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Molecular Endocrinology

分子内分泌学

(第三版)

Franklyn F. Bolander

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Molecular Endocrinology

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分子内分泌学

（第三版）

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第三版序

15年前，本书的作者正在讲授分子内分泌学的课程，令他失望的是竟找不到一本在广度和深度上能涵盖此领域的书作为教材，因此他撰写了第一版《分子内分泌学》。此后十余年来，一些有关信号转导的书籍相继面世，尽管这些书籍对于信号转导通路本身的描述详尽而充分，但仍未能包含激素作用的全貌，也未充分阐明内分泌调控的核心内容——激素与信号分子相互作用的关系。基于上述的原因及近年来分子内分泌学的快速发展，促使了本书第三版的出版。

《分子内分泌学》是第一本，也是非常重要的一本内分泌学教材。为了兼顾那些并不了解本学科的读者，本书的前言部分详细地介绍了内分泌学的基础知识。前言部分的内容是理解后续内容的关键，它帮助我们了解激素分子水平作用机制，以及各信号通道之间为何会以特定的方式相互协同或拮抗。前言之后，后续章节分别讲述受体、第二信使及信号转导，最后几章则是一些相关专题。然而无论哪一章节，都始终围绕着激素的作用及整合这一核心而展开。例如第十二章的后半部分，围绕着某些激素对信号转导及其细胞作用的联系进行了系统的介绍。此外，还以糖原代谢与平滑肌收缩为例，阐述第二信使与激素间相互作用的关系。第十三章则深入到细胞核内，进一步在转录水平讨论激素的作用。通过这些讨论，作者将信号的分子特性与激素生物效应有机地结合起来。

本书增加了一些新的章节。如前所述，在第十二章中对一些重要激素具体传导途径进行了详细地介绍。从分子水平对激素的功能进行讨论，这在几年前是不可想象的，然而现在却变成了现实，由此可以看出最近几年分子内分泌学取得的巨大进步。本书新增加的第四章可以看作是第二部分的前言。由于内分泌学科的进展是整体性的，不可能仅强调某个方面而忽略其他。例如，受体是激素所遇到的第一个细胞器，所以作者将受体放在第一章进行介绍。而调节受体的磷酸化作用及相关的激酶则在后续章节才得以详述。如果把激酶放在受体前面讲述，那么读者就不能正确理解受体和激活受体的那些激酶的关系，受体的重要性也就得不到充分体现。换言之，每个主题都是后续其他内容的基础。第四章的作用就在于，使读者在阅读后续章节之前对受体和第二信使的核心内容有个大致地了解。

本书还加入了许多最新的研究进展。自从本书第二版面世以来，许多重要受体和转录因子的三维结构都已揭晓，其功能及作用机理也已经得到阐明。另外，在信号通路的分子本质方面有了很大的进展，人们逐渐认识到信号网络的重要性。最后，在内分泌系统进化和比较内分泌学的章节内，还增加了一些物种的基因组的序列，并结合新兴的蛋白质组学进行了阐述。

本书在写作风格上也作了重大调整，用一些最新的综述性文献代替了众多详细的原始参考文献。这就大大节省了各章节的篇幅，使最新的文献资料得以呈现。如果读者们想获得针对于本书中某个具体问题更详细的文献资料，欢迎与作者联系。

（田慎鹏 译　陈璐璐 校）

Preface to the Third Edition

The first edition of *Molecular Endocrinology* was published 15 years ago. It was originally written out of desperation: the author was teaching a course of the same name and could not find a textbook that covered this field in the depth and breadth that he required. About a decade later, several texts on signaling began to appear; although their coverage of signaling pathways was adequate, they still failed to embrace the full range of hormone action and did not closely relate signaling to hormone effects and interactions, which are the core of endocrine control. This deficiency, coupled with tremendous advances in the field of molecular endocrinology, provided the impetus for writing the third edition.

