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内分泌与生殖系统 第二版

Endocrine & Reproductive Systems

SECOND EDITION

Sanders, Debuse 著

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Series editor
Daniel Horton-Szar
BSc (Hons), MB BS (Hons)
GP Registrar
Northgate Medical Practice
Canterbury
Kent

Faculty advisor
Dr Susan Whiten
MA PhD
Senior Lecturer
School of Medicine
University of St Andrews
Fife

Endocrine and Reproductive Systems

SECOND EDITION

Stephan Sanders
BMedSci (Hons)
Nottingham Medical School
University of Nottingham

First Edition Author
Madeleine Debuse

Mosby

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Preface

Without the endocrine system the world would be populated by very short and infertile people with an incredibly low life expectancy. It is clearly an advantage to have such a system, although this can be forgotten when you need to learn how it works. It is easy to get bogged down by the details of individual hormones whilst forgetting how subtly they work together to regulate so many vital processes.

This book aims to present the endocrine and reproductive systems in a clear and concise manner. It focuses on information that is useful in clinical medicine and also on subjects that frequently come up in examinations.

The first page of each chapter that deals with a hormone system contains a summary of the important points, including a diagram of how that hormone system works. I hope these will act as a quick revision tool for those vital moments of panic knowledge acquisition before an exam.

It is important to note that this book will not teach you to spell the word 'epididymis'. If you find that you can spell this word you may want to investigate a career outside of medicine.

'Hic sunt dracones.'

Stephan Sanders

Nowadays, instead of thinking of yourself as a medical student, you may be encouraged to consider yourself as a 'doctor in training', entering a professional environment from the very first days of your Medical School education. You are certainly entering a profession that will change beyond our recognition within your professional lifetime. Medicine continues to be an enormous challenge: that is why it is so fascinating and why it can bring such enormous satisfaction.

You probably have impossibly high expectations of becoming a brilliant, empathetic clinician, happily juggling a sophisticated social life with your research and teaching responsibilities. The reality is that there is scarcely time to be successful in even one of these areas! Modern evidence-based medical practice depends on advancing scientific knowledge, but we all have to compromise between breadth and depth of knowledge in any field. Medical educators in all disciplines are struggling to define 'core' knowledge in order to rationalize the medical curriculum. Core knowledge is the body of information that forms the basis for understanding both wider issues and future developments. The philosophy of the Crash Course books is based on the fact that successful students have a very good idea of what that core is. They are close to the information, quick to see the difficult areas that require explanation, and bring a lively approach to the subject.

You will find a wealth of well-organized information in this book, reviewed in a way that will facilitate your understanding. I particularly recommend that you use the self-assessment section: it is a very powerful means of learning. I wish you every success in your study of Endocrinology and in your chosen profession.

Dr Susan Whiten
Faculty Advisor

In the six years since the First Editions were published, there have been many changes in medicine, and in the way it is taught. These Second Editions have been largely rewritten to take these changes into account, and keep Crash Course up to date for the twenty-first century. New material has been added to include recent research and all pharmacological and disease management information has been updated in line with current best practice. We have listened to feedback from hundreds of students who have been using Crash Course and have improved the structure and layout of the books accordingly: pathology material has been closely integrated with the relevant basic medical science; there are more multiple-choice questions and the clarity of text and figures is better than ever.

The principles on which we developed the series remain the same, however. Medicine is a huge subject, and the last thing a student needs when exams are looming is to waste time assembling information from different sources, and wading through pages of irrelevant detail. As before, Crash Course brings you all the information you need, in compact, manageable volumes that integrate basic medical science with clinical practice. We still tread the fine line between producing clear, concise text and providing enough detail for those aiming at distinction. The series is still written by medical students with recent exam experience, and checked for accuracy by senior faculty members from across the UK.

I wish you the best of luck in your future careers!

Dr Dan Horton-Szar
Series Editor (Basic Medical Sciences)

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On a more personal level, my thanks to: Steve Holden, Phil Webster and Doug Forrester for their friendship and for making life entertaining, Peter and Deborah Sanders for their support and DNA and Piers Sanders for being that little bit less tough than me (officially true now—it's a published fact). Finally, thank you to Imogen Hart for being the most amazing person I have ever met and her revelations in geography.

