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Series Editor: Andrea Lenzi
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Principles of Endocrinology and Hormone Action

Springer

Endocrinology

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Within the health sciences, Endocrinology has an unique and pivotal role. This old, but continuously new science is the study of the various hormones and their actions and disorders in the body. The matter of Endocrinology are the glands, i.e. the organs that produce hormones, active on the metabolism, reproduction, food absorption and utilization, growth and development, behavior control and several other complex functions of the organisms. Since hormones interact, affect, regulate and control virtually all body functions, Endocrinology not only is a very complex science, multidisciplinary in nature, but is one with the highest scientific turnover. Knowledge in the Endocrinological sciences is continuously changing and growing. In fact, the field of Endocrinology and Metabolism is one where the highest number of scientific publications continuously flourishes. The number of scientific journals dealing with hormones and the regulation of body chemistry is dramatically high. Furthermore, Endocrinology is directly related to genetics, neurology, immunology, rheumatology, gastroenterology, nephrology, orthopedics, cardiology, oncology, gland surgery, sexology and sexual medicine, psychology, psychiatry, internal medicine, and basic sciences. All these fields are interested in updates in Endocrinology. The Aim of the MRW in Endocrinology is to update the Endocrinological matter using the knowledge of the best experts in each section of Endocrinology: basic endocrinology, neuroendocrinology, endocrinological oncology, pancreas with diabetes and other metabolic disorders, thyroid, parathyroid and bone metabolism, adrenals and endocrine hypertension, sexuality, reproduction and behavior.

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Principles of Endocrinology and Hormone Action

With 125 Figures and 53 Tables

Springer

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Series Preface

Is there an unmet need for a new MRW series in Endocrinology and Metabolism? It might not seem so! The vast number of existing textbooks, monographs and scientific journals suggest that the field of hormones (from genetic, molecular, biochemical and translational to physiological, behavioral, and clinical aspects) is one of the largest in biomedicine, producing a simply huge scientific output. However, we are sure that this new series will be of interest for scientists, academics, students, physicians and specialists alike.

The knowledge in Endocrinology and Metabolism limited to the two main (from an epidemiological perspective) diseases, namely hypo/hyperthyroidism and diabetes mellitus, now seems outdated and perhaps closer to the practical interests of the general practitioner than to those of the specialist. This has led to endocrinology and metabolism being increasingly considered as a subsection of internal medicine rather than an autonomous specialization. But endocrinology is much more than this.

We are proposing this series as the *manifesto* for **Endocrinology 2.0**, embracing the fields of medicine in which hormones play a major part but which, for various historical and cultural reasons, have thus far been "ignored" by endocrinologists. Hence, this MRW comprises "traditional" (but no less important or investigated) topics: from the molecular actions of hormones to the pathophysiology and management of pituitary, thyroid, adrenal, pancreatic and gonadal diseases, as well as less usual and common arguments. Endocrinology 2.0 is, in fact, the science of hormones, but it is also the medicine of sexuality and reproduction, the medicine of gender differences and the medicine of well-being. These aspects of Endocrinology have to date been considered of little interest, as they are young and relatively unexplored sciences. But this is no longer the case. The large scientific production in these fields coupled with the impressive social interest of patients in these topics is stimulating a new and fascinating challenge for Endocrinology.

The aim of the **MRW in Endocrinology** is thus to update the subject with the knowledge of the best experts in each field: basic endocrinology, neuroendocrinology, endocrinological oncology, pancreatic disorders, diabetes and other metabolic disorders, thyroid, parathyroid and bone metabolism, adrenal and endocrine

hypertension, sexuality, reproduction and behavior. We are sure that this ambitious aim, covering for the first time the whole spectrum of Endocrinology 2.0, will be fulfilled in this vast Springer MRW in Endocrinology Series.

Andrea Lenzi
Emmanuele A. Jannini

Preface

The endocrine system involves a complex signaling network that regulates essential functions involved in growth, reproduction, and homeostasis. We are increasingly recognizing that this regulatory system comprises not only hormones secreted by the classical endocrine glands, but also hormones and regulatory factors produced by many organs and tissues, such as the heart, gut, bone, and adipose tissue, and that it involves extensive cross talk with the neural and immune system that are the other two crucial regulatory networks. At the same time, our knowledge of hormone synthesis, release, and transport as well as the molecular basis of hormone action has been greatly and rapidly expanded. Endocrine disorders include hormone deficiency or excess as well as peripheral resistance to selective hormones. Some of these disorders, such as thyroid diseases and type 2 diabetes mellitus, represent real social health problems for their high prevalence in the population and severe clinical complications. Several other disorders are less frequent but equally critical for health or otherwise important for their social implications, such as disorders involving impairment of growth or fertility. Emerging aspects include the notion that common endocrine disorders, such as insulin resistance and related conditions, may increase cancer risk and that the endocrine system contributes to regulate the process of aging.

Understanding the complexity of endocrine system physiology is crucial to prevent endocrine disorders and their complications, to improve the sensitivity of our diagnostic tools, and to provide the rationale for pharmacological, immunological, or genetic interventions.

Thanks to recent advances in this field, endocrine disorders can be now correctly assessed not only clinically but also by sensitive laboratory hormone measurements and by genetic and/or immunological testing as needed. Besides, as the endocrine system regulates the functions of all organs and apparatus, it is difficult to underestimate the relevance of endocrine physiology to all fields of Internal Medicine, including the prevention and treatment of common diseases such as cardiovascular diseases and cancer.