Molecular Endocrinology is first and foremost an endocrinology text. Indeed, it begins with an introductory unit on basic endocrinology for those readers who have not yet been exposed to the discipline. Such an introduction is critical for understanding how hormones act at the molecular level and why their signaling pathways synergize or antagonize each other in the manner they do. This section is followed by units on receptors, second messengers, transcription, and a final section on a few special topics. However, the emphasis is always on hormone action and integration. For example, in the latter half of Chapter 12, there is a comprehensive discussion of several hormones that have signaling pathways linked to their cellular actions. In addition, glycogen metabolism and smooth muscle contraction are discussed with respect to how the second messengers of the regulating hormones interact. In Chapter 13, this discussion is carried into the nucleus, where it is applied to transcription. Through these discussions the molecular aspects of signaling can be related to the gross effects of hormones in organisms.

This edition contains several new sections. As noted previously, in Chapter 12 there is a discussion of step-by-step pathways for several important hormones. Such a molecular analysis of hormone action would have been impossible just a few years ago; its presentation in Chapter 12 attests to how far molecular endocrinology has advanced. There is also a new chapter: Chapter 4 is a brief synopsis of signaling and prefaces Part 2. Its creation arose from the fact that the processes of endocrinology are so integrated that it is impossible to present one topic without encountering several others. For example, receptors are presented first because they are the first cellular structure hormones encountered. However, receptors are regulated by phosphorylation, and the relevant kinases are not discussed until later. If the kinases were covered first, then the readers would have no appreciation of the receptors and signaling pathways that activated them. In other words, every subject appears to be a prerequisite for discussing any other subject. Chapter 4 is designed to provide the reader with key concepts and components of receptors and second messengers prior to their detailed discussions in subsequent chapters.

The text has also been extensively updated. Since the second edition, the three-dimensional structure of many important receptors and transcription factors has been published, and the mechanisms of action of these receptors and factors have been elucidated. In addition, there have been major advances in the understanding of the modular nature of signaling and the importance of compartmentalization. Finally, the new discipline of proteomics combined with the sequence of the genomes from several species has added flesh to the chapter on the evolution of the endocrine system and comparative endocrinology.

There is also a major stylistic change: detailed references to specific facts have been replaced by recent review articles. This change freed up considerable space for the updated material and was made possible by the abundance of reviews currently available in the literature. However, if readers would like to have the specific reference for any statement of fact in this text, they are welcome to contact the author.

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PART 1

Introduction and General Endocrinology

CHAPTER 1

Introduction

CHAPTER OUTLINE

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Definitions

Endocrinology is the study of hormones; but what are hormones? The question is far more difficult to answer today than it was a few decades ago. The classic definition is that hormones are chemical substances produced by specialized tissues and secreted into blood, where they are carried to target organs. However, this definition was constructed when most of the available knowledge of endocrinology was restricted to vertebrate systems. As the field of endocrinology has expanded, new hormones and new systems that previously would not have been included under this definition have been discovered. It is useful to describe these discrepancies so that a more functional definition can be developed.

1. *Specialized tissues for hormone synthesis.* Discrete endocrine glands exist only in arthropods, mollusks, and vertebrates, even though chemical substances that have hormonal activity have been identified throughout the animal, plant, and fungal kingdoms. Even in vertebrates, there exists a class of hormones, the *parahormones,* designed to act locally. Because parahormones are made wherever they are needed, they tend to have a nearly ubiquitous distribution. Finally, many vertebrate growth factors are synthesized in multiple locations.

2. *Blood for hormone distribution.* First, blood is unique to vertebrates. The addition of hemolymph to the definition would permit arthropod hormones to be included in the definition, but those of plants and lower animals would still be omitted. Second, even in vertebrates, the parahormones diffuse through the extracellular fluid to reach their local targets. Other hormones are released by neurons and also have local effects. Finally, the classic definition would exclude *ectohormones,* hormones that traverse air or water to act between or among individuals. These hormones are particularly well developed in certain insect species and include *pheromones* (sexual attractants), *gamones* (inducers of sexual development), and *allomones* and *kairomones* (interspecies attractants).