Figure acknowledgements

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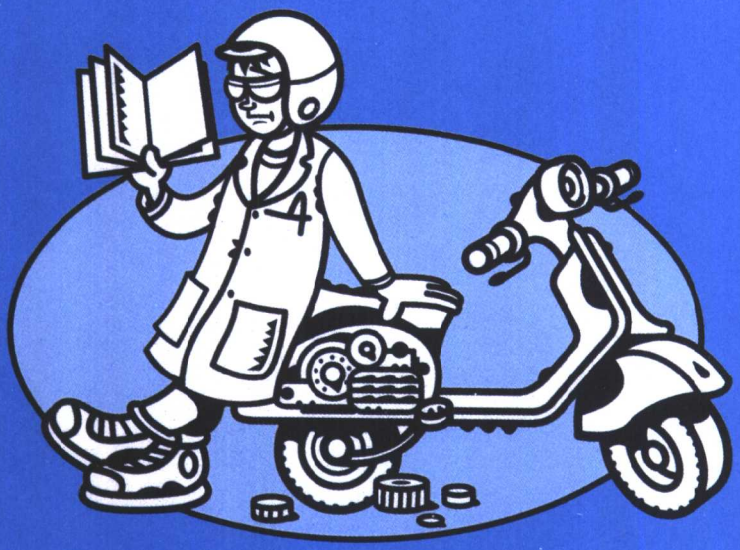
Contents



ENDOCRINOLOGY

1. Overview of the Endocrine System

The role of the endocrine system

The endocrine system allows cells to communicate using chemical messengers called hormones. This communication is essential for the maintenance of homeostasis (Greek for 'staying the same'). Homeostasis is an ongoing process that minimizes change from the ideal physiological conditions, creating a suitable environment for life. As a result, hormones are important components of all major body systems; you cannot escape them.

The endocrine system also regulates long-term changes in the body, including:

- Growth.
- Sexual development.
- Pregnancy.

After reading this chapter you should be able to:

- Explain what is meant by the term 'hormone'.
- Picture the general organization of the endocrine system.
- Understand how hormone secretion is controlled.
- Describe the synthesis of the main types of hormones.
- Understand how these hormones act through their cellular receptors.
- Discuss the integration and role of the endocrine and nervous systems.

Important words:
Hormone: A chemical signal transported in the blood that is secreted by endocrine cells
Endocrine tissue: A group of cells that secrete hormones
Target cell: A cell that responds to a specific hormone
Receptor: A protein in target cells that detects hormones
Second messenger: A chemical that transmits the hormone message from the receptor to the effector
Effector: A protein regulated by a hormone that brings about the cellular effects

Hormones and endocrine secretion

Hormones

Classical definition

Classically a hormone is described as a chemical substance that is secreted by specialized endocrine cells directly into the blood to exert an effect on distant target cells. This process is endocrine secretion.

The word 'endocrine' means 'internal secretion' while 'hormone' is derived from the Greek verb '*hormao*' meaning 'I excite'.

Modern definition

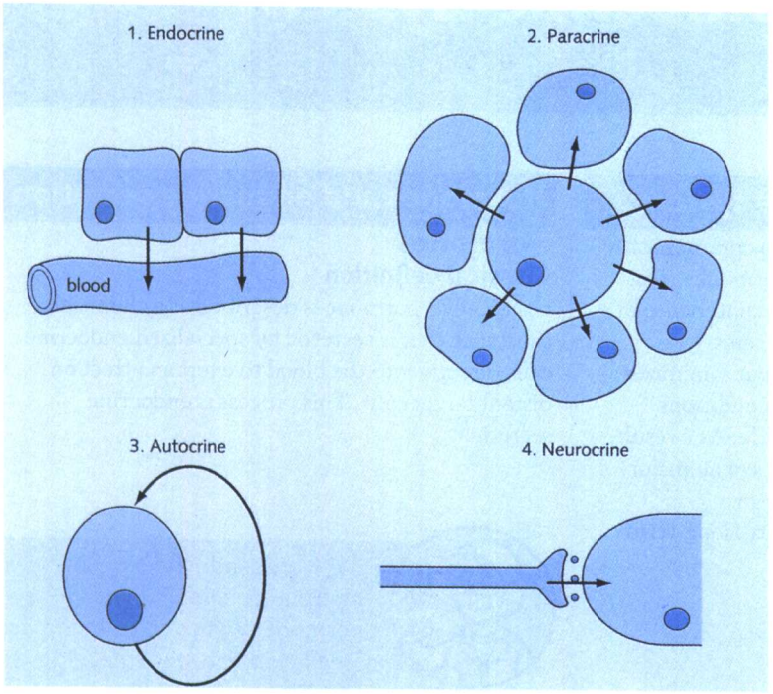
Recent research has revealed many locally acting chemical substances that have challenged the classical definition of hormones. Four modes of delivery are recognized (Fig. 1.1). They are:

- Endocrine—chemicals that act on distant cells via the blood stream, e.g. thyroxine.
- Paracrine—chemicals that act on the surrounding cells without entering the blood, e.g. gut hormones.
- Autocrine—chemicals that act on the cell they are secreted from, e.g. nitric oxide.
- Neurocrine—signals between neurons, e.g. neurotransmitters.

Different textbooks suggest different explanations of the term 'hormone' ranging from the classical definition to a definition that encompasses all chemical signals external to cells. If clinicians talk about hormones, they generally mean chemical signals that pass through the blood (endocrine delivery).

Types of hormone

Three classes of hormone are secreted into the blood; the characteristics of these are explained later in the chapter:



- Polypeptides (also called proteins).
- Steroids.
- Modified amino acids.

Endocrine tissues

Definition

An endocrine tissue is simply one that secretes a hormone. These tissues respond to signals that either stimulate or inhibit the release of the specific hormone.

Arrangement of endocrine tissues

Endocrine tissues contain cells that secrete hormones; these cells can be arranged in three patterns:

- As an endocrine organ devoted to hormone synthesis, e.g. the thyroid gland.
- As clusters of cells within an organ, e.g. the islets of Langerhans in the pancreas.
- Individual cells scattered diffusely throughout an organ, e.g. the gastrointestinal (GI) tract.

Endocrine organs

The term 'endocrine organ' originally referred to organs in which specialized endocrine cells formed a significant component. These 'traditional' endocrine organs are shown in Fig. 1.2 along with the hormone they secrete.

However, we now know that almost all organs contain some endocrine tissue, for example:

- Adipose tissue, secretes leptin.
- Lungs, secrete 5-hydroxytryptamine (5-HT; serotonin).
- Heart, secretes atrial natriuretic factor (ANF).

Organization of the endocrine system

The regulation and control of many major hormones follows a similar pattern that starts in the brain and ends with a hormone being secreted. Understanding this pattern is the key to understanding how the endocrine system works. There are three steps, each of which involves the secretion of a hormone that stimulates the next step (Fig. 1.3). The control of hormones released by the thyroid gland will be used to illustrate this pathway throughout.

The main components

Hypothalamus

The endocrine system is coordinated by the hypothalamus. This is a part of the brain that acts as a bridge between the nervous system and endocrine system, translating neural messages into chemical (hormonal) signals. It initiates the secretion of

