

ENDOCRINE PHARMACOLOGY

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Summary

Hormones from endocrine glands circulate to different organs in the body to regulate

growth and maturation, to maintain metabolic balances, and to control reproduction. As another section is dedicated to the regulation of reproduction, this topic will not be included here. This section discusses the regulation of growth and metabolic balances and the pharmacology of drugs regulating these processes.

In the introduction, we lay the basic concept of endocrinology with a focus on hormones from the pituitary gland and their target peripheral endocrine organs, followed by the target systems and cells. We also discuss the impact of endocrinology on science and modern evidence-based medicine. In section 2, we discuss pituitary gland hormones in detail. We will cover the target organs and physiological functions of these hormones. Drugs used to treat common hormone deficient and excessive disorders are also discussed. Chapter 3 is dedicated to thyroid gland hormones, in relation to physiological and pathological conditions. In chapter 4, we focus on pancreatic islet hormones and the link to diabetes. Current therapeutic drugs used for diabetes management are also discussed.

1. Introduction

All multicellular organisms need coordinating systems to regulate and integrate the function of differentiating cells. Both the nervous system and endocrine system perform this function in higher animals. The endocrine system acts through the release (generally into the blood) of chemical agents and is vital to the proper development and function of organisms. It has been recognized that the integration of developmental events such as cellular proliferation, growth and differentiation, as well as the coordination of metabolism, respiration, excretion, movement, reproduction, and sensory perception depend on "chemical cues", substances synthesised and secreted by the specialised cells within the animal-Endocrine cells.

The term *Endocrine* was first introduced by Starling to contrast the action of hormones secreted internally (endocrine) with those secreted externally (exocrine) or into a lumen, such as the gastrointestinal tract [1]. This terminology continues today but makes the specialty somewhat opaque to the general public, who are more familiar with the term *hormone* or with particular disorders of the endocrine system.

The major physiologic processes controlled by hormones include (1) growth and maturation, (2) intermediary metabolism, and (3) reproduction. As there is a chapter dedicated to reproduction, we will only discuss the first two processes here. The clinical specialty of endocrinology is most clearly delineated by diseases that afflict the classic glands: hypothalamus, pituitary, thyroid, parathyroid, pancreatic islets, adrenal gland, etc. Additional clinical disorders, such as hypertension, nutrition, obesity, osteoporosis, and hyperlipidemia, now also fall within the scope of endocrinology.

The basic science of endocrinology has evolved from studies of hormone action. Concepts of receptors, intracellular signaling, and many aspects of transcriptional regulation remain an essential component of the field. Endocrinology is ultimately the study of intercellular communication. Classically, hormones mediate communication between organs, as exemplified by the action of parathyroid hormone (PTH) on bone or kidney. In some cases, the communication occurs within the same tissue, as exemplified

by autocrine (acting on the same cell) and paracrine (acting on the neighboring cells) actions of insulin-like growth factor 1 (IGF-1). In this era of genomics and proteomics, the traditional boundaries that separate endocrinology from other physiologic disciplines are becoming blurred.

1.1. Concept of Hormone Action

The fundamental actions of hormones include basic concepts such as hormone biosynthesis and secretion, regulation by other hormones, feedback effect of autocrine action, hormone-receptor binding and activation of receptors, and initiation of intracellular signaling. These principles are broadly applicable and can be applied to the physiology of other subspecialties.

1.1.1. Hormone Synthesis and Secretion

Hormones can be divided into five major classes: (1) amino acid derivatives such as dopamine, catecholamines, and thyroid hormone; (2) small neuropeptides such as gonadotrophin-releasing hormone (GnRH), thyrotrophin-releasing hormone (TRH), somatostatin, and vasopressin; (3) large proteins such as insulin, growth hormone (GH), luteinising hormone (LH), and parathyroid hormone (PTH) produced by classic endocrine glands; (4) steroid hormones such as cortisol and estrogen that are synthesized from cholesterol-based precursors; and (5) vitamin derivatives such as retinoids (Vitamin A) and Vitamin D. Generally, amino acid derivatives (except for thyroid hormones), peptide and protein hormones interact with cell surface membrane receptors. Steroids, thyroid hormones, vitamin D and retinoids are lipid soluble and interact with intracellular receptors affecting the cell nucleus.

