ESSENTIALS OF ENDOCRINOLOGY

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Preface

This book is intended for those beginning to study endocrinology. The authors approach the subject from their different viewpoints, morphological, physiological, biochemical, pharmacological and clinical, and the text brings together these diverse views. It is based on the teaching given during the second year of the Basic Medical Sciences Course at The Middlesex Hospital Medical School, and we hope that it will appeal to medical students and those taking a science degree.

The opening chapter describes the underlying principles of modern endocrinology, at cellular, biochemical and physiological levels. The ensuing chapters are based on single glands or functional groups of glands. No attempt has been made to impose a rigid format on these chapters as each system lends itself to a slightly different emphasis. In general however, in each chapter, the introduction is an outline of the history of the subject, to provide an inkling of the basic, long established principles. Then the morphological and embryological basis for function is presented, and this leads onto the biochemical and physiological aspects. Clinical disorders are then considered from the viewpoint of the insight they give to the understanding of endocrine-physiology. The link between basic endocrinology and clinical endocrinology is so close, that it seems very reasonable to do that, while attempting at the same time, to show that a knowledge of the scientific basis of endocrinology helps to explain the consequences of endocrine disease and the rationale of its treatment.

We would like to thank all those who contributed to this book. The authors have been very patient with us as we have brought together and edited the work of so many people and have striven to help the reader avoid the pitfalls of a multiauthor book. The authors can justly claim credit for the virtues of this book, while the editors must accept responsibility for any faults that may be detected. Apart from authors, there are many to whom we are indebted. Dr Howard Jacobs very kindly advised in the writing on the chapter on reproductive endocrinology and many useful comments and suggestions were received from Professors J. F. Tait FRS, F. Hobliger and E. Neil and Drs N. J. Marshall and P. Sanford on the chapters in their specialist fields. The many

secretaries who contributed to the typing of manuscripts for this book are also gratefully acknowledged.

We hope that this book will stimulate its readers in endocrinology and that they will see how the various endocrine glands form a closely regulated, integrated system that is essential for homeostasis.

February 1982

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P. G. Malan
R. P. Gould

Contents

1 The endocrine system and the molecular basis for hormone action

The endocrine system is one of the two great control systems of the body, the other being the nervous system. They are responsible for monitoring changes in an animal's internal and external environments and directing the body to make any necessary adjustments to its activities so that it adapts itself to these environmental changes. The nervous system mediates its activity through nerves directly supplying the organs and structures concerned, while the endocrine system operates through chemical messengers or hormones which circulate in the blood to their respective target organs and modify their activity. The term 'hormone' was introduced in 1905 by Starling and is derived from the Greek, meaning 'to arouse' or 'to excite', though it should be stressed that not all hormonal effects are stimulatory, some being inhibitory. The endocrine glands secrete hormones into the circulation and therefore differ from exocrine glands which secrete their products into ducts, rather than the circulation.

Unicellular organisms and simple multicellular organisms are exposed to their environment and react to it, but cannot control it or insulate themselves from it. In contrast, in higher organisms such as man (in whom there are about 10^{14} cells and 100 or more cell types), only relatively few cells are exposed to the outside world. Nevertheless, all the cells are affected directly or indirectly by external changes and can only survive if the constancy of their internal environment is controlled. For this, the endocrine system is important. It responds to recurrent environmental changes, such as meals, and helps the organism to adapt to changing habits. The endocrine system is also important for controlling development and growth, puberty and sexual maturation. Thus the secretion of hormones, apart from maintaining the body's internal environment, can also induce important long-term changes in an organism's behaviour.

In their original experiments in 1902, Bayliss and Starling studied the control of the exocrine secretion of the pancreas. They collected pancreatic secretion and showed that introduction of acid into a denervated segment of jejunum increased the production of alkaline pancreatic juice. Since this occurred after denervation, it could not be the result of a nerve reflex and they postulated that there must in fact be a chemical reflex. They then prepared extracts of intestinal mucosa and injected these intravenously and showed that these extracts could also stimulate pancreatic secretion and they gave the name 'secretin' to the active principle in these extracts.