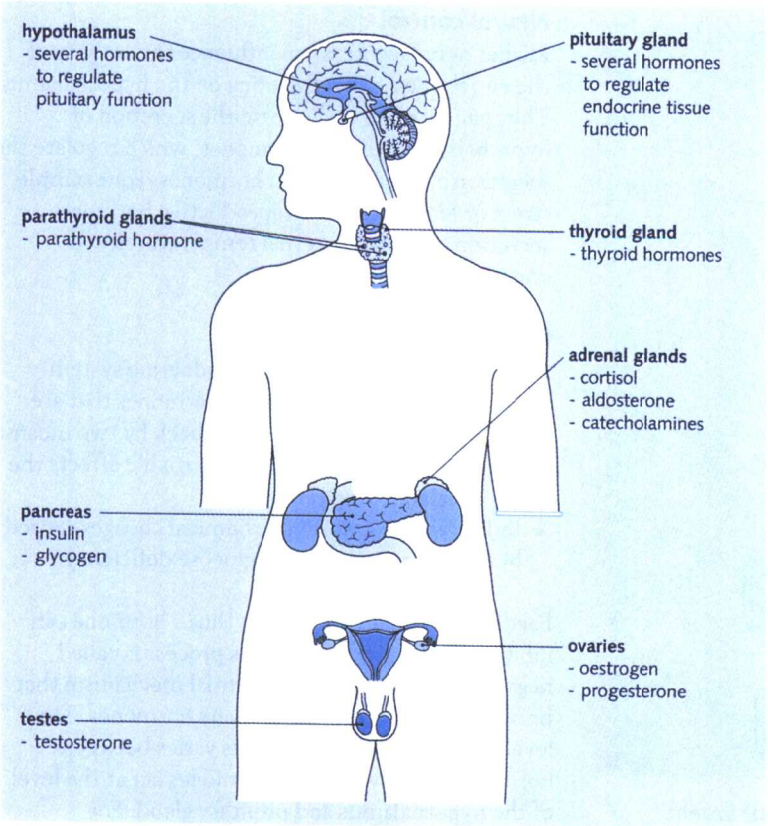


Fig. 1.2 The location of major endocrine organs and the hormones secreted by them.

Endocrinology is a relatively new medical science. The first hormone was only demonstrated in 1902, and the connection between the endocrine and nervous systems through the hypothalamus was not found until halfway through the 20th century.

hormones by controlling the function of the pituitary gland via 'releasing hormones'. These hormones do not act directly on peripheral endocrine tissues. Hormones secreted from the hypothalamus are released in pulsatile manner often with a circadian rhythm (regular changes through a 24 h cycle). Thyrotrophin-releasing hormone (TRH) is secreted into the blood by the hypothalamus; this initiates the hormone cascade resulting in the release of thyroid hormones.

Pituitary gland

The pituitary gland is found at the base of the brain beneath the hypothalamus. It releases hormones into the blood in response to signals from the hypothalamus. The hormones from the pituitary gland regulate the function of peripheral endocrine tissues throughout the body. TRH from the hypothalamus acts on the pituitary gland to cause the release of thyroid stimulating hormone (TSH) into the blood stream.

Peripheral endocrine tissues

The hormones secreted by the pituitary gland act on peripheral endocrine tissues. These tissues respond by increasing or decreasing secretion of specific hormones into the blood. It is the hormones secreted by these peripheral tissues that affect the state of the body by acting on target cells. TSH from the pituitary gland stimulates the thyroid gland to release thyroid hormones into the blood.

Target cells

Different hormones act on different, specific cells. The cells that respond to a specific hormone are called its target cells; they can be found anywhere in

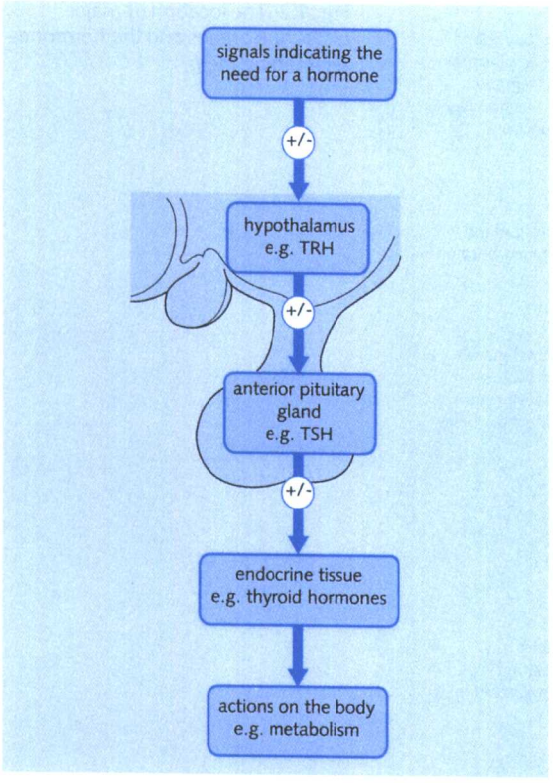


Fig. 1.3 The organization of the endocrine system.

the body. All target cells have receptors to detect the specific hormone, but the effect of the hormone can vary between cells. Thyroid hormones from the thyroid gland act on almost every cell in the body to increase the rate of metabolism through receptors on the cell surface.