3. *A separate target organ.* Some parahormones, once secreted, not only diffuse to surrounding cells but also stimulate the cells originally synthesizing them. This positive feedback is referred to as *autocrine* function, and it results in the synthesizing cell becoming its own target organ. Furthermore, bacteria make several regulatory molecules for internal use. These signal molecules, called *alarmones,* are usually modified nucleotides and are produced in response to a particular stress such as starvation or a vitamin deficiency.

Because of these limitations, a broader definition is used in this book: a *hormone* is a chemical, nonnutrient, intercellular messenger that is effective at micromolar concentrations or less. In other words, hormones are chemical substances that carry information between two or more cells. This definition includes all of the preceding examples except the alarmones. This exclusion is clearly the bias of mine, but the essence of endocrinology is the chemical coordination of bodily functions, and alarmones are used exclusively with single cells. However, other bacterial hormones that signal sporulation, competence (ability to take up exogenous DNA), conjugation, and other activities that are coordinated among individual bacteria are included. The restriction of hormones to chemical substances seems initially to be a logical one, even though species such as fireflies can use light to induce behavioral patterns in others. However, because the visual pigment rhodopsin and the G protein-coupled receptors (GPCRs) are homolo-

gous, one could also argue that, under certain circumstances, light is a hormone. Finally, metabolic pathways can be induced or repressed by substrate levels; indeed, substrate flow is an important regulator in many systems. Therefore nutrients are also excluded in the hormone definition. The inclusion of the concentration clause is used to eliminate other miscellaneous inducers; the one thing that sets hormones apart from other chemical regulators is their effectiveness at extremely low concentrations, usually in the nanomolar range or below. Plant hormones are unusual in that a few are required in larger amounts; it is for that reason that the micromolar limit is used.

The importance of endocrine regulation is apparent from the examination of the genomes of those organisms for which a complete sequence is available. For example, the genome of the nematode *Caenorhabditis elegans* contains about 20,000 genes. The single most abundant group, at 3.5% of the total, is the group of genes for GPCRs, which are receptors for hormones and other small molecules. The second most abundant group, at 2.6%, is the group of protein kinases, which are integral components of many signaling pathways. Finally, the third most abundant group, at 1.4%, is a transcription factor class that includes the nuclear receptors for steroids and other hydrophobic hormones. In metazoans, cellular communication and coordination are essential for successful development and survival, and their significance is reflected in the proportion of the genome allotted for endocrine functions.

The study of hormone action at the cellular and molecular level is called *molecular endocrinology,* which is the subject of this treatise. In particular, this book concentrates on the molecular mechanisms of hormone action and interaction. However, the topic of hormonal synergism and antagonism at the molecular level is better understood against a background knowledge of hormone action in the whole organism; for example, the progesterone inhibition of prolactin receptors and second messengers in the mammary gland is just an isolated fact unless one knows the general function of these hormones in the reproductive cycle. Therefore the function of this unit is to provide the reader, in general, and the novice, in particular, with sufficient background information to appreciate the molecular interrelationships that are discussed in later units. It is obvious that a complete presentation of general endocrinology cannot be accomplished in only three chapters: the coverage is specifically oriented and just sufficient to prepare the reader for the remainder of the book. However, it is hoped that the reader will become interested enough to consult any of the excellent and far more comprehensive texts listed in the General References section at the end of this chapter.

The rest of this chapter is concerned with identifying the basic characteristics of hormones and their regulation, and it concludes with an illustrative example, the hormonal control of calcium metabolism. Then, in Chapter 2, the other classical endocrine systems are examined. Finally, Chapter 3 briefly covers nonclassical and nonvertebrate hormones, such as growth factors, parahormones, and the hormones of plants and insects.

Hormone-Target Relationships

As noted previously, the classic endocrine system involves a hormone being made in one part of the body and reaching its target in another part of the body through the bloodstream (Fig. 1-1, *A*). However, there are many other types of interactions that can occur. In a paracrine system, the hormone remains in the

tissue, where it reaches nearby cells by diffusion (Fig. 1-1, *B*). The *juxtacrine* system represents another mechanism for limiting the diffusion of hormones. In this case, the hormone is synthesized as a membrane-bound precursor. Although this precursor is usually cleaved to yield a soluble peptide, it may also remain attached to the plasma membrane, where it retains its biological activity. Therefore its effects are limited to the length of its tether (Fig. 1-1, *C*). Hormones that may act in this fashion include the epidermal growth factor, transforming growth factor α, tumor necrosis factor α, colony-stimulating factor 1, and the Kit ligand (see Chapter 3). In some cases, the intracellular domain of the hormone anchor is coupled to second messengers so that receptor engagement generates signals in both cells (Fig. 1-1, *D*). The ephrins are examples of this *bilateral* or *reverse signaling*. Finally, juxtacrine signaling may also include hormones whose diffusion is limited by the fact that they are tightly bound to the extracellular matrix.

The hormone may even influence the cell that originally secreted it; this is often part of either a negative or positive feedback loop (Fig. 1-1, *E*). This is called an *autocrine* system. The *intracrine* system was originally defined as one where hormone synthesis and receptor binding occurs intracellularly; a possible example would be the nuclear receptors for various lipid intermediates. For example, the liver X receptor binds cholesterol-like sterols, whose synthesis it regulates. Normally, this would not be considered a hormone system by this text, but there are three variations of the definition that would qualify: the endogenous generation of hormones from precursors synthesized elsewhere by (1) executing the final synthetic steps, (2) hydrolyzing hormones inactivated by conjugation, or (3) cleaving the hormone from its protein precursor (Fig. 1-1, *F*). The thyroid