With this experiment they introduced an important approach into the investigation of endocrine function, which was to study the effects of the injection of tissue extracts into the bloodstream. Another approach is to investigate the effects of removal of a

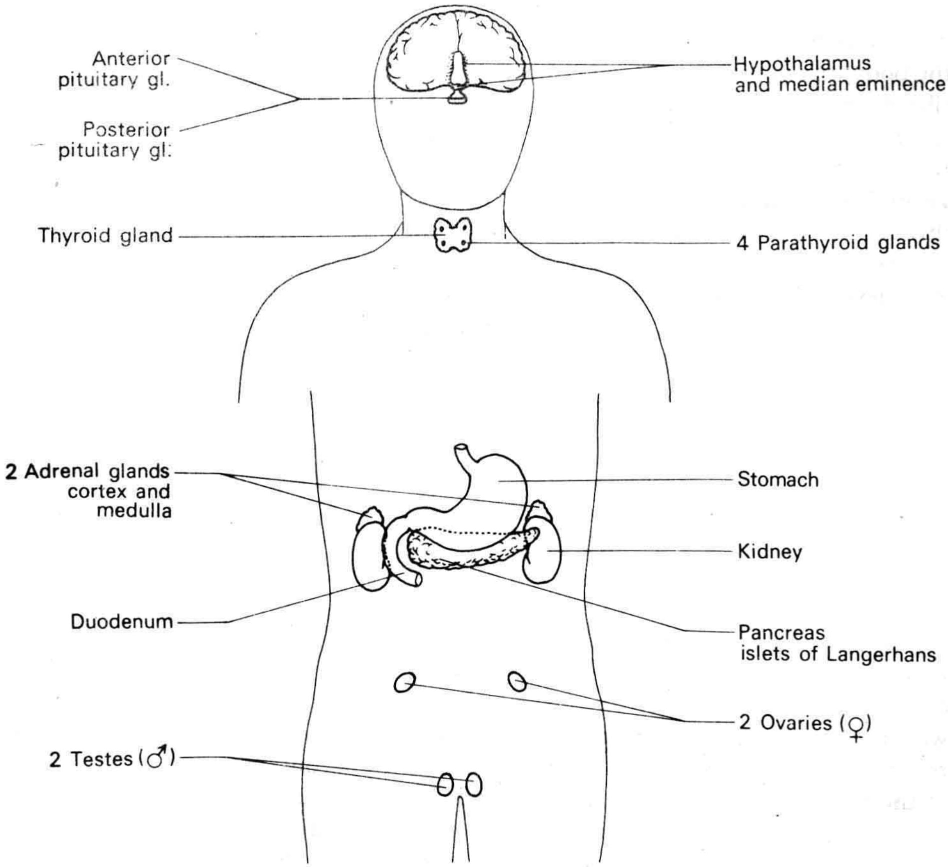

Fig. 1.1 The sites of the principal endocrine glands.

putative endocrine organ. Berthold used this in studying the effect of castration, and showed that the testes were necessary for the maintenance of male characteristics in the cock and eventually the hormone testosterone was isolated from the testes. It also follows that the disturbance produced by removal of an endocrine organ should be correctable by injection of extracts from the organ, for example, insulin extracted from the pancreas can control the diabetes mellitus that follows pancreatectomy. Transplantation or re-implantation of the endocrine gland should also correct the effects of deficiency.

Clinical studies also can be valuable in understanding the function of an endocrine gland since disease can cause overproduction or underproduction of hormones. Thus in 1500 BC the clinical features of diabetes mellitus were described and this was long before the isolation of insulin by Banting and Best in 1921. Similarly, the features of thyrotoxicosis were described and

Table 1.1 The principal endocrine glands of the body and the hormones they produce.

Gland	Hormone	Molecular characteristics
Hypothalamus/median eminence	*Releasing and inhibiting hormones:*	
	Thyroid releasing hormone	
	Somatostatin	Peptides
	Gonadotrophin releasing hormone	
	Corticotrophin releasing factor	
	Growth hormone releasing factor	?
	Prolactin inhibiting factor (Dopamine)	Biogenic amine
Anterior pituitary	Thyroid stimulating hormone	
	Luteinizing hormone	Glycoproteins
	Follicle stimulating hormone	
	Growth hormone	
	Prolactin	Proteins
	Adrenocorticotrophin	
Posterior pituitary	Vasopressin (antidiuretic hormone)	Peptides
	Oxytocin	
Thyroid	Thyroxine and triiodothyronine	Tyrosine derivative
	Calcitonin	Peptide
Parathyroid	Parathyroid hormone	Peptide
Adrenal cortex	Aldosterone and cortisol	Steroids
Medulla	Adrenaline and noradrenaline	Catecholamines
Stomach	Gastrin	Peptide
Pancreas (islets of Langerhans)	Insulin	
	Glucagon	Proteins
	Somastostatin	
Duodenum and jejunum	Secretin	Proteins
	Cholecystokinin	
Ovary	Oestrogens and progesterone	Steroids
Testis	Testosterone	Steroid

