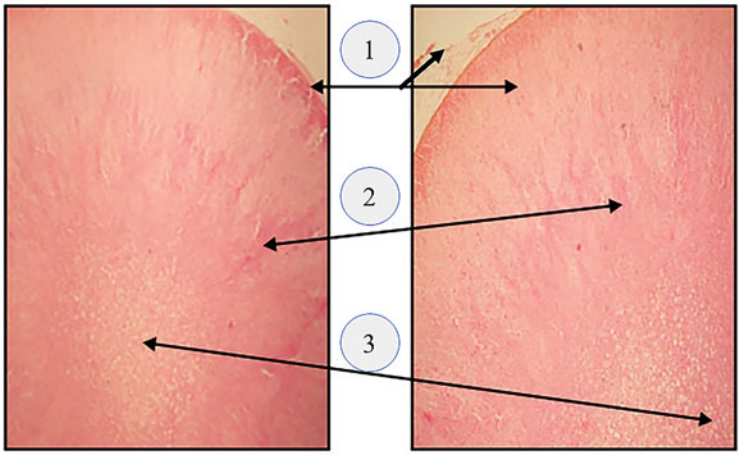


Fig. 7.2 Cross-section in the adrenal gland showing (1) capsule, (2) cortex, and (3) medulla (H&E ×4 and ×10)

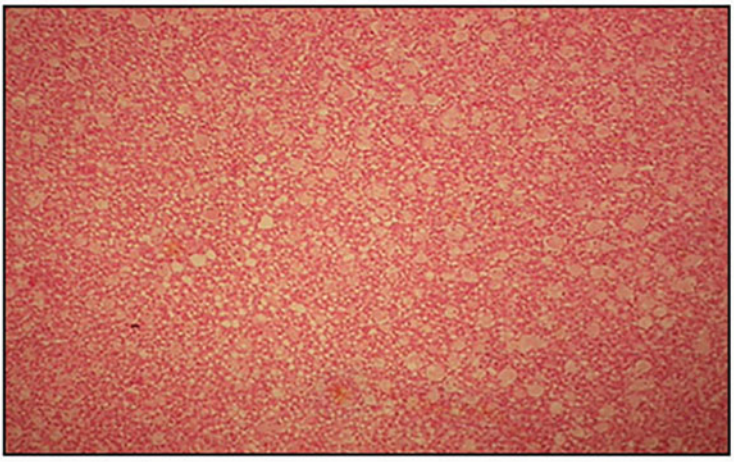


Fig. 7.3 Cross-section of the medulla area of the adrenal gland (H&E ×40) showing the catecholamine-secreting chromaffin cells

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).

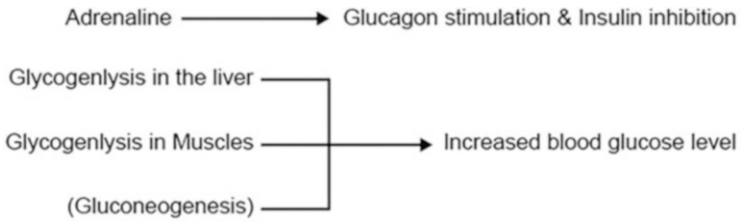
- **Effect of catecholamines on smooth muscle tissue**: The catecholamines act on smooth muscle tissues other than those in blood vessels. They help relax the smooth muscles of the bronchioles via β receptors. So, it could be used as a bronchodilator for the alleviation of asthma. Catecholamines increase 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

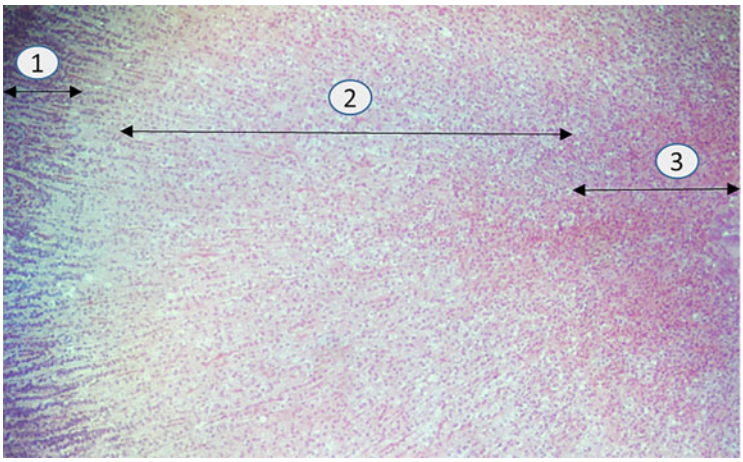


Fig. 7.4 Cross-section of the adrenal cortex showing its three zones: (1) the zona glomerulosa (dark pink) covers a narrow area, (2) middle: the zona fasciculate (pale pink) covers a wide area in the form of extended cords, and (3) the zona reticularis (H&E magnification 100×)

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.