This volume has the ambitious aims to provide a comprehensive coverage of the current view of the physiology of the endocrine system and hormone synthesis and release, transport, and action at the molecular and cellular level. It is intended to

provide essential as well as in depth information to the medical students, but also to specialists in Endocrinology, Gynecology, Pediatrics, and Internal Medicine.

Each chapter has been written by a recognized expert in the specific field, and we wish to warmly express our gratitude and appreciation to all the authors who enthusiastically agreed to contribute to this endeavor and have made a remarkable effort to provide a complete, updated, yet easy to read, and fresh overview of the current knowledge in endocrine physiology.

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About the Editors

Antonino Belfiore is Professor of Endocrinology and Head of the Endocrine Unit at the University of Catanzaro, Italy. He obtained his M.D. degree at University of Catania, Italy, and graduated in Endocrinology and Metabolic Diseases (University of Catania) and Nuclear Medicine (University of Padoa). He completed his postgraduate training at the University of Naples (Ph.D.), at the University College of London, Clinical Immunology Department (1985–1987), and at the University of San Francisco, Diabetes Research Branch. He has been Assistant Professor in Endocrinology at the University of Catania till 1998, when he moved to the University of Catanzaro, first as Associate Professor, and from 2006 as Full Professor of Endocrinology.

Dr. Belfiore has a long-standing interest in the epidemiology, clinical aspects and biology of thyroid diseases, and in endocrine-related tumors. He is the Head of the research laboratory of Endocrinology at the University of Catanzaro, and current main interests of his research group concern the study of the IGF system dysregulation in human cancer, with particular focus on the role of the insulin receptor, its isoforms, and molecular modulators of these receptors in cancer.

Derek LeRoith is currently Interim Chief and Director of Research in the Division of Endocrinology, Diabetes and Bone Disease, Icahn School of Medicine at Mount Sinai, New York.

Dr. LeRoith received his medical and research training at the University of Cape Town, South Africa, and completed his postgraduate training in London, United Kingdom. Subsequently, he was a member of the medical faculty at Ben-Gurion University Medical School in Israel.

Dr. LeRoith worked for the National Institutes of Health (NIH) from 1979 until 2005 in the field of

endocrinology and diabetes, and he advanced to Diabetes Branch Chief at the NIH in Bethesda, Maryland. His research interests include the role of insulin and insulin-like growth factors in normal physiology and in disease states, including obesity, type 2 diabetes mellitus (T2DM), and cancer. His clinical interests primarily involve the pathophysiology and management of obesity and T2DM. Dr. LeRoith has published more than 600 research and review articles on these topics, as well editing numerous textbooks and is currently Editor in Chief of the AACE journal *Endocrine Practice*.

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Part I

Introduction to the Endocrine System

The Endocrine System

1

Angela M. Leung and Alan P. Farwell

Abstract

The endocrine system allows for the communication between the multiple cells and organs and is comprised of complex network of hormones, hormone receptors, carrier molecules, and signaling pathways. Characteristic of this system is that hormones generally act on cells that are physically separated from the secretory cell/gland, often traveling through the circulatory system to reach target tissues. Hormonal regulation is achieved by the ability of hormones to have specific biologic activity at their target tissues, important for energy production and metabolism, somatic growth and development, reproduction, and ability for the body to respond to internal and external stimuli. These complex interactions utilize controlled mechanisms of hormone synthesis and secretion and communication with other signaling molecules. Hormone deficiency or excess can each result from glandular or extraglandular processes and can be assessed clinically by laboratory testing that may include provocative testing if indicated.

Keywords

Endocrine • Hormone • Hormone receptor • Signaling

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Introduction

The *endocrine system* refers to the complex, interrelated mechanisms of communication between cells of an organism. The system is comprised of a diverse series of signaling mechanisms required for the regulation, processes, and functions required of multiple organs. Communication in the endocrine system is made possible by *hormones*, biologically active chemical substances that are secreted from ductless glands in the body and circulate through the bloodstream to act on target cells or organs. The actions of hormones in the endocrine system allow for the exquisite regulation of energy production and metabolism, somatic growth and development, reproduction, and responses to internal and external stimuli.

Hormone action can be classified into endocrine, paracrine, and autocrine actions (Fig. 1). The *endocrine action* of hormones refers to the transport of hormones in circulation to exert their metabolic actions at target tissues. Hormones can bind to carrier proteins in the circulatory system and thus exist in both their unbound (also termed free) and bound forms. However, in most cases, only the unbound/free hormone has biological activity. The differential affinity of binding proteins to hormones enables the precise availability of hormones in circulation and at target