Control of hormone secretion

Overall control

Endocrine tissues are regulated by signals from a variety of neural and systemic sources. These signals are processed by cells to determine the rate of hormone secretion. The strength and importance of the signals varies so that hormone secretion fits the needs of the body.

Hormone secretion rates can vary by the minute, hour, day, month, and stage of life.

Neural control

Higher neural centres can influence the activity of the endocrine system by acting on the hypothalamus. They can increase or decrease the secretion of hypothalamic releasing hormones, which regulate the secretion of pituitary gland hormones. For example, stress or fear will inhibit reproductive hormone secretion, and cold external temperatures will stimulate TRH.

Hormonal feedback

An almost universal feature of endocrine system regulation is feedback from the hormones that are released. The hormones can feed back by two means:

- Directly—e.g. the hormone thyroxine affects the hypothalamus and pituitary.
- Indirectly—e.g. through chemical changes caused by the hormones, such as glucose deficiency.

Feedback is usually inhibitory, thus a hormone can inhibit its own production; this process is called negative feedback. It is an essential mechanism that prevents excess secretion of many hormones. The level at which the feedback acts varies between hormones, however, many hormones act at the level of the hypothalamus and pituitary gland. For example, thyroid hormones feed back to the anterior pituitary where they inhibit the release of TSH (Fig. 1.4).

Why is it so complex?

At first glance the endocrine system seems incredibly complex for no obvious reason. Many students wish that the system had fewer hormones and organs, but there are a number of advantages.

Amplification

As described, endocrine signals begin in the hypothalamus and result in a cascade of hormones

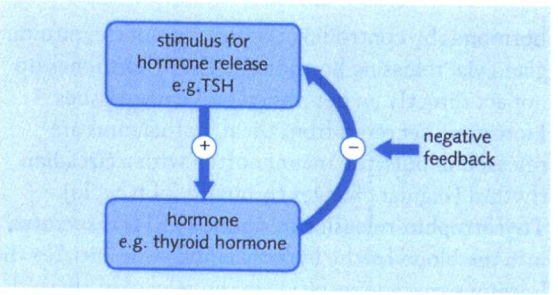


Fig. 1.4 Negative feedback.

from different endocrine glands. There is only a small population of cells in the hypothalamus that secrete each hormone; for example, about 2000 neurons secrete gonadotrophin releasing hormone (GnRH). Because of the small number of cells involved, they are able to respond to important but small neural signals, but they cannot secrete large amounts of hormone.

The very small quantities of hormone secreted directly into the blood stream by the hypothalamus can be detected by the closely related pituitary gland. This gland is able to secrete a greater quantity of hormone than the hypothalamus, but it is still too small to secrete enough for the whole body.

In response to hormones from the pituitary gland the peripheral endocrine tissues secrete hormones in large quantities that can act throughout the body. In this manner the signal of a small number of neurons in the hypothalamus is amplified in three stages to affect the entire body.

Control

The endocrine system regulates all major body processes that are essential for life including:

- Metabolic rate.
- Nutrient levels.
- Cardiac output and blood pressure.
- Reproduction.

Since they are so important, these processes must be controlled very tightly. The complex interactions of the endocrine system allow for many sites of control in order to prevent excessive or deficient hormone release, and to maintain homeostasis.

Hormone types and secretion

This section describes the properties and synthesis of the three classes of hormone (Fig. 1.5).

Polypeptide hormones

As their name suggests, polypeptide hormones are proteins that act as hormones. The size of the polypeptide varies widely from 3 to 200 amino acid residues; they cannot pass through cell membranes due to their size and water-soluble nature. Protein hormones are the most numerous type (often a safe bet in an exam). Accordingly they are secreted by many glands, including:

- Hypothalamus—TRH, GnRH, growth hormone releasing hormone (GHRH), etc.
- Pituitary—TSH, follicle stimulating hormone (FSH), luteinizing hormone (LH), oxytocin, etc.
- Pancreas and GI tract—insulin, glucagon, cholecystokinin (CCK), etc.

Synthesis

Polypeptide hormones are synthesized in the same manner as any other protein. DNA in the nucleus is transcribed to mRNA and translated into the protein by ribosomes. The protein is then processed by the Golgi apparatus and stored in secretory granules. Many hormones undergo changes in the Golgi apparatus or secretory granules including:

- Cleavage reactions to free a smaller polypeptide hormone from the larger prohormone.
- Addition of carbohydrate groups to form glycoproteins.

Comparison of different types of hormone

	Polypeptides	Modified amino acids	Steroids
Size	Medium–large	Very small	Small
Ability to cross cell membrane	×	✓	✓
Receptor type	Cell-surface	Cell-surface or intracellular	Intracellular
Soluble in:	Water	Water	Fat
Action	Protein activation	Protein activation or synthesis	Protein synthesis
Transport in the blood	Dissolved in the plasma	Dissolved in the plasma or bound to plasma proteins	Bound to plasma proteins

Fig. 1.5 Comparison of the different types of hormone.

Secretion

The secretory granules are released by exocytosis, in which the membrane of the granule fuses with the membrane of the cell causing the contents to be ejected. This process is triggered by calcium entering the cell. Polypeptide hormone release is controlled mainly by regulating secretion rather than synthesis.

Polypeptide secreting cells

Polypeptide secreting cells all have a similar histological appearance (Fig. 1.6):

- Large, prominent nuclei.
- Small amount of cytoplasm.
- Prominent Golgi apparatus.
- Abundant rough endoplasmic reticulum (RER).
- Large numbers of secretory granules.
- Surrounded by fenestrated blood sinusoids.

Steroid hormones

Steroids are small, fat-soluble molecules that can pass through cell membranes but must circulate bound to plasma proteins since they are insoluble in the blood. They are secreted by:

- Adrenal cortex—cortisol and aldosterone.
- Ovaries—oestrogen and progesterone.
- Placenta—oestrogen and progesterone.
- Testes—testosterone.

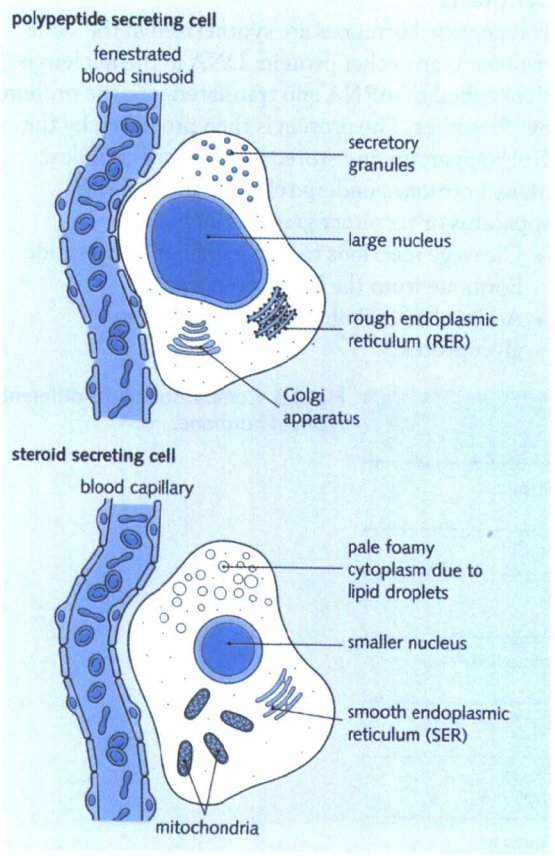


Fig. 1.6 Appearance of a polypeptide secreting cell and steroid secreting cell.

Synthesis

Steroids are derived from cholesterol by a series of reactions in the mitochondria and smooth endoplasmic reticulum (SER). Cholesterol is acquired from the diet or synthesized within the cells; it is stored within lipid droplets seen in the cytoplasm of steroid cells. All steroids have the same basic structure formed by four rings of carbon (Fig. 1.7), but individual hormones differ in the following ways:

- Side chains attached to these rings.
- Bonds within the rings (double or single).

The exact sequence of reactions to synthesize each hormone varies, since there are many different enzyme pathways. However, the vast majority of steroid hormones share two common steps.

Step 1

Cholesterol is converted into pregnenolone by the desmolase enzyme found within the mitochondria of steroid-producing cells. Desmolase removes six carbon atoms from the cholesterol side chain of ring D. This reaction is the rate-limiting step in steroid synthesis.

Step 2

Pregnenolone is converted to progesterone by enzymes found in the mitochondria and cytoplasm. This reaction involves:

- Isomerization—the double bond moves from ring B to ring A.
- Oxidation—the hydroxyl group (OH) of ring A becomes a keto group (O).

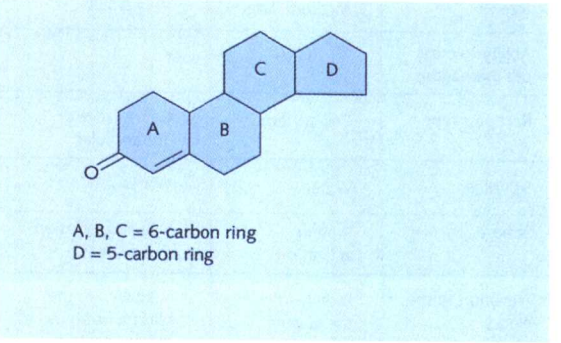


Fig. 1.7 Basic structure of a steroid hormone.

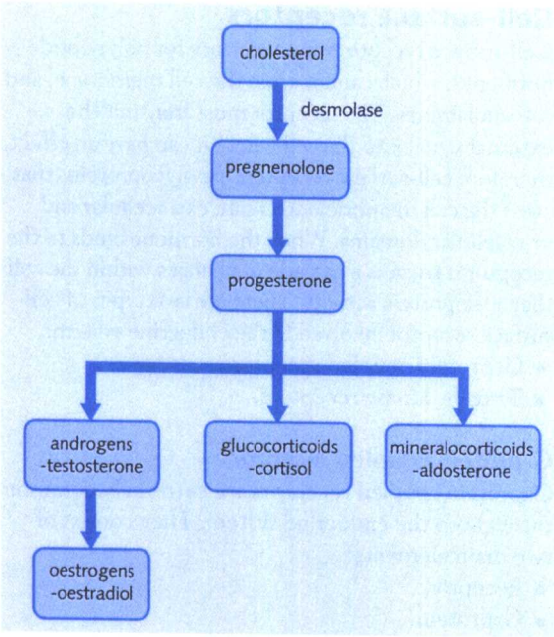


Fig. 1.8 Steroid synthesis. The initial stages are the same for all steroid hormones.

Further steps are very variable but the general pattern is shown in Fig. 1.8.

Secretion

The steroid hormone is released immediately so the rate of release is determined by the rate of synthesis, especially the synthesis of pregnenolone.

Steroid secreting cells

Steroid secreting cells also have a similar histological appearance to each other (see Fig. 1.6):

- Small, rounded nuclei.
- Large amount of cytoplasm.
- Large numbers of lipid droplets (foamy appearance).
- Abundant SER.
- Many mitochondria.
- Surrounded by blood capillaries.

Modified amino acids

Several hormones are formed by altering the structure of amino acids, producing small, water-soluble hormones that can cross cell membranes. They are secreted by the:

- Thyroid gland—thyroid hormones.
- Adrenal medulla—catecholamines (noradrenaline and adrenaline).
- Hypothalamus—dopamine.
- Pineal gland—melatonin.

Synthesis

These hormones are synthesized from two amino acids:

- Tyrosine—precursor of thyroid hormones, dopamine, and catecholamines.
- Tryptophan—precursor of melatonin and 5-HT.

The reactions to modify these amino acids vary significantly between hormones so the synthesis is described in the individual chapters. The hormones are stored in secretory granules except thyroid hormones, which uniquely are stored in follicles.