Many peptide and protein hormones are produced from precursor polypeptides. Structurally, characteristic signal or leader sequences target these peptides and proteins for extracellular transport via secretory granules. Some precursors, such as the pro-opiomelanocortin (POMC) or preproglucagon, encode multiple biologically active peptides that are subsequently generated by specific processing enzymes. Other precursors, such as proinsulin and preprovasopressin, encode single hormones that are excised from larger proteins. The secretion of peptide hormones is tightly controlled by intracellular signals that regulate vesicle transport, fusion with the plasma membrane and exocytosis, resulting in hormone release into the extracellular milieu. Steroid hormones such as progesterone, cortisol, and testosterone are synthesized from cholesterol derivatives by a series of enzymatic steps. These enzymes are expressed specifically in steroidogenic tissues such as the adrenal gland and gonads. Their enzymatic activities are regulated in response to trophic hormones such as adrenocorticotrophic hormone (ACTH), LH, or follicle stimulating hormone (FSH). Thyroid hormone is produced by modifications (iodination) of tyrosines in thyroglobulin. Vitamin D and retinoic acid are derived in part from dietary sources but can also be generated and activated by endogenous synthetic pathways.

1.1.2. Feedback Regulation

The elucidation of negative feedback has made a significant impact on endocrinology. This principle holds that hormones have a particular set point that is controlled by

down-regulating stimulatory pathways when the set point is exceeded, and up-regulating stimulatory pathways when hormone levels fall below the set point. Probably every hormone is regulated in this manner, although the regulatory pathways may not as yet be clear for newly discovered hormones. These regulatory loops are well illustrated by the major hypothalamic pituitary hormone axes and include both stimulatory (e.g. TRH stimulates thyroid-stimulating hormone (TSH) secretion from the pituitary gland; TSH stimulates T4/T3 production in the thyroid gland) and inhibitory components (e.g. T4/T3 suppress TRH and TSH in the hypothalamus and pituitary gland). Feedback regulation also occurs for endocrine systems that do not involve the pituitary gland. For example, calcium (Ca^{2+}) feeds back to inhibit PTH, glucose inhibits glucagon secretion, and leptin acts on hypothalamic pathways to suppress appetite. While these pathways regulate hormone levels, they provide useful insights into endocrine testing paradigms. For example, dexamethasone suppression of the corticotrophin-releasing hormone (CRH)/ACTH axis is used to diagnose Cushing's disease, which is characterized by impaired negative feedback regulation. Another example is that a deficient adrenal response to exogenous ACTH is used to document primary adrenal insufficiency.

1.1.3. Paracrine and Autocrine Regulation

Whereas feedback mechanisms control many endocrine pathways, local regulatory systems, often involving growth factors, play critical roles in almost all tissues. Paracrine regulation refers to hormones released by one cell that act on an adjacent cell in the same tissue. For example, somatostatin secretion by pancreatic islet delta cells inhibits insulin secretion from nearby beta cells. The anatomical relationships of cells have an important influence on paracrine regulation. Autocrine regulation describes the action of a hormone on the same cell from which it is produced. IGF-1 acts on many cells that produce it, including chondrocytes, breast epithelium, and gonadal cells. Intracrine regulation refers to effects within a cell. The term is not commonly used but captures the important concept that many signaling and enzymatic pathways are influenced by other pathways or by substrate or product local concentrations. For example, 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis, is inhibited by the end product, cholesterol.

1.1.4. Hormone Rhythms and Pulsatility

Hormone rhythms are used to adapt to environmental changes, such as seasons of the year, the daily light-dark cycle, sleep-wake cycle, meals, and stress. In many animal species, reproduction is seasonal, presumably a mechanism to ensure survival of the offspring. In extreme northern or southern hemispheres, calcium absorption and bone remodeling decline during winter, when vitamin D production is reduced. The human menstrual cycle is also a repeated phenomenon every 28 days, reflecting the time required for follicular maturation and ovulation. Essentially, all pituitary hormone rhythms are entrained to the sleep cycle and the circadian cycle, which in turn is dictated by sunlight exposure. The hypothalamic-pituitary-adrenal (HPA) axis, for example, exhibits characteristic peaks of ACTH and cortisol production before dawn and a nadir between late afternoon and midnight. Recognition of these rhythms is important for endocrine testing and treatment. Patients with Cushing's syndrome exhibit inappropriately increased midnight cortisol levels. The HPA axis is more susceptible to suppression by

glucocorticoids administered at night because they blunt the early morning rise of ACTH. Understanding this diurnal rhythm provides the basis for more physiologic hormone replacement by using larger glucocorticoid doses in the morning than in the afternoon.

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Biographical Sketch

Chen Chen is a Professor and Chair of Endocrinology at the School of Biomedical Sciences, The

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