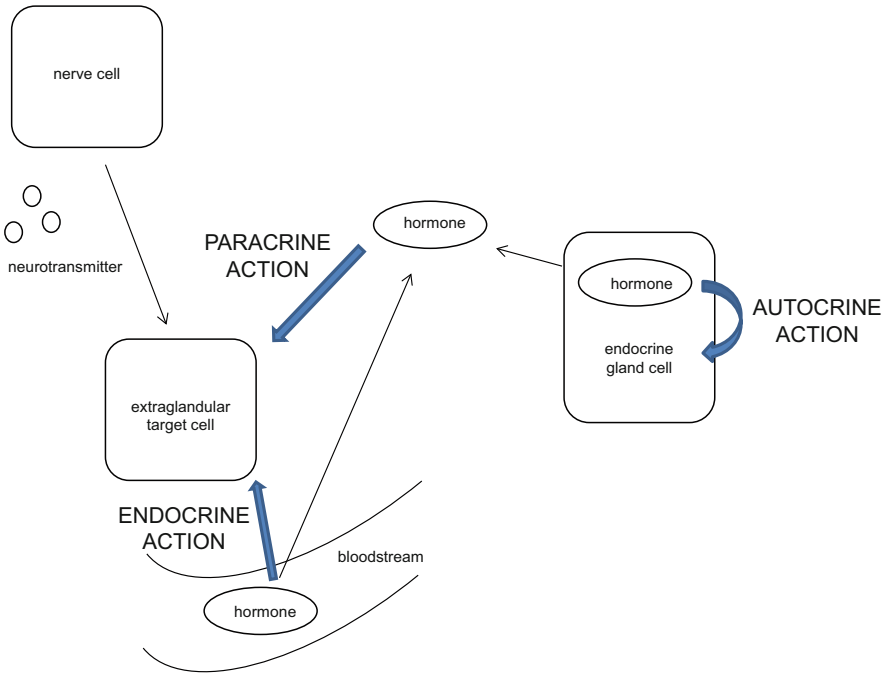

Fig. 1 Classes of hormone action

site(s). Once at their target sites, hormones interact with *hormone receptors*, proteins which recognize a unique binding site of the hormone. Hormone receptors facilitate the transmission of information carried by the hormone to generate a cellular response. Hormone receptors may be located on the target cell's surface or intracellularly, the latter which requires a mechanism of entry of the hormone into the cell to exert its action.

However, some hormones also or exclusively have *paracrine actions*, in which hormones are locally secreted to act upon surrounding cells. Examples of paracrine actions include the release of testosterone by the testes to control spermatogenesis, insulin-like growth factor in most tissues to control cell proliferation, somatostatin by the delta cells of the pancreatic islets to inhibit secretion of insulin from the beta cells and glucagon from the alpha cells, and growth factors in bone. Paracrine factors are usually produced and secreted in much smaller quantities than hormones which have endocrine action, given the specificity of the paracrine factor at local tissues and absence of the need to circulate throughout the body. Finally, a hormone can also act on its own cell of origin (*autocrine action*), such as the inhibitory action of insulin on its own secretion by the pancreatic beta cells.

The ability to achieve high hormone concentrations within a tissue is also facilitated by local diffusion of the hormone from its site of secretion. One example is the delivery of testosterone from the Leydig cells of the testes to the adjacent spermatogenetic tubules. Additionally, the local production of active hormone from

a circulating hormone precursor can increase the intracellular concentration of a hormone. This is demonstrated by the conversion of testosterone to dihydrotestosterone (DHT) in the prostate and the production of 3,5,3′-triiodothyronine (T3) from the deiodination of thyroxine in the pituitary, within the brain, and in other tissues.

The above definitions are adequate to define the concepts of hormones and receptors in most cases. However, increased understanding of the actions of other molecules has led to some broadened definitions. Regulatory molecules that mainly act as *neurotransmitters*, such as catecholamines and acetylcholine, may also act as classic hormones. Conversely, small peptides, such as thyrotropin-releasing hormone (TRH) that is produced in the hypothalamus and acts on the anterior pituitary to release thyrotropin and prolactin, are also found in neurons throughout the body and can function as neurotransmitters.

The classic endocrine glands, whose primary function is hormone production, include the thyroid, pituitary, adrenal, and parathyroid glands and the pancreatic islets. However, not all hormones are produced by pure endocrine glands. The ovary and testes, which produce the sex hormones, also produce oocytes and sperm. The brain is a major source for many peptide hormones, including proopiomelanocortin (POMC), the precursor molecule for corticotropin (ACTH), endorphins, and melanocyte-stimulating hormone (MSH). Lipotropin is synthesized not only in the anterior pituitary but also in the placenta and the gastrointestinal tract. Other body systems that produce hormones, yet while serving other primary functions, include the heart (which secretes atrial natriuretic factor), the liver (which secretes insulin-like growth factor-I and angiotensinogen and enables the conversion of thyroxine (T4) into the metabolically active T3), the kidney (which secretes erythropoietin and the active form of vitamin D), and the gastrointestinal tract (which secretes gastrin, cholecystokinin, somatostatin, and other hormones).

Interrelationships with Other Systems

The functions and actions of the endocrine system overlap considerably with the nervous system and the immune system, which also have key roles in extracellular communication. Like the endocrine system, the nervous system has evolved to release regulatory substances from nerve cells that act across synaptic junctions to transmit a signal to adjacent cells. As noted above, these neurotransmitters may also function as true circulating hormones, while some hormones also function as neurogenic mediators in the central nervous system. Thus, if a regulatory molecule is released into the circulation to act, it is considered a hormone; if it is released from a nerve terminal to act locally, it is a neurotransmitter. The same regulatory molecule may therefore be both a hormone and a neurotransmitter.