associated with disease of the thyroid gland in the 19th century before it was realized that there was overproduction of the thyroid hormones, thyroxine and triiodothyronine, which were only isolated many years later. Another example of the value of clinical observation was Addison's description of the effects of deficient secretion of the adrenal cortex; he associated the condition with disease of the adrenal glands long before the isolation of the adrenal hormones cortisol and aldosterone which are steroids secreted by the adrenal cortex. Another example of the usefulness of clinical studies in characterizing the role of a hormone concerns prolactin. Its importance in fertility was only recognized after it became possible to measure circulating prolactin, when it was then found that some cases of infertility were due to overproduction of prolactin. In other cases, of course, it has been understanding the physiology of a hormone which has led to the recognition of the effects of disordered secretion. Thus, in the case of aldosterone, the effects of overproduction were only recognized once the hormone had been isolated and then it was found that some cases of muscle weakness with potassium deficiency were due to overproduction of aldosterone.

THE EFFECTS OF HORMONES

Some hormones have a general importance in the body as a whole rather than acting on a specific target tissue. These include growth hormone, underproduction of which in children leads to dwarfism while overproduction causes gigantism. In adults overproduction of growth hormone causes acromegaly, with enlargement, for example, of the hands and feet and coarsening of the facial appearance. Thyroxine, too, acts on most tissues of the body, and if present in excess the basal metabolic rate increases, while if there is a deficiency of the hormone the metabolic rate declines. Insulin also acts on several tissues, including the liver, muscle and adipose tissue; this implies that receptors for the hormone are widespread.

In contrast, many other hormones only act on one tissue, for example, thyrotrophin, adrenocorticotrophin and the gonadotrophins are secreted by the anterior pituitary and have specific target tissues, namely, the thyroid gland, the adrenal cortex and the gonads, respectively. A further example of a hormone with specific target tissues is parathyroid hormone; this is secreted from the parathyroid glands which are located in the neck close to the thyroid gland and it controls the concentration of calcium in the circulation, acting particularly on bone and the kidney.

Types of hormones

From the chemical standpoint, there are three groups of hormones. Firstly, there are derivatives of the amino acid tyrosine; secondly, peptide and protein hormones and thirdly, steroid hormones.

DERIVATIVES OF TYROSINE

These include adrenaline (Fig. 1.2), which is secreted by the adrenal medulla, and noradrenaline, which can be produced in the adrenal medulla but is also produced at sympathetic nerve endings where it acts as a neurotransmitter. Dopamine is another derivative of tyrosine which is a neurotransmitter that can also act as a hormone. It is released from the median eminence and

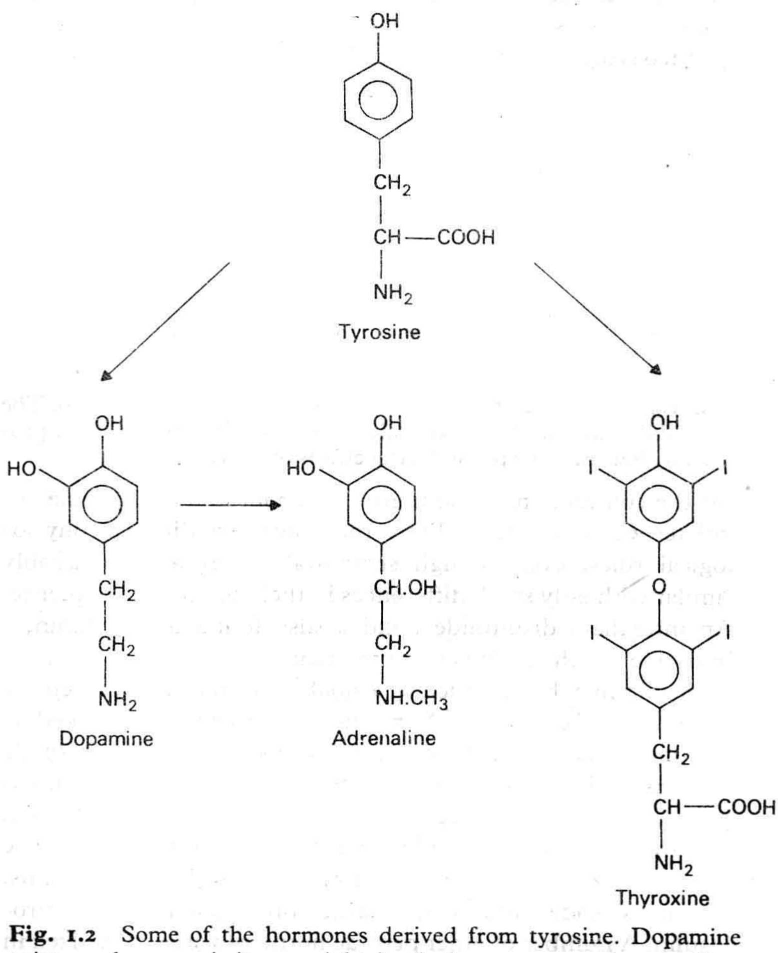

Fig. 1.2 Some of the hormones derived from tyrosine. Dopamine exists as a hormone in its own right, but it also occurs as an intermediate in the synthesis from tyrosine of adrenaline and noradrenaline (lacking the methyl group in the amino position).

suppresses the secretion of prolactin from the anterior pituitary. The thyroid hormones, thyroxine and triiodothyronine, each have two molecules of tyrosine fused together; thyroxine itself has four iodine atoms attached to the amino acid rings while triiodothyronine has three iodine atoms.

THE PROTEIN AND PEPTIDE HORMONES

These vary considerably in size and may be quite small and consist of only a single chain of amino acids. For example, thyrotrophin releasing hormone, secreted from the hypothalamus, has only three amino acid residues, while many of the hormones from the gastrointestinal tract, such as secretin from the duodenum and gastrin from the stomach, are larger with up to 34 amino acids, while parathyroid hormone is larger still with 84. Ring structures linked by disulphide bridges are present in some hormones, including the two hormones from the pituitary gland, oxytocin and vasopressin (Fig. 1.3): oxytocin is important

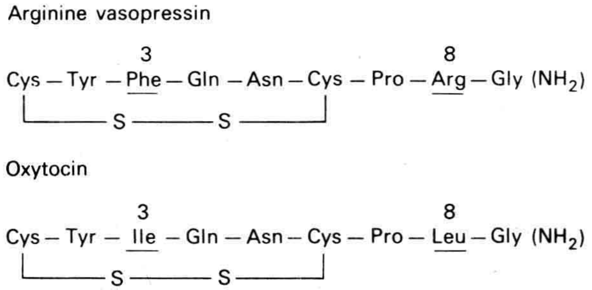

Fig. 1.3 The structures of arginine vasopressin and of oxytocin. The small differences in their chemical structure are underlined. They profoundly influence the physiological effects of the two hormones.

for the contraction of the uterus in labour and vasopressin regulates water excretion. Thus, they have very different physiological roles, even though structurally they are remarkably similar with only small differences in their amino acid sequence. An interchain disulphide bond is also found in calcitonin, a hormone which can lower serum calcium.

Insulin may be regarded as a small protein or a large peptide and it has two chains, the A and the B chains which are linked by interchain disulphide bonds. Initially, insulin is made as a single chain peptide and subsequently part of this is removed; this is referred to as the C peptide or connecting peptide which is removed after the disulphide bonds have been formed, and once it is removed, there are two linked chains (Fig. 1.4). Thus, insulin is made initially as a larger precursor molecule, proinsulin. A number of other peptide hormones are synthesized in larger precursor forms which are modified before the hormone is secreted.

Some hormones are quite large proteins, for example the glycoprotein hormones from the anterior pituitary which each have two peptide chains. The two gonadotrophins (follicle stimulating hormone and luteinizing hormone) and also thyrotrophin each have two chains referred to as the α and β subunits not linked by disulphide bridges. The α subunit in each of the three hormones is very similar, but the β subunits are different and it is the β subunit that confers the biological specificity on the hormone.

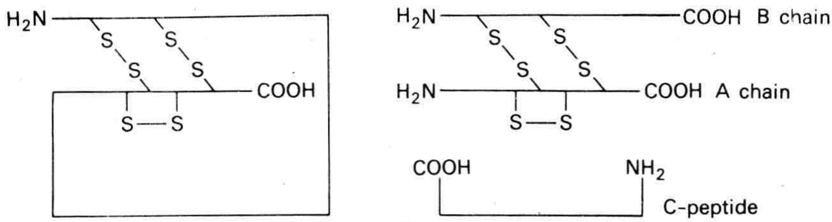

Fig. 1.4 A schematic representation of proinsulin (*left*) and insulin (*right*).

THE STEROID HORMONES

These include the hormones produced by the adrenal cortex such as cortisol and aldosterone, and the important sex steroids, testosterone (from the testis) and progesterone and oestradiol (from the ovary). The steroid hormones are important in many respects, affecting carbohydrate metabolism, salt and water balance and reproductive function. Small changes in the basic chemical structure cause dramatic changes in the physiological action of the hormones.

HORMONE BIOSYNTHESIS AND SECRETION

It is useful at this stage to consider some general principles concerning the synthesis, secretion and action of these different groups of hormones.

Peptides and proteins

SYNTHESIS

Protein or peptide hormone synthesis follows the conventional sequence of reactions which have been elucidated in the last 20–30 years (Fig. 1.5). Deoxyribonucleic acid (DNA), the genetic material, resides in the nucleus of the eukaryotic cell. It carries information for expression of genetic information in the form of a code of nucleotide bases arrayed in triplet sequences along the

DNA strands. The triplet code is transcribed from the DNA to nucleotides in strands of ribonucleic acid (RNA) in reaction sequences catalysed by DNA-dependent RNA polymerases. There are several forms of RNA which are produced in the nucleus (or nucleolus) of the cell, and which serve different functions in protein synthesis. The first is ribosomal RNA (rRNA), which is a major component of the ribosome units in the cell cytoplasm; ribosomes involved in the synthesis of

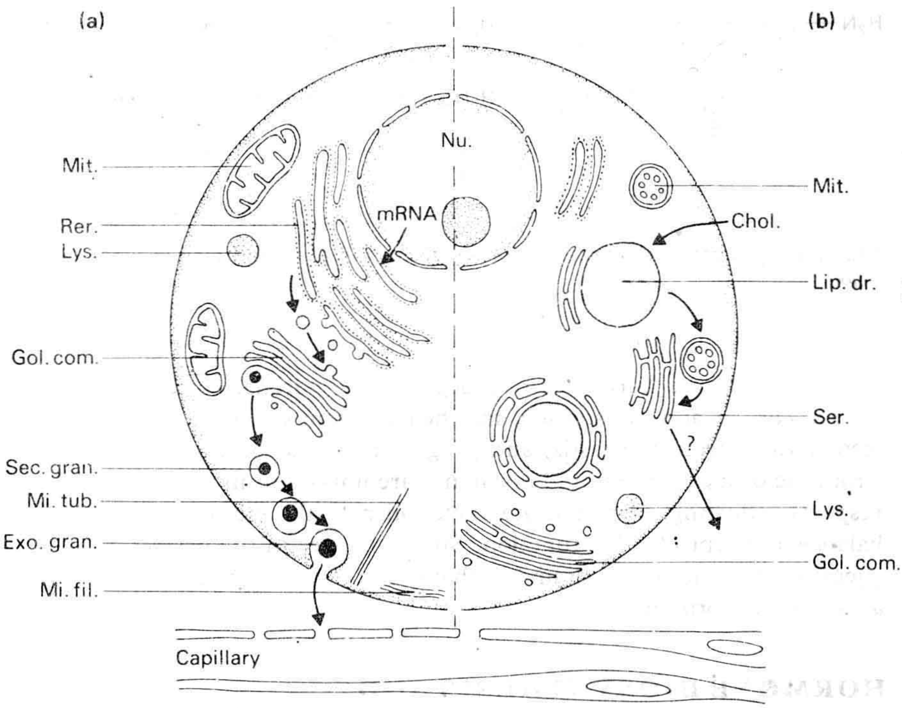

Fig. 1.5 The cytological features of a peptide hormone synthesizing cell (a), and a steroid hormone synthesizing cell (b).

(**a**) Messenger RNA (mRNA) leaves the nucleus and is translated on the ribosomes of the rough endoplasmic reticulum (ReR). The nascent protein (hormone) moves to the Golgi complex (Gol. com.) where it may be further modified and packaged into secretory granules (Sec. gran.). The granules move to the cell membrane with the involvement of microtubules (Mi. tub.) and actin microfilaments (Mi. fil.). The granule membrane fuses with the plasma membrane and granule (hormone) release through exocytosis occurs. The hormone then passes through the fenestrations of the capillary into the bloodstream.

(**b**) Cholestrol (Chol.) enters the cell and is stored as cholesterol esters in the lipid droplets (Lip. dr.) until required. Cholesterol then moves to the mitochondria (Mit.) where it is converted to pregnenolone. Pregnenolone is then transported to the surrounding smooth endoplasmic reticulum (Ser) where it is transformed by a series of reactions into the appropriate steroid hormone. The mode of egress of the hormone from the cell is not certain. Lysosomes (Lys.) are involved in the removal of unwanted secretory granules (crinophagy) and cytoplasmic organelles.

proteins for export from the cell are attached to certain intracellular membranes to yield the rough endoplasmic reticulum, and when grouped together in this fashion are called polysomes. Messenger RNA (mRNA) is the material which carries the message for protein structure; it is transcribed from the DNA and is used as a template for protein synthesis when bound to ribosomes in the cell cytoplasm. Transfer RNAs (tRNAs), each carrying an individual amino acid, recognize the triplet base-code on the mRNA-ribosome complex, and synthesis of a protein strand occurs in a 'zipper' fashion: this process is called *translation* of the message to form protein.

PACKAGING

Most peptide hormones are synthesized as a pre-pro-hormone, and the small 'pre-' fragment of a short chain of amino acids is normally cleaved as the peptide crosses the membrane from the ribosome into the cisternal space of the endoplasmic reticulum. Any disulphide bridges between peptide chains that are needed are formed at this stage of protein synthesis. The newly formed protein travels through the endoplasmic reticulum, and if it is a glycoprotein, certain carbohydrates may be added at this stage. From the endoplasmic reticulum the protein or peptide hormone is transferred in vesicles to the Golgi complex, where further carbohydrate additions may occur including the terminal sialic acid residues. The completed protein is then packaged into membrane-bounded vesicles. For certain hormones, it has been shown that particular specific enzymes are packaged in an inactive form along with the prohormone. In this case, the enzyme is a specific endopeptidase which is capable of cleaving the 'pro-' portion of the protein chain, as in the case of the C-peptide of insulin (Fig. 1.4).

STORAGE

Protein or peptide hormone secreting cells store the newly synthesized hormone in small vesicles. These vesicles may be observed under the electron microscope as electron-dense material scattered around the periphery of these cells, just inside the cell membrane. Movement of the vesicles from the Golgi apparatus to a position near the cell membrane appears to be influenced by two types of filamentous structure called microtubules and microfilaments which are found in all eukaryotic cells so far examined. Microtubules are made up of polymerized protein molecules (tubulin), which form rods of approximately 20 nm in diameter within the cell. Associated with the microtubules are at least three different enzymes, though their functions are at present obscure. The microfilaments are made up of the 'muscle-like' protein actin, and are about 5 nm in diameter. Groups of microfilaments are arranged in bundles at different positions within the cell. Actin is associated with myosin subunits, and is probably involved in the movement and control of the positions of subcellular vesicles within the cell. It has been suggested that tubulin acts as the cytoskeleton, giving the cell some degree of rigidity, and also that it provides a framework on which the other cytoskeletal elements, such as microfilaments, are able to control the movement of subcellular organelles within the cell. However, although both filamentous structures are probably involved in the control of secretion processes, their exact role remains to be elucidated.

SECRETION

Peptide and protein hormones (stored as granules in vesicles at the periphