Endocrine Disrupting Chemicals-induced Metabolic Disorders and Treatment Strategies
Emerging Contaminants and Associated Treatment Technologies

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Endocrine Disrupting Chemicals-induced Metabolic Disorders and Treatment Strategies
This book is dedicated
To
My Beloved and Adorable Little Twinkles
Muhammad Aqdas Akash
&
Zainab Akash
Foreword

I am delighted to write the foreword for “Endocrine disrupting chemicals-induced metabolic disorders and treatment strategies” The editors; Dr. Akash, Dr. Rehman and Dr. Hashmi have met the need of our research society by compiling the basics through the advances. Although this book undoubtedly justifies having an extensive readership, it should be more professionally read by researchers in the field and specialists of endocrinology with expertise in clinical practice. Rather truthfully, this book has been edited by the authors, other than whom no one else could have probably written it in this way.

Dr. Akash and accompanied editors of this book have excelled in the field of metabolic diseases and environmental pollutants and their impact on health. This book highlights the role of endocrine disrupting chemicals in inducing, progressing and/or prevailing metabolic disorders. The different segments that this book serves including endocrine physiology, intro to endocrine disruptors and their association with metabolic disorders, contributes to the endocrine science. Dr. Akash and his able companion editors have sensibly provided the updated art and science of endocrine physiology particularly involved or “at risk” for metabolic disorders on exposure to endocrine disruptors. Moreover, they have also focused wisely on these factors relating to their sources of exposure and mechanism of pathogenesis. Most interestingly they have also provided the probable preventive as well as treatment approaches for these endocrine disrupting chemicals induced metabolic disorders. These categorical discussions in the book represent the staircase evolutionary approach for taking the basics of metabolic disorders and understanding of endocrine disrupting chemicals to the development of metabolic diseases. This is followed by the probable intervention which suggests possible preventive and curative measures. This unique compiling effort gives an affirmative sign to be the hallmark for the success of this book in future.

In addition, this book not only serves as a source of providing major endocrine disruptors and metabolic disorders on a single platform to researchers, but is designed to also serve as a companion resource to clinicians, including endocrinologists. It may also assist the educational basis for many post graduate students enrolled or preparing for admissions in similar disciplines like Medicine, Pharmacy,
Nursing, Gastroenterology, and Endocrinology. I would like to mention here that this is a valuable work done by Dr. Akash and team for providing each chapter with evidence-based background material highlighting principal science, envisioned not only for the professional who already possesses a basic understanding of the principles of endocrinology and associated diseases but also for early stage researchers.

It is my expectation and belief that this book will deliver an effective knowledge and understanding based on practical work done so far for researchers and professionals considerate for patient care to help reduce the exposure to endocrine disruptors and improve incidences of associated metabolic disorders. I believe that “Endocrine disrupting chemicals-induced metabolic disorders and treatment strategies” will stand as one of the opening cornerstones as so far, no book has been published that provides the comprehensive compilation of what this book depicts relating endocrine disruptors and metabolic disorders. I wish this book had been available countless years ago!

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Foreword

Endocrine Disrupting Chemicals-Induced Metabolic Disorders

We live in a world surrounded by environmental pollutants and toxicants, including endocrine-disrupting chemicals (EDCs) which pose a significant health risk to current and future generations of humans and animals alike. Some of these EDCs are understudied or, even more frightening, undiscovered. Other chemicals currently deemed safe may be dangerous, and their adverse outcomes are not yet measurable. Therefore, high-quality research and publications are necessary to raise awareness and guide scientists, policymakers, and the public.

This book introduces the normal and maladaptive processes of the endocrine system, glands, and associated disorders, including EDCs-induced metabolic ones. The essential material detailed within is the preventive and intervention treatment strategies potential in combating these illnesses. The many authors of these different chapters have contributed to highlighting the therapeutic impact of these bioactive compounds, further adding to this work’s importance and educational value.

Enduring damaging effects of EDCs is something that will arouse interest in readers, herein debating hot topics from alterations in the gut microbiota to enhanced antibiotic resistance. Discussion to positive lifestyle changes in metabolic disorders are given relating to intermittent fasting and some bioactive compounds present in food, is of interest to the layperson. This may reveal candidate targets for pharmaceutical drug development, as responsivity is needed to fight our widening obesity pandemic.

The dual basic/clinical nature of this book allows researchers from both ends of the spectrum to read and learn. Providing knowledge and understanding based on studies thus far allows this book to act as a companion resource for both undergraduate and post-graduate students in the Health Sciences.
Metabolic disorders (MDs) are promptly aggregating in the increasing population globally. This is greatly affecting the social and financial status of individuals particularly of developing and/or underdeveloped countries. Unfortunately, specifically these countries are also victims of environmental contaminants and habitual impurities that can be considered as the foremost keystones not only for initiating the occurrence but also for flourishing the progress of MDs. These contaminants include a major contribution of endocrine-disrupting chemicals (EDCs). According to the World Health Organization (WHO), these EDCs are “mostly man-made, found in various materials such as pesticides, metals, additives or contaminants in food, and personal care products” and that “Human exposure to EDCs occurs via ingestion of food, dust, and water, via inhalation of gases and particles in the air, and through the skin.” This accentuates the urge to better comprehend the principal disease mechanisms, which will not only help in eradicating these underpinning causative factors but may also propose targeted therapy for the MDs caused by EDCs.

This book entitled “Endocrine-Disrupting Chemicals-induced Metabolic Disorders and Treatment Strategies” is envisioned to first provide an introduction to the endocrine system and MDs followed by a profound discussion on the role of various EDCs and/or sources of EDCs in causing the induction, prevalence, and even progression of MDs. Lastly, in the third part of this book, we have deliberated the potential account of prevention and therapeutic intervention by elaborating the treatment strategies of EDCs-induced metabolic disorders.

We considered writing this book as till now, there is no such comprehensive text available in a compiled book format that can actually provide the broad notion of EDCs-induced MDs under one roof in a co-jointed manner. Nevertheless, existing books on the said topic seem to be presented in a fragmented way limited to the introduction of either endocrine or MDs. They deliver more like a repetition of basic endocrinology rather than a rational staircase compiling the physiology of the endocrine system and related metabolic disorders which comprehensively provide endocrine gland’s physiology; moreover, we have also discussed in detail all the associated endocrine metabolic disorders, i.e. hyperthyroidism, hypothyroidism, iodine deficiency, hypoparathyroidism, adrenal insufficiency, Cushing’s syndrome,
acromegaly, galactorrhea, erectile dysfunction, central diabetes insipidus, hypopituitarism, pituitary apoplexy, and diabetes mellitus. Further, we have included the deficiency of some enzymes which are involved in the normal metabolic pathways of carbohydrates like fructose, galactose, and glycogen. They are mostly autosomal recessive disorders that occur extensively in MDs. Similarly, impaired lipid metabolism and thyroid function along with mitochondrial dysfunction, inherited metabolic disorders have also been expanded in great detail with their direct and/or indirect association for inducing and progressing MDs.

We felt the presence of a huge gap existing among the fundamentals of endocrinology, induction of MDs, and role of EDCs in inducing MDs in the text of available books on the topic, for which everyone needs to hop between the explanation of elementary perceptions of the endocrine system and the description of associated disorders occurring due to any dysfunction in the system. Therefore, we have tried our best to relate each vital component of the endocrine system as depicted above for proper body regulation as well as its dysfunction for induction of MDs.

Another addition to the valuable totaling of this book is a description of occurrence and exposure of endocrine-disrupting chemicals to the human being which include but are not limited to polychlorinated biphenyls for electronics, paints and floor coats, fire retardants used in furniture and textiles, phthalates used in plastics and scents, parabens used for the protection of products such as lotions and sunscreens, and alkylphenols used in detergents and pesticide formulation. The increased accumulating evidence of EDCs in our environment includes persistent organic pollutants, bisphenol A, and phthalates that illustrate their important role in the occurrence of metabolic diseases (obesity, T2DM, and metabolic syndrome). One of the noteworthy public health apprehensions of these EDCs is their enduring damaging effects. The role and influence of endocrine disruptors and their link to the ecosystem and human health have already been deeply covered over several years. However, several questions arise about the mechanisms of action of the EDCs, and further research is required. In this book, we have given the current understanding of the probable health dangers of EDCs in humans which highlight a requisite for increasing awareness of EDCs exposure and their enduring damaging health effects. Why we are talking about these “enduring damaging health effects” with great emphasis here? The answer to this is these EDCs-induced MDs are becoming a big source for antibiotic resistance. Yes! Some pathogens are also becoming resistant to the use of antibiotics to treat infections that are associated with EDCs-induced metabolic disorders. Besides, gut microbiota become altered because of EDCs-induced metabolic disorders. So we have also provided information on how EDCs can influence the gut microbiome and finally lead to the development of MDs. Other EDCs that have been taken into account for inducing MDs which are included in this book, including polychlorinated biphenyls (aromatic hexagonal biphenyl compounds), furans (an EDCs found in processed food, industrial process, pharmaceutical products, and smoke), heavy metals (such as cadmium and arsenic), flame-retardants (fire extinguisher such as halogenated, organophosphophosphate, nitrogenous, inorganic, and intumescent coatings), phthalates, pesticides, perfluoroalkyl substances, polycyclic aromatic hydrocarbons, tobacco, pharmaceut-
tical products waste, and parabens. As we also have laboratory experience working on some of these EDCs to experimentally explore the mechanistic details of them by inducing pathological alteration and causing diseases like hepatotoxicity, mutagenicity, nephrotoxicity, genotoxicity, teratogenicity, and immunotoxicity, we also felt the potential urge for exposing the roles of bisphenol A (a toxic, mutagenic, carcinogenic, and endocrine disruptor) and aflatoxins (substituted bisfuranocoumarins, a secondary fungal metabolite).

We think that this communal etiology we have so far provided from the introduction of endocrinology till the dysfunction and occurrence of MDs with a potential role of EDCs can significantly support the need for a better understanding of these dysfunctions to reveal unusual therapeutic targets for the development of pharmaceutical drugs. This can be achieved by utilizing nanotechnology, a rapidly flourishing field that has emerged as cutting-edge technology in the twenty-first century indicating a promising future. Therefore, we are successful in showing how such novel technologies along with other therapeutic candidate molecules or techniques and/or preventive methods can ameliorate the hazardous effects of EDCs that occur in the form of induction and prevalence of MDs. The most important ones that we have discussed here, though certainly not the only ones, are the roles of nanoparticles in the management of metabolic disorders, intermittent fasting, herbs, and spices as a natural medicine for MDs. Similarly, bioactive compounds like polyphenols, phytosterols, carotenoids, prebiotics, vitamins, and flavonoids can effectively be used in treating EDCs-induced diabetes mellitus, hypertension, obesity, hyperlipidemia, and non-alcoholic fatty liver disease.

The chapters given in this book actually depict a comprehensive view into the rising areas of research in the pathobiology of EDCs-induced MDs. This book also includes in-depth assessments on a variety of therapeutic targets of the endocrine system that can be either focused on reverting the MDs or preventing enduring damage to bypass the occurrence and/or progression of MDs. We are confident that the contents of this book will motivate and encourage not only the challenging deliberations but will also instigate innovative paths of research to further widen the information, awareness, and responsiveness towards pathogenic EDCs with the eventual objective of rendering this information provided in this book into therapeutic novelties.

Faisalabad, Pakistan  Muhammad Sajid Hamid Akash
Faisalabad, Pakistan  Kanwal Rehman
Islamabad, Pakistan  Muhammad Zaffar Hashmi
Acknowledgement

The editors would like to express their warm thanks especially to the authors of every chapter in this book who supported us and cooperated with us at every point and without whom it would have been impossible to accomplish this task. It is wholeheartedly expressed that the contribution of each author proved to be a milestone in the accomplishment of our end goal.