The hypothalamus serves as a direct connection between the nervous and endocrine systems, as the source of both hormones that are stored in the posterior pituitary and releasing peptides that regulate hormone secretion from the anterior pituitary. The autonomic nervous system often exerts control over the function of endocrine tissues. The pituitary, pancreatic islets, renal juxtaglomerular cells, and the adrenal

gland all respond to neural stimulation. Thus, the same cell can function as both an endocrine and a neural cell.

The immune system, initially thought to function autonomously, is now known to be subject to both neural and endocrine regulation. The cytokine regulators of the immune system are not usually considered hormones, but they clearly fit the definition as regulatory molecules that are secreted by one cell and influence another cell. The actions of cytokines are not limited to immunomodulation, as interleukins, interferons, and tumor necrosis factor produced by the immune system during systemic illness exert a major influence on hormone metabolism, especially that of thyroid hormone. Similarly, corticosteroids are major immunomodulators, as are the metabolic derangements produced by endocrine dysfunction, such as hyperglycemia in uncontrolled diabetes mellitus. Thus, while the central focus of endocrinology is on hormones, it is clear that not all hormones belong to the endocrine system and that there is considerable overlap between the endocrine, nervous, and immune systems.

Classes of Hormones

Hormones can be categorized into three classes according to their major components: peptide hormones, amino acid analogues, and steroid hormones (Table 1).

Peptide hormones are the most prevalent and diverse. They include hormones that are defined by a wide range of sizes, composition, number of chains, modification of groups, and mechanisms of production. Some examples are large single-chain peptides, such as the 192-amino acid growth hormone (GH), the cyclic peptide of TRH that is comprised of just three amino acids, and prolactin. The anterior pituitary hormones, thyrotropin (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are glycosylated and consist of two chains each, one of which is common to all three hormones (α chain), while the other is distinct and confers specificity to the hormone (β chain). Insulin is comprised of two chains that are derived from posttranslational cleavage of a single gene product (preproinsulin), while adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), and β-endorphin are single-chain proteolytic products of a large precursor molecule, proopiomelanocortin (POMC).

The *amino acid analogue hormones* are water-soluble and derived from amino acids. Specifically, the *amines* are derived from tyrosine and secreted from the thyroid (these are termed *iodothyronines*) and adrenal medulla. The precursor of the iodothyronines is thyroglobulin, a 660,000-Da glycoprotein that is synthesized by the thyroid follicular cell containing >100 tyrosine residues. The iodothyronines are formed by iodination and coupling of two tyrosines and are the only iodinated compounds with significant biologic activity. In the adrenal catecholamine-secreting cells, tyrosine is converted sequentially to dopamine, norepinephrine, and epinephrine. Serotonin (5-hydroxytryptamine) is derived from tryptophan.

Steroid hormones are derivatives of cholesterol containing a similar core known as the cyclopentanoperhydrophenanthrene ring. Synthesis of the steroid hormones

Table 1 Classes of hormones

Peptide hormones	
Small peptides	Vasopressin (ADH)
	Oxytocin
	Melanocyte-stimulating hormone (MSH)
	Thyrotropin-releasing hormone (TRH)
	Gonadotropin-releasing hormone (GnRH)
Intermediate peptides	Insulin
	Glucagon
	Growth hormone (GH)
	Prolactin (PRL)
	Parathyroid hormone (PTH)
	Calcitonin
	Corticotropin (ACTH)
	Corticotropin-releasing hormone (CRH)
	β-Endorphin
	Gastrointestinal peptides
	Cytokines
	Growth factors
Glycoproteins	Proopiomelanocortin (POMC)
	Follicle-stimulating hormone (FSH)
	Luteinizing hormone (LH)
	Thyrotropin (TSH)
	Chorionic gonadotropin (CG)
Amino acid analogues	
Iodothyronines	Thyroxine (T4)
	3,5,3′-Triiodothyronine (T3)
	3′,5′,3-Triiodothyronine (rT3)
Amines	Dopamine
	Epinephrine
	Norepinephrine
	Melatonin
	Serotonin
Steroid hormones	
	Estrogens
	Progesterone (P)
	Testosterone (T)
	Dihydrotestosterone (DHT)
	Cortisol
	Aldosterone
	Vitamin D
	Retinoic acid
	Prostaglandins

occurs as a result of enzymatically induced changes to the cholesterol core. Synthesis of the adrenal and sex steroids occurs in the adrenal cortex and testes or ovaries, respectively.

Hormone-Receptor Binding

Hormone action requires binding of the hormone to a receptor at the target cell. This allows the hormone to be distinguished from all other substances and to activate a cellular response upon hormone binding. Further regulation is achieved by a variable number of hormone receptors per type of target cell. Hormones can be grouped into two categories according to the location of its receptor at the target cell: on the cell surface (*cell surface receptors*) or intracellularly at the level of the nucleus (*nuclear receptors*). Most peptide hormones bind to cell surface receptors, while the amino acid derivatives and steroid hormones are usually ligands for nuclear receptors. In some instances, mutational changes in the structure of a hormone receptor result in the constitutive inactivation or activation of the hormone binding, leading to clinical scenarios of hormone deficiency and excess, respectively.