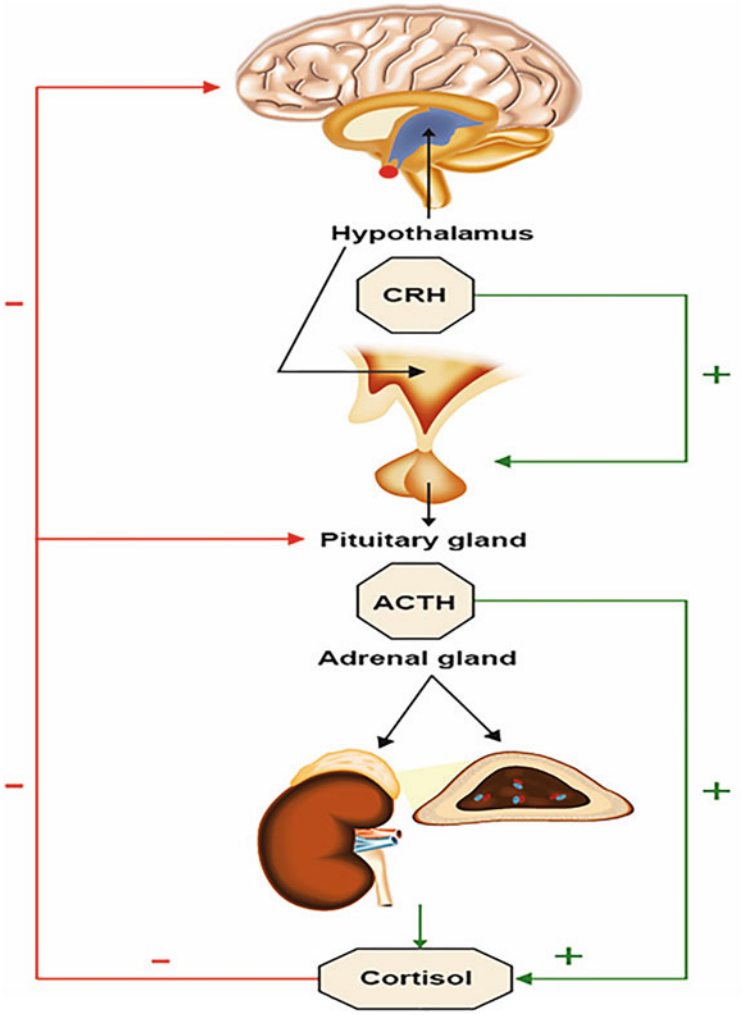


Fig. 7.5 Mechanisms of secretion of the adrenal cortex hormones through (the hypothalamus-pituitary-adrenal gland axis)

- 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

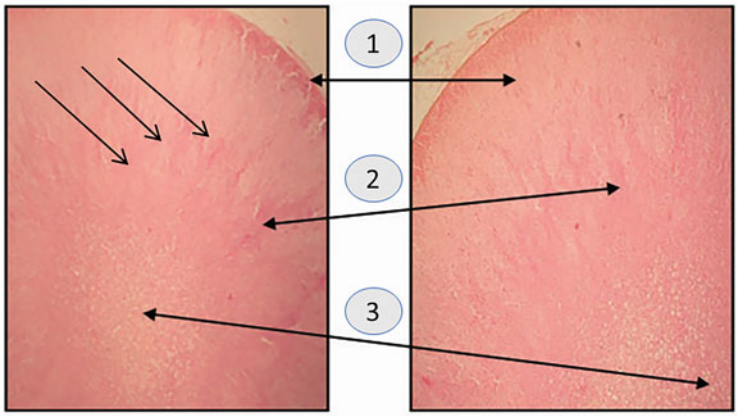


Fig. 7.6 Cross-section of the adrenal cortex shows (small arrows) the possible sites of adrenal stem cells. (1) The zona glomerulosa (dark pink) covers a narrow area, (2) middle: the zona fasciculate (pale pink) covers a wide area in the form of extended cords, and (3) the zona reticularis, H&E magnification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