The support and the technical contribution of “Higher Education Commission” (HEC) of Pakistan are highly appreciable. Without their provision and funding, it would have been impossible to reach the objective. The credit for the accomplishment of this work goes to the research grants (21-667/SRGP/R&D/HEC/2016, 21-1061/SRGP/R&D/HEC/2016, 5661/Punjab/RPU/R&D/HEC/2016, 6429/Punjab/NRPU/R&D/HEC/2016, and 8365/Punjab/RPU/R&D/HEC/2017) awarded by HEC to the editors of this book, as these projects and their outcomes have provided us the importance and significant health consequences of environmental pollutants/toxicants including heavy metals and endocrine-disrupting chemicals (EDCs). These projects have helped us to determine the positive relation of diabetic parameters with heavy metal exposure and influence on antioxidant status (Project# 21-667/SRGP/R&D/HEC/2016); they have also helped us to explore the new pathways and factors like smoking involved in the pathogenesis of metabolic disorders like diabetes and obesity and extent of at-risk patients in our community (Project# 6429/Punjab/NRPU/R&D/HEC/2016). Similarly, the sources for EDCs exposure and introduction of the cost-effective treatment for EDCs-induced metabolic disturbance have been also focused (Project#5661/Punjab/RPU/R&D/HEC/2016, 6429/Punjab/NRPU/R&D/HEC/2016, and 8365/Punjab/RPU/R&D/HEC/2017). Nevertheless, gender differences have also been identified to influence the inflammatory biomarkers of insulin resistance in diabetes mellitus (Project#21-1061/SRGP/R&D/HEC/2016).

Interestingly, as in this book, many chapters have also highlighted the therapeutic impact of bioactive compounds to be a cutting-edge treatment approach for many metabolic diseases caused by EDCs. This reflects the positive work done by the editors of this book under HEC-funded projects for which the editors are highly indebted to, as this funding proved to be a landmark effort towards the success of the project.
In the end, we editors, wholeheartedly wish to recognize the valuable words written by Dr. Shuqing Chen, Professor of Biochemistry and Molecular Biology, Department of Precision Medicine and Biopharmaceuticals, College of Pharmaceutical Sciences, Zhejiang University, China and Dr. Ciarán Martin Fitzpatrick, Editor-in-Chief, BMC Endocrine Disorders and Department of Drug Design and Pharmacology, University of Copenhagen, Denmark for their tiring efforts done to accomplish this book.
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Part I

Introduction to Endocrine System and Metabolic Disorders
Chapter 1
Physiology of Endocrine System and Related Metabolic Disorders

Anam Ahsan, Ajab Khan, Muhammad Asim Farooq, Muhammad Naveed, Mirza Muhammad Faran Ashraf Baig, and Wen-xia Tian

Abstract Endocrine system is comprised of multiple glands. All of these glands secrete different hormones into the body. Most of the body’s functions, i.e., metabolism, growth, development, electrolyte balance, and reproduction, are regulated by these endocrine hormones. Numerous releasing and inhibitory hormones are secreted by the hypothalamus which eventually stimulates the pituitary gland’s hormonal secretions. Some of these pituitary hormones act directly on the target organs, while others act on organs situated in different regions of the body. Pituitary gland secretes growth hormone (GH), thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), prolactin, and oxytocin. Other endocrine glands include thyroid gland (secreting thyroid hormone T3 and T4, calcitonin), parathyroid gland (secreting parathyroid hormone), adrenal gland (secreting catecholamines, mineralocorticoids, glucocorticoids, androgens, and cortisol), pancreas (secreting insulin and glucagon), gonads (secreting sex hormones), pineal gland (secreting melatonin), and thymus gland (secreting thymosin hormone). Most of the endocrine hormones are regulated by negative feedback mechanism. There are many metabolic disorders associated with the over and under production of all these hormonal secretions by different glands. In this chapter along with describing endo-
crine gland’s physiology, we have discussed in detail all the associated endocrine metabolic disorders, i.e., hyperthyroidism, hypothyroidism, iodine deficiency, hypoparathyroidism, adrenal insufficiency, Cushing’s syndrome, acromegaly, galactorrhea, erectile dysfunction, central diabetes insipidus, hypopituitarism, pituitary apoplexy, diabetes mellitus, hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic nonketotic coma.

Keywords Endocrine system · Physiology · Glands · Hormones · Metabolic disorders

Introduction

The endocrine system is a system that controls the release of chemical/physiological messenger called hormones from ductless glands in particular organs. Hormones play a role as “messengers” and are transported via blood into diverse cells of the body that deduce and perform action on this information. A small chemical that can enter the bloodstream and exerts its effect at a distant site in the body seems to be an incredible idea. However, this happens in our bodies every day in our life. These hormonal secretions in the body are responsible to act on received stimuli and maintain homeostasis. The vital functions of the body, i.e., growth, offspring production, maintenance of constant temperature, and the ability to perform basic functions and activities, are not possible without these hormones [1].

The endocrine system offers an electrochemical connection from the cerebral hypothalamus to all relevant parts of the body that involve in controlling of metabolism, development, reproduction as well as in growth. Two kinds of endocrine hormones exist, i.e., (1) steroidal (2) non-steroidal (protein based). Except child birth (special situation), endocrine system has a negative feedback check on all the hormones. If there is an increased activity related to a particular hormone, as a feedback action its activity is eventually decreased. There are other factors and also immune system is involved in maintenance of constant hormonal level [1].

Endocrine Glands and Respective Hormones

Glands are structures that synthesize and secrete chemical substances. There are two types of glands either exocrine or endocrine. Exocrine glands secrete their secretions outside the body like tears and sweat or inside a body cavity, e.g., Digestive pancreatic as well as salivary enzymes. While endocrine glands secrete their hormones directly into the bloodstream. These hormones travel and bind to specific receptors on the target tissue or organ and exert their effect. This specialized
The system of endocrine glands and their hormones is collectively known as the endocrine system [2].

The main endocrine glands comprise the adrenal gland, thyroid gland, parathyroid gland, pituitary gland, gonads (ovaries and testes), and pancreas as illustrated well in Fig. 1.1. The hormones secreted by such glands involve in controlling growth, metabolism, homeostasis, reproduction as well as development via transferring information straight to receptors situated on their corresponding or relevant organs of the body. A composite feedback loop scheme works in coordination to uphold a balance among all hormone levels [3].

Hormone concentration or amount of its secretion can be regulated by positive or negative feedback mechanisms. An increase in specific hormone levels inhibits secretion, and a decrease in specific hormone levels stimulates secretion. The pituitary gland (Fig. 1.2) is frequently mentioned to as the “master gland” as secretions of this gland coordinate the activities of additional ductless glands of the endocrine system [2]. The hypothalamus is positioned right at the uppermost of pituitary gland and is a portion of the brain that controls functions like observing the physical condition and maintaining homeostasis of body. The hypothalamus comprises numerous control centers that control emotions as well as various physiological actions. This one is the most important connections among nervous system as well as endocrine system [4] (Table 1.1).

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**Fig. 1.1** An illustration of the location of various endocrine glands present in the human body. Figure adapted from after some modifications (www.physio-pedia.com, 2019)
Pituitary Gland

Hypothalamus constitutes the inferior part of diencephalons; in addition, it is present directly above the brainstem. The pituitary gland is connected by a slender stem (infundibulum) to the bottom of the hypothalamus. There are two regions, i.e., (a) the anterior pituitary gland (anterior lobe or adenohypophysis) (b) the posterior pituitary gland (neurohypophysis or posterior lobe). Hypothalamus involves in

**Fig. 1.2** Illustration of different endocrine glands and their hormones. Adapted from Abrahamson and Mosesso [2]

<table>
<thead>
<tr>
<th>Table 1.1 Types of glands</th>
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<tbody>
<tr>
<td><strong>Endocrine glands</strong></td>
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<td>These are the type of glands which do not possess any duct and secrete their hormones directly into blood or interstitial fluid</td>
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<tr>
<td>For example, Adrenal gland, pituitary gland, thyroid gland, parathyroid gland, and gonads and pancreas</td>
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**Pituitary Gland**

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controlling of all secretions of pituitary gland together with various internal processes [5]. After receiving signals from systemic receptors, hypothalamus controls the physical and chemical characteristics of the blood such as blood pressure, nutrition, temperature, and water content. Whenever there is alteration in the homeostatic function or some other developmental alterations are needed, a cellular activity is induced by hypothalamus in desired body areas by stimulating release of pituitary hormones. Stimuli or signals from approximately entire areas/parts of nervous system are received by hypothalamus that is itself negatively controlled by pituitary regulatory hormones [1, 5].

**Anterior Pituitary Gland’s Hormones**

**Growth Hormone**

Release of growth hormones from anterior pituitary is being controlled by hypothalamus. Hypothalamus secretes both inhibitory hormone [growth hormone releasing inhibitor (GHRIH) or somatostatin] and secretary hormone [growth hormone releasing hormone (GHRH)] into the hypothalamohypophyseal portal system. Both IGF-1 and GH negatively respond to pituitary gland and hypothalamus [6]. Negative feedback regulatory mechanism of hormones regulated by frontal lobe of pituitary gland is illustrated in Fig. 1.3. The stimuli which increase the growth hormone secretion are categorized as:

- Elevated quantities of peculiar amino acids (A.A) in plasma
- Hypoglycemia and fasting
- Stressful/distressing stimuli

The secretion of growth hormone (GH) decreases with increasing levels of glucose, cortisol, and free fatty acids (FFA) in the plasma as well as during rapid eye movement sleep. The main functions of GH include the following:

- It stimulates the growth of bone, cartilage, and soft tissue by the action of IGF-1 (insulin-like growth factor or formerly known as hormone C). Its secretion in the liver, kidney, and other tissues is increased in response to GH.
- It stimulates the mobilization of fat by releasing fatty acids from adipose tissue.
- It increases the rate of protein synthesis in all body cells.
- Hepatic glucose output is increased by GH.
- The rate of glucose consumption is reduced all over the body due to reduced uptake of glucose by cells (i.e., it is counter regulatory to insulin).
- K+ and Na+ excretion are decreased, while Ca2+ absorption from the intestine is increased.
- It promotes erythropoiesis [7].
Prolactin

Prolactin stimulates the secretion of milk immediately after delivery by inducing direct effect on the breast. Prolactin initiates and maintains lactation along with estrogen and progesterone. Hypothalamus releases dopamine into hypothalamohypophyseal portal system, thereby inhibiting its release. Release of prolactin releasing hormone from the hypothalamus can erratically enhance prolactin secretion, for example, whenever the infant sucks on breast [6].

Thyroid Stimulating Hormone (TSH)

Hypothalamus secretes the thyrotropin releasing hormone and transports it through the hypothalamohypophyseal portal system to the pituitary gland, thereby producing and releasing TSH from the anterior pituitary. The hypothalamus can also inhibit TSH secretion by releasing somatostatin, just as inhibition of growth hormone (GH) happens. Free T4 as well as free T3 in blood stream negatively respond/feedback the pituitary and hypothalamus in order to control the concentration of these circulating hormones.
Thyroid stimulating hormone (TSH) enhances entire known actions of cells located in thyroid gland and increases the making as well as release of T4 (thyroxine) and T3 (triiodothyronine). There is increased vascularity and thyroid hypertrophy as a result of constant elevated levels of TSH [6].

Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

In women and men, the production of FSH as well as LH, respectively, in anterior pituitary is controlled via release of gonadotropin releasing hormone (GRH) from hypothalamus, which is transmitted to pituitary gland in hypothalamohypophyseal portal system. Feedback effects of testosterone, estrogen as well as statin (made in testes and ovaries in response to Follicle stimulating hormone stimulus) on the hypothalamus and together with anterior pituitary gland control levels of LH and FSH in blood stream.

In females, FSH is responsible for early maturation of ovarian follicles, while in men, spermatogenesis through Sertoli cells in the testes is stimulated by FSH. In females, LH is accountable for the final stage of maturation of follicles located in ovaries and hence the release of estrogen, while in men it makes Leydig cells in testes to release testosterone [6].

Adrenocorticotropic Hormone (ACTH)

ACTH is released from anterior lobe of pituitary gland, and is translocated along the hypothalamohypophyseal portal system to pituitary, once the hypothalamus secretes the corticotropin releasing hormone (CRH). Any type of stress that stimulates the hypothalamus is responsible for CRH release that leads to the release of ACTH in anterior pituitary, followed by secretion of cortisol from adrenal cortex. To stabilize plasma cortisol concentrations, there is a direct feedback mechanism of cortisol hormone on the hypothalamus and anterior pituitary gland.

Release of androgens as well as cortisol (hydrocortisone) from zona fasciculata and zona reticularis of adrenal cortex is stimulated by ACTH. Adrenocorticotropic hormone also has influence on zona glomerulosa cells, allowing them to make aldosterone in order to respond to decreased total sodium concentration, elevated potassium levels or higher amount of angiotensin, or in the body [6].

Posterior Pituitary Gland’s Hormones

Antidiuretic Hormone (ADH)

Supraoptic nucleus of hypothalamus is mainly responsible for production of ADH. The secretion of ADH is caused by elevated plasma osmotic pressure, pain, reduced extracellular fluid volume (EFV), in addition to other stress situations, and also includes certain drugs like barbiturates and morphine. Alcohol inhibits the