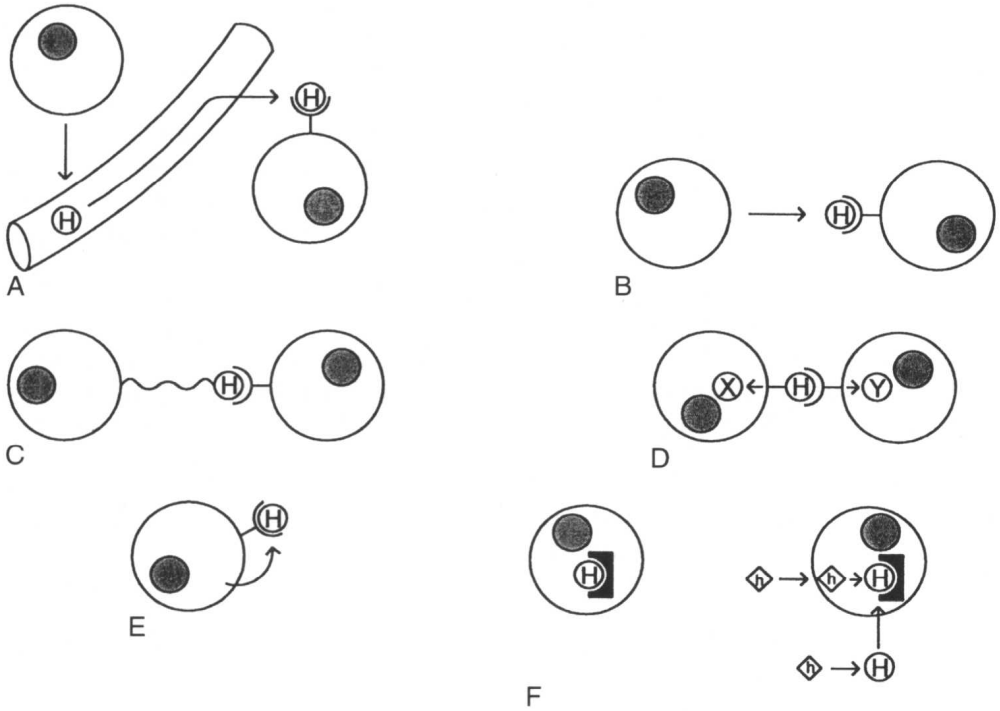

Fig. 1-1. Hormone-target relationships. (A) Classical endocrine; (B) paracrine; (C) juxtacrine; (D) juxtacrine with bilateral signaling; (E) autocrine; (F) intracrine; (G) transsignaling; (H) cryptocrine; and (I) neurocrine. *H*, Hormone; *encircled H*, active hormone; *h within a diamond*, prohormone; *X and Y*, second messengers.

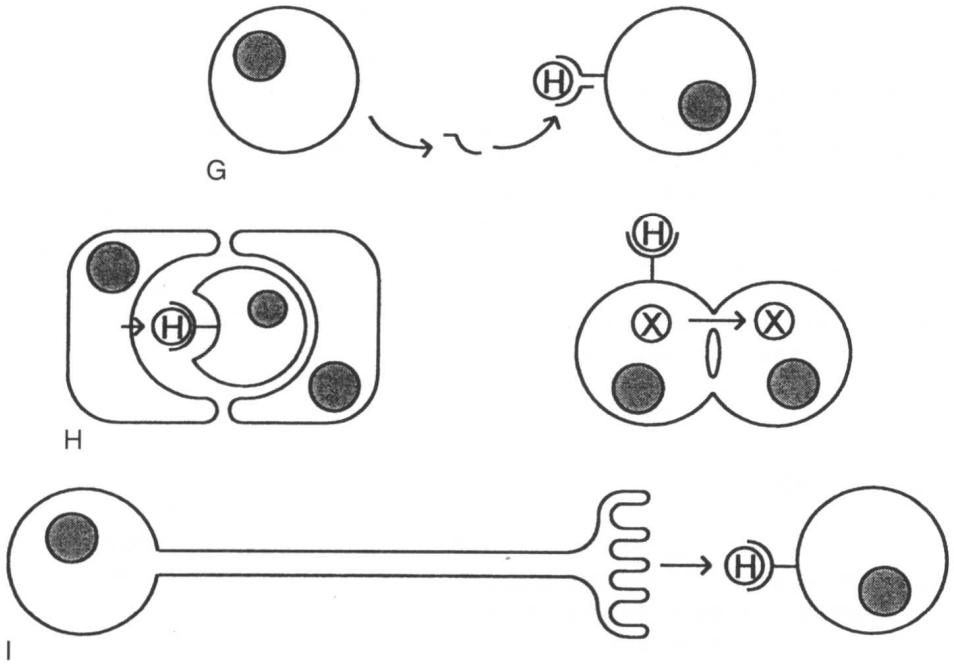

Fig. 1-1 *(continued)*

hormones represent an example of the first variation: the thyroid gland secretes predominantly thyroxine; this compound is converted to the active form, triiodothyronine, by peripheral enzymes. The sex steroids represent another example; 40% of all androgens in males and 75% to 100% of estrogens in postmenopausal females are generated in target tissues from adrenal precursors. This generation is accomplished by 5α-reductase and aromatase, respectively. Steroids can also be produced locally by steroid sulfatases: many steroids are inactivated by sulfation, and some peripheral tissues, like the breast, reactivate these steroids by deconjugating them. Finally, certain peptide hormones, such as the hepatocyte growth factor and the transforming growth factor β, are secreted as inactivate precursors that are cleaved locally to generate the activate hormone. These enzymes allow the tissue to adjust the hormone levels to local conditions.

Transsignaling is a process by which one cell supplies the high specificity, high affinity receptor subunit to another cell, which has the core receptor subunits. For example, many cytokine receptors have multiple subunits, some of which may be cleaved to produce soluble proteins. The receptor for interleukin 6 (IL-6) consists of two membrane-bound receptors, a 130 kDa glycoprotein (gp130) and IL-6R. IL-6 and gp130 are constitutively synthesized, but the affinity between IL-6 and gp130 is too low to generate a signal. During inflammation, defense cells invade the tissue and shed IL-6R, which then combines with gp130 to form the active receptor (Fig. 1-1, *G*). Essentially, the soluble receptor is analogous to a parahormone. A variation of this process is seen in monocytes, which constitutively produce IL-15. IL-15 is not secreted but remains tightly bound to its high affinity subunit, IL-15Rα. This pair is presented to target cells that only possess the other two components of the receptor complex, IL-2Rβ and γ_c. In this example, the IL-15Rα subunit acts like a juxtacrine hormone. A similar phenomenon is observed in the IL-12 family, except that the ligand and constitutively bound receptor α subunit are soluble.

All of the systems discussed thus far are open; that is, there are no diffusion barriers, and selectivity of target cells is determined by the presence or absence of receptors to that hormone. In contrast, a *cryptocrine* system involves the secretion of a hormone into a closed environment. This system obviously requires a very special intimacy between cells, such as that between Sertoli's cells and spermatids or thymic nurse cells and T lymphocytes (Fig. 1-1, *H*). Another example of this phenomenon is the transfer of second messengers, such as cyclic nucleotides or inositol trisphosphates, through gap junctions between adjacent cells. Finally, the *neurocrine* system is the secretion of chemical messengers by neurons (Fig. 1-1, *I*). However, some authorities consider the synapse to be a restricted environment and neurotransmission to be a variation of cryptocrine signaling.

Chemical Nature

Structurally, hormones are extremely diverse (Fig. 1-2). The most abundant and most versatile of these are the peptide and protein hormones, which range in size from a simple tripeptide (thyrotropin-releasing hormone) to 198 amino acids (prolactin). Some protein hormones, such as human chorionic gonadotropin, are even larger because of multiple subunits and glycosylation. In addition to full proteins, individual amino acids have been modified to yield hormones; the most common amino acid precursors are tyrosine (the catecholamines and thyroid hormones), histidine (histamine), and tryptophan (serotonin and indoleacetic acid).

The lipids are another rich source of hormones. The steroids form an entire group by themselves. Fatty acid derivatives include the prostaglandins and related compounds; some insect pheromones are also synthesized from fatty acids. Finally, the structure of platelet activating factor is similar to that of phosphatidylcholine.

The nucleotides would seem to be an unusual source, but they too are well represented: some pheromones, the cytokinins (plant hormones), 1-methyladenine (a starfish hormone), and cyclic AMP (cAMP) (in slime molds). In addition, several purine derivatives act as parahormones in mammals.

Oligosaccharide hormones were first characterized in plants, where they are produced from the breakdown of the plant cell wall in response to certain plant infections. These elicitors then trigger a defense response within the plant cell. Carbohydrate hormones have now been postulated to occur in animals: the aggregation factor of sponges is a glycan, one of the mediators of insulin action appears to be an oligosaccharide (see Chapter 11), and β-glucan and pectin can act as secretagogues (secretion stimulators) in vertebrates. In the latter case, the physiological relevance is still uncertain.

Finally, even gases are represented. Ethylene ripens fruit in plants, and nitric oxide is a potent vasodilator in mammals. Carbon monoxide and hydrogen sulfide have also been proposed as physiological gaseous hormones; both are vasodilators.

Although the structural diversity of hormones is great, there is one property that is particularly important: water solubility (Table 1-1). Hydrophobic hormones are difficult to store because they pass through membranes so easily; as a result, they are synthesized as they are needed. The thyroid hormones are an exception and are discussed further in Chapter 2. Hydrophobic hormones do not