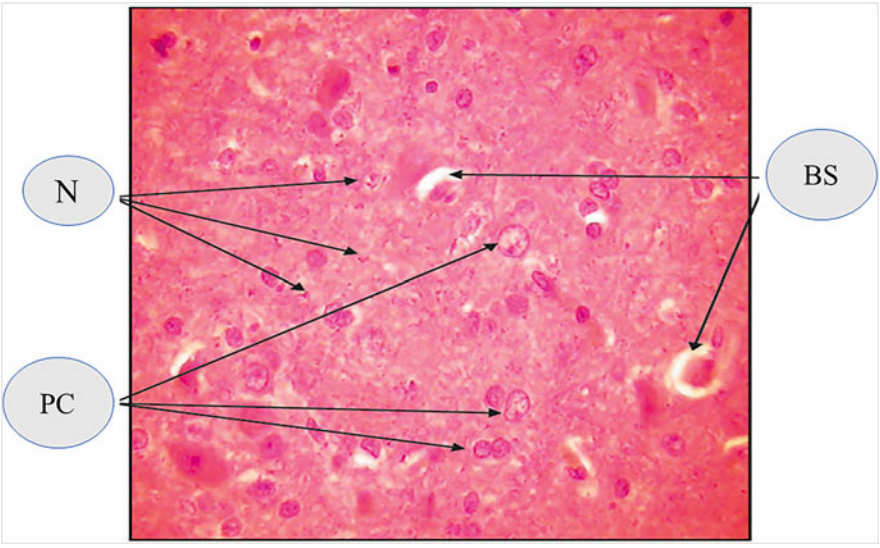


Fig. 7.8 Cross-section of a calcified pineal gland showing the multi-nuclear poorly stained cytoplasm, pineal chief cells (PC) neuroglia (N) and pineal brain sand (BS) H&E magnification 100×)

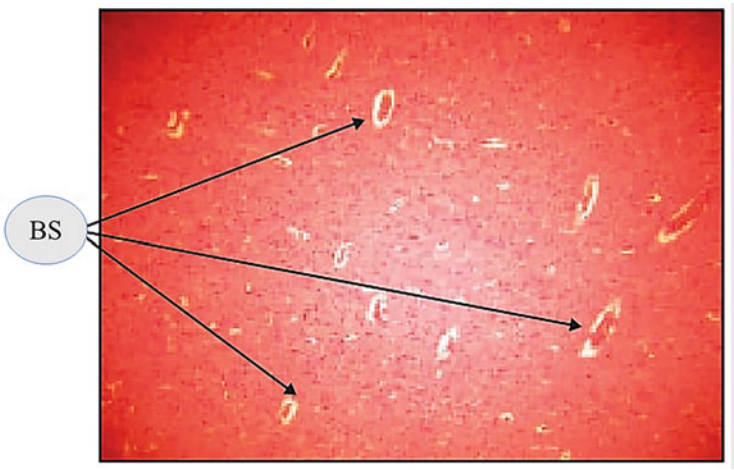


Fig. 7.9 Cross-section of a calcified pineal gland showing the pineal tissue and pineal brain sand (BS) H&E magnification 100×

- **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).

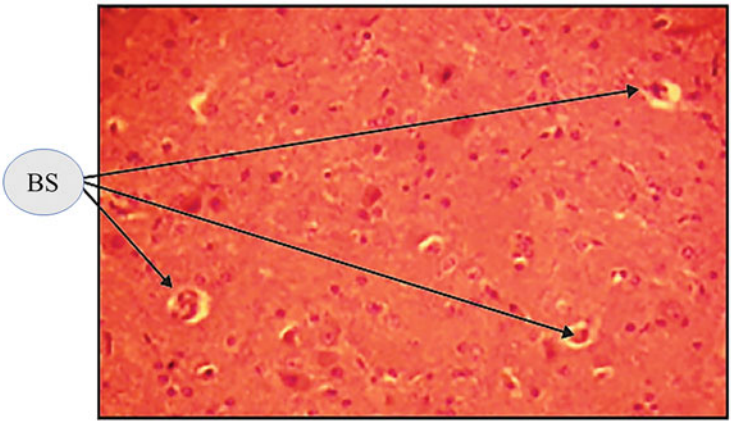


Fig. 7.10 Cross-section of a calcified pineal gland showing the pineal tissue and pineal brain sand. Dark and light cell are present (H&E magnification 400×)

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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