Hormones Binding to Cell Surface Receptors

Cell surface receptors are glycoproteins that are highly mobile within the plasma membrane. Hydrophilic portions of the receptor are exposed at the cell surface, while the hydrophobic portions of the molecule are buried within the lipid bilayer. Cell surface receptors bind water-soluble hormones, such as peptide hormones, monoamines, and prostaglandins. Since these water-soluble hormones are not able to transverse the lipid bilayer to enter the cell, the cell surface receptor serves to transmit the hormonal "message" to the interior of the cell. The binding of the hormone to the cell surface receptor is reversible, allowing the receptor to be activated repeatedly, although the hormone-receptor complex may also be internalized, thus producing a single response from a single ligand-receptor interaction. Although there may be a variable number of cell surface receptors, the principal target tissues for a particular hormone generally contain the largest complement of receptor molecules and are exposed to the highest concentration of hormone.

The binding of a hormone to a cell surface receptor stimulates a cascade of complex events through the generation of second messengers. The activation of protein kinases results in phosphorylations and altered conformation of a diverse number of molecules, which then produces a series of metabolic effects. Posttranslational modifications of the receptor can affect downstream signaling pathways. Pathologic factors, such as genetics, autoimmune processes, and exogenous toxin exposures, may further contribute toward regulation of hormone sensitivity.

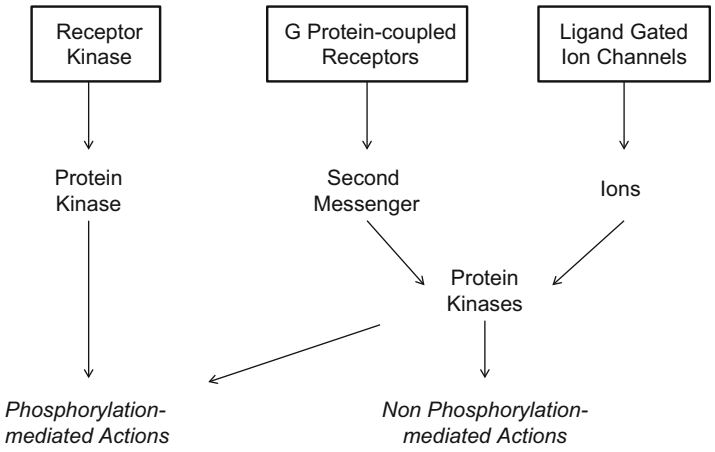

Fig. 2 Cell surface receptor response pathways

Cell surface receptors which trigger intracellular signaling pathways can be subcategorized by their different molecular mechanisms: ligand-gated ion channels, receptor tyrosine kinases, receptor serine/threonine kinases, receptor guanylate cyclase, G-protein-coupled receptors, and cytokine receptors (Fig. 2). The action of G-protein-coupled receptors and cytokine receptors depends on the recruitment of other molecules, while the remaining types of cell surface receptors can also function as ion channels or enzymes to achieve effector function. Thus, hormones may utilize a variety of intracellular mediators, and a given hormone may utilize one or more of these intracellular pathways. The metabolic events regulated by the activation of cell surface receptors may either be rapid alterations in ion or substrate flux across the plasma membrane or slower alterations in protein levels by modulation of gene transcription.

Hormones Binding to Nuclear Receptors

Lipid-soluble hormones are small ligands (molecular mass $<1{,}000$ Da) and thus able to penetrate the plasma membrane to interact with intracellular nuclear receptors, which are much larger proteins (molecular mass 50,000–100,000 Da) (Fig. 3). The classic nuclear receptors are those for the thyroid and steroid hormones, the latter which include aldosterone, cortisol, estradiol, progesterone, and testosterone. Vitamins A and D metabolites are other lipophilic signaling molecules that also utilize nuclear receptors.

While most lipid-soluble hormones enter cells by passive diffusion, the thyroid hormones utilize active transport proteins, such as monocarboxylate transporter 8 (MCT8), MCT10, and organic anion transporting polypeptide 1 (OATP1C1), to

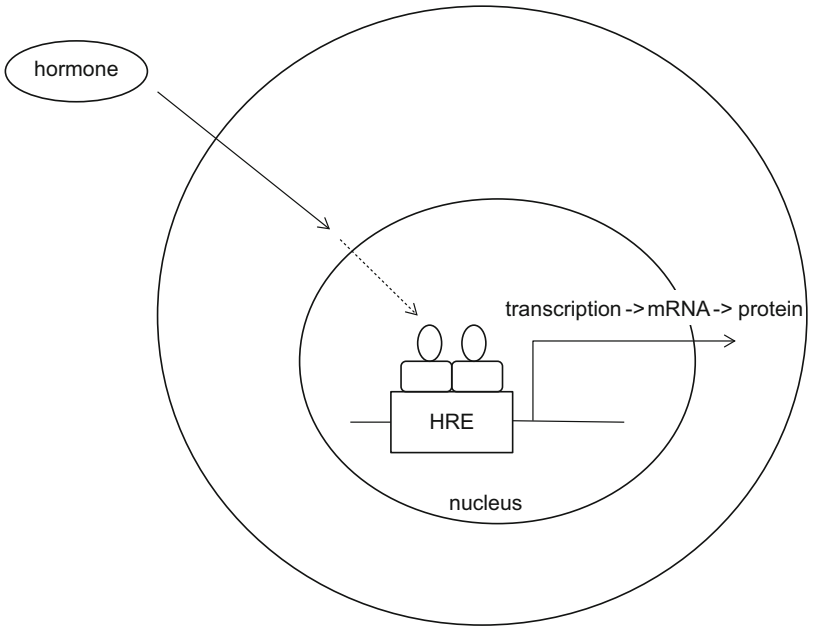

Fig. 3 Nuclear receptor signaling pathways

interact with the thyroid nuclear receptors. Vitamin A is stored in the liver and metabolized to retinoic acid, which acts as a ligand for the retinoic acid receptor (RARs) in the nucleus, or if converted to its isomer, another nuclear receptor termed the retinoid X receptor (RXR). Vitamin D3 is produced in the skin as a result of the action of ultraviolet radiation on 7-dehydrocholesterol. Vitamin D3 is transported to the liver, where it is converted to 25-hydroxy vitamin D, and then to the kidney tubule to be converted to its active form, 1,25-dihydroxy vitamin D. This active form of vitamin D binds to the vitamin D receptor (VDR) that is located in cells of almost all organs.

Nuclear hormone receptors can also be encoded by more than one gene, such as thyroid and estrogen; both of these receptors have an α and a β gene. Some receptors can also mediate the signals of more than one hormone, such as the androgen receptor that can interact with both DHT and testosterone.

Nuclear receptors bind to lipophilic ligands with high affinity. This binding is mediated by the C-terminal ligand-binding domain and domains D and E of the nuclear receptor. Meanwhile, specificity of ligand-receptor binding is accomplished by binding of the C domain of nuclear receptors to the hormone response element (HRE) gene sequences of the ligand. Most nuclear receptors bind to HREs as dimers. As the metabolic effects of these proteins are then produced by the translation products of the thyroid or steroid hormone-regulated mRNAs, the actions of these hormones are relatively slow, compared to cell surface receptors.

Roles of Hormones

Hormones have many roles that work together to achieve the exquisite regulation required of many body processes. This regulation by the endocrine system is often the result of different mechanisms at many targets, thereby allowing the body to respond to a diverse variety of concurrent physiologic changes and pathologic insults. The major body processes regulated by hormones include energy production, utilization and storage (intermediary metabolism), growth, development, reproduction, and maintenance of the internal environment (mineral and water metabolism and cardiovascular effects).

Energy Production

Hormones are the primary mediators of substrate flux and the conversion of food into energy production. The utilization of glucose and other fuels is regulated by a number of different hormones. Catecholamines, ghrelin, growth hormone, testosterone, and cortisol induce the breakdown of lipids and the hydrolysis of triglycerides into glycerol and free fatty acids (lipolysis). Glucocorticoids, catecholamines, growth hormone, cortisol, and glucagon promote hyperglycemia. Consistent with the occasional need for rapid mobilization of fuels, many of these catabolic hormones exert their actions by the activation of adenyl cyclase. In contrast, insulin and the insulin growth factors (IGFs) are anabolic hormones and store fuel for later use. Finally, the thyroid hormones directly affect energy production at the level of the mitochondria, which have their own specific thyroid hormone receptors.

Intermediary Metabolism, Growth, and Development

Hormones are crucial for normal somatic growth and development. The major hormones involved in development and growth are thyroid hormone, growth hormone, the sex steroids, insulin, and other growth factors. Thyroid hormone affects both growth and development and has a particularly critical role in early neurodevelopment. Growth hormone primarily regulates growth, and the sex steroids mainly regulate sexual development.

Androgens, estrogens, growth hormone, thyroid hormone, and prolactin can act as growth factors. The action of some of these is reliant on the availability of other hormones to act as growth factors. One example is growth hormone, which requires thyroid hormone for its normal synthesis and secretion, in part through the stimulation and action of IGF-1 by thyroid hormone. In contrast, glucocorticoids in excess and somatostatin inhibit the secretion of growth hormone and TSH.

Reproduction

Hormonal regulation is essential for normal reproductive processes. Hormones are required for both the production of ova and sperm from the gonads and the

dimorphic anatomical, functional, and behavioral development of males and females that is essential for sexual reproduction. Regulation is achieved by the negative feedback within the hypothalamic-pituitary-gonadal axis. Gonadotropin-releasing hormone (GnRH) is secreted in pulsatile fashion from the hypothalamus to stimulate gonadotropin production in the pituitary. The gonadotropins are essential regulators of ovarian and testicular function and the subsequent secretion of the sex steroids from the gonads. The sex steroids control functions crucial for pregnancy and for sexual differentiation and development.

Mineral and Water Metabolism

Aldosterone, parathyroid hormone (PTH), and vitamin D have primary functions in ion regulation, while vasopressin (also termed antidiuretic hormone, ADH) regulates water metabolism. These hormones bind to specific receptors at various target tissues. Aldosterone binds to mineralocorticoid receptors (MRs) located in the kidney, distal colon, heart, central nervous system (hippocampus), brown adipose tissue, and sweat glands and is important for the regulation of extracellular volume and potassium homeostasis. The mineralocorticoid receptor (MR) can be stimulated by both aldosterone and cortisol. Parathyroid hormone binds to one of the two parathyroid hormone receptors: parathyroid hormone 1 receptor (PTH1R) is expressed in bone and kidney to increase serum calcium concentrations, while parathyroid hormone 2 receptor (PTH2R) is expressed in the central nervous system, pancreas, testes, and placenta. The nuclear vitamin D receptor (VDR), which binds 1,25-dihydroxy vitamin D, is more diverse and located in cells of almost all organs. In addition, several other hormones (insulin, glucagon, catecholamines, thyroid hormone, and glucocorticoids) have secondary effects on water and electrolyte metabolism.

Cardiovascular Functions

While not usually considered an endocrine organ, the heart, specifically the atria, produces atrial natriuretic peptide (ANP), which has extensive effects on the cardiovascular system. Important to the regulation of water, sodium, and potassium, ANP acts on the kidneys to decrease extracellular fluid volume, renal arterial pressure, and urinary potassium excretion.

Many other hormones also affect cardiovascular function, including catecholamines, thyroid hormone, mineralocorticoids, and the sex steroids. Catecholamines increase pulse, blood pressure, myocardial contractility, and cardiac conduction velocity. Thyroid hormones have an important role in maintaining heart rate, stroke volume, peripheral vascular resistance, and cardiac contraction. Mineralocorticoids maintain fluid and sodium homeostasis that is important within the cardiovascular system. Finally, the sex steroids have varied roles in cardiovascular health: testosterone stimulates the renin-angiotensin-aldosterone system, while estrogen inhibits this; progesterone has both vasodilatory and vasoconstrictive effects.

Tropic Actions

Some hormones have primary roles to regulate the production of other hormones (tropic effects), and many of these are produced in and secreted from the anterior pituitary. TSH regulates thyroid hormone production, LH regulates estrogen production in the female and testosterone production in the male, and ACTH regulates glucocorticoid production in the adrenal gland. These hormones share a similar mechanism by the activation of adenyl cyclase to increase the rate of hormone synthesis and secretion. They may also promote cell division to result in enlargement (hyperplasia) of the target gland.

Hormone Synthesis, Storage, and Secretion

Some hormones are secreted in their active forms, while others later undergo activation in order to be biologically active. The rates and mechanisms of hormone synthesis, storage, and secretion are generally different between the peptide and amine hormones, compared to the steroid hormones.

Peptide and Amine Hormones

Cells that synthesize peptide or amine hormones store the hormones in granules and, thus, have a readily releasable pool of hormone. Specific subcellular pathways consist of interactions between the endoplasmic reticulum (ER), Golgi apparatus, and secretory granules. Upon the appropriate stimulus, the storage granules migrate to the cell surface and fuse with the plasma membrane, and hormone is secreted into the extracellular space (exocytosis). In some cells, this process is dependent upon calcium influx into the cell. In the second pathway of intracellular hormone transport and secretion, vesicles instead mediate this process and enable the movement of hormone stored within them toward the cell surface.

In some pathways, the stimulus for hormone release also induces synthesis of new hormone, resulting in a biphasic secretion pattern. There is an early release of preformed hormone from secretory vesicles, followed by release of newly synthesized hormone.

Steroid Hormones

The release of steroid hormones provides the stimulus for increased synthesis of hormone. Secretion of steroid hormones follows simple bulk transfer pathways involving concentration gradients into the circulation. While the tropic hormones from the anterior pituitary are secreted in the microgram range, their corresponding peripheral hormone levels are usually produced in milligram

amounts and have much longer half-lives. The classic steroid hormones are the thyroid hormones and corticosteroids (aldosterone, cortisol, estradiol, progesterone, and testosterone).

Thyroid hormone synthesis requires the uptake on iodine from circulation into the thyroid follicular cell. Iodine is transferred to the follicular lumen and becomes oxidized by thyroid peroxidase for the iodination of thyroglobulin to form the thyroid hormone precursors, MIT and DIT. Stimulation of the thyrocyte by TSH results in proteolysis of thyroglobulin and release of the thyroid hormones, T3 and T4, into circulation. However, despite a large amount of preformed hormone stored in the thyroid gland, secretion of thyroid hormone does not respond as quickly to the stimulus, in contrast to the peptide and amine hormones.

The corticosteroids are synthesized from cholesterol within the zona glomerulosa of adrenal cortical cells. Low-density lipoprotein (LDL) binds to LDL receptors on the cell surface of adrenal tissue, then undergoes endocytosis, and fuses with lysozymes to produce cholesterol. Cholesterol can also be synthesized within the adrenal cortex or be derived from other lipid subfractions. Cholesterol then undergoes various hydroxylations, methylations, and demethylation processes that ultimately result in the production of glucocorticoids, androgens, estrogen, and their derivatives. Most of the steroidogenic synthetic actions are mediated by cytochrome P450 enzymes.

Rates of Hormone Secretion

The secretion rates of hormones are dependent on usually multiple signals, including nutrient intake, stress, and adrenergic pathways. Pathways are interconnected with and adapt to the local environment. In general, only limited quantities of hormones are stored within the body, and even stores of peptide hormones are depleted within hours to days. Most peptide hormones are secreted in episodic bursts at irregular intervals on daily, hourly, or minute-by-minute frequencies.

The pattern of secretion of some hormones is dependent on local stimuli. Sleep-related release occurs with many hormones, including growth hormone (mostly secreted during slow-wave sleep) and prolactin from the anterior pituitary. Other hormones are subject to circadian variation (which is dependent on environmental cues, primarily light exposure), such as ACTH, and subsequent cortisol, secretion. Insulin is secreted upon nutrient intake and other signals. Prolactin secretion is relatively tonic, but peaks in episodic bursts when prompted by suckling. Parathyroid hormone secretion is stimulated by decreasing serum calcium concentrations. The frequency of pulses of secretion of some of the tropic hormones, such as the gonadotropins, determines whether these hormones will be stimulatory or inhibitory.

Ultimately, the rate of release of hormone is determined by its rate of synthesis. Two exceptions are thyroid hormone and vitamin D. Both hormones are stored in large amounts, providing a safeguard against long periods of iodine deficiency or

absence of sunlight exposure, respectively. The thyroid gland contains an approximate 2-month supply of stored thyroid hormone for this purpose.

Transport of Hormones

For the most part, hormones must be transported some distance to their target organs. Thus, they must be synthesized in relatively higher concentrations, compared to their requirement at target cells. The primary transport medium is the plasma, although the lymphatic system and the cerebrospinal fluid are also important. Since delivery of the hormone to its target tissue is required before a hormone can exert its effects, the presence or absence of specific transport mechanisms plays a major role in mediating hormonal action.

The water-soluble hormones (peptide hormones, catecholamines) are transported in plasma in solution and require no specific transport mechanism. Because of this, the water-soluble hormones are generally short-lived, circulating in the plasma in concentrations in the femtomolar range. These properties allow for rapid shifts in circulating hormone concentrations, which is necessary with the pulsatile tropic hormones or the catecholamines. This is consistent with the rapid onset of action of the water-soluble hormones.

The lipid-soluble hormones (thyroid hormone, steroids) circulate in the plasma bound to specific carrier proteins. This ensures the appropriate distribution of the water-insoluble ligands and prevents the loss of the hormones through urine or bile excretion routes. Many of the proteins have a high affinity for a specific hormone, such as thyronine-binding globulin (TBG), sex hormone-binding globulin (SHBG), and cortisol-binding globulin (CBG). Nonspecific, low-affinity binding of these hormones to albumin also occurs.

Carrier proteins act as reservoirs of hormone, resulting in picomolar to micromolar circulating hormone concentrations. Since it is generally believed that only the free hormone can enter cells and, thus, can exert its biological actions, a dynamic equilibrium must exist between the bound and free hormone. The protein-bound hormones are in rapid equilibrium with the unbound, or free, fractions, thus ensuring the immediate availability of the free hormones to target cells. Thus, alterations in the amount of binding protein available or in the affinity of the hormone for the binding protein can markedly alter the total circulating pool of hormone without affecting the free concentration of hormone.

Carrier proteins act as buffers to both blunt sudden increases in hormone concentration and diminish degradation of the hormone once it is secreted. The half-life of hormones that utilize carrier proteins is thus longer than those that are not protein bound. Indeed, carrier proteins have a profound effect on the clearance rate of hormones; the greater the capacity for high-affinity binding of the hormone in the plasma, the slower the clearance rate. In some instance, the carrier proteins allow slow, tonic delivery of the hormone to its target tissue. This is consistent with the slower onset of action of the lipid-soluble hormones.

Hormone Metabolism

Clearance of hormones from the circulation plays a critical role in the modulation of hormone levels in response to varied physiologic and pathologic processes. The time required to reach a new steady-state concentration in response to changes in hormone release is dependent upon the half-life of the hormone in circulation. Thus, an increase in hormone release or administration will have a much more marked effect if the hormone is cleared rapidly from the circulation as opposed to one that is cleared more slowly.

Hormone metabolism is also linked to the processes that they regulate. For example, insulin and catecholamines participate in rapid cellular responses, and their short half-lives facilitate the wide swings in their levels that are essential for their regulatory actions. Conversely, hormones that participate in transcriptional regulation control more long-term cellular responses; their longer half-lives buffer rapid fluctuations in free hormone levels. Most peptide hormones have a plasma half-life measured in minutes, consistent with the rapid actions and pulsatile nature of secretion of these hormones.

Rapid clearance of hormone is achieved by the lack of protein binding in the plasma, degradation or internalization of the hormone at its site of action, and ready clearance of the hormone by the kidney. Binding to serum proteins markedly decreases hormone clearance, as is observed with the steroid hormones and the iodothyronines. Metabolism of the steroid hormones occurs primarily in the liver by reductions, conjugations, oxidations, and hydroxylations that serve to inactivate the hormone and increase their water solubility, facilitating their excretion in the urine and the bile. Metabolic transformation also may serve to activate an inactive hormone precursor, such as the deiodination of thyroxine to form T3 and the hydroxylation of vitamin D at the 1 and 25 positions.

Hormone metabolism is not as tightly regulated as hormone synthesis and release. However, alterations in the metabolic pathways may be clinically important. Drugs that increase activity of the liver P450 enzymes, such as phenytoin, rifampin, carbamazepine, and large doses of barbiturates also increase the turnover of steroid and thyroid hormones and may expose latent adrenal insufficiency or decreased thyroid reserve. More commonly, the administration of these drugs may require increases in the dose of steroids or thyroid hormone administered to achieve the same effect. Thus, large doses of barbiturates may decrease the effectiveness of oral contraceptives.

Alterations in the binding capacity of serum transport proteins also alter the dynamic equilibrium between bound and free hormone, leading to changes in hormone release or replacement requirements. For example, the estrogen-induced increase in TBG may be one possible explanation for the frequently observed increase in the administered dose of L-thyroxine required in the pregnant patient with hypothyroidism. Finally, starvation and illness markedly inhibit the activity of the 5′-deiodinase in the liver. This results in decreased serum T3 concentrations due to the impaired production of T3 from T4 and increased concentrations of the