Secretion

The granules are released by exocytosis in the same way as polypeptide hormones. The rate of release is regulated mainly by secretion.

Modified amino acid secreting cells

The cells that secrete modified amino acid hormones vary more than the cells secreting polypeptide or steroid hormones, however the following features are often found:

- Large nuclei.
- Many mitochondria.
- Abundant RER.
- Prominent Golgi apparatus.
- Large numbers of secretory granules.
- Surrounded by blood capillaries.

A single hormone may have multiple actions, equally multiple hormones may have the same action. This is demonstrated by insulin and the regulation of blood glucose respectively.

The perineum

Eicosanoids

Although eicosanoids are not always considered as hormones and they do not form one of the main classes of hormones, they are important in many physiological processes. They are, therefore, included in most endocrine courses. They are small,

lipid-soluble molecules that act in a paracrine (local) manner. They are derived from a phospholipid found in the cell membrane called arachidonic acid which is broken down by the enzyme phospholipase A_2. There are two pathways, which synthesize different groups of eicosanoids:

- Cyclooxygenase pathway—forms prostaglandins and thromboxanes.
- Lipoxygenase pathway—forms leukotrienes.

Eicosanoids are released immediately and readily cross cell membranes. Their action varies between cells and the specific eicosanoid molecule that is formed.

Aspirin and NSAIDs produce their anti-inflammatory action by blocking the cyclooxygenase pathway to prevent prostaglandin synthesis.

Hormone receptors

Target cells possess unique receptors that bind specific hormones; without these receptors the hormones can have no effect. The number of receptors per cell can be increased or decreased to alter the strength of the hormone's effect. Receptors are found in two locations:

- Cell-surface receptors—for polypeptides and catecholamines; they activate or inhibit enzymes, which may affect protein synthesis.
- Intracellular receptors—for steroids and thyroid hormones; they stimulate or inhibit protein synthesis directly.

The response to a hormone varies between target cells so that the same hormone can have different actions on different tissues. This variation is partly due to different receptor types but also the response to receptor stimulation.

Hormones that act via cell-surface receptors can respond faster than those stimulating intracellular receptors because the activation of pre-existing enzymes takes less time than synthesizing new proteins. This explains why catecholamines released for the 'fight-or-flight' response use cell-surface receptors even though they can cross cell membranes.

Cell-surface receptors

Cell-surface receptors are necessary for polypeptide hormones, which cannot cross the cell membrane, and catecholamines. The receptor must transmit the external signal into the cell where it can have an effect, therefore cell-surface receptors are glycoproteins that cross the cell membrane to create extracellular and intracellular domains. When the hormone binds to the receptor it triggers a cascade of changes within the cell that alter protein activity. There are two types of cell-surface receptor involved in the endocrine system:

- G-protein coupled receptors.
- Tyrosine kinase receptors.

G-protein coupled receptors

G-protein coupled receptors are extremely common throughout the endocrine system. They consist of two main elements:

- Receptor.
- G-protein.

The receptor is a glycoprotein with a hormone binding site on the extracellular surface and a G-protein binding site on the intracellular surface. When the hormone binds the receptor changes shape affecting the attached G-protein.

The G-protein is an enzyme that can break down guanosine triphosphate (GTP), hence the name. It is made of two functional subunits:

- α-subunit—bound to guanosine diphosphate (GDP) in the resting state.
- βγ-complex—bound to the α-subunit if GDP is present.

When the hormone binds, causing the receptor to change shape, the α-subunit exchanges the GDP for GTP. The G-protein splits into the two subunits described above, both of which leave the receptor and bind to effector proteins also found on the inside of the cell membrane.

These effector proteins often include the enzyme adenylate cyclase that synthesizes cyclic AMP (cAMP) from ATP. cAMP acts as a second messenger: a chemical signal that can enter the cell to activate or inhibit enzymes to bring about the effects of the hormone. The activated enzymes are often kinases, which add phosphate to other proteins, thereby activating them.

When the hormone signal stops, the α-subunit breaks down GTP into GDP and inorganic phosphate. The βγ-complex rejoins the α-subunit to form the G-protein, and this once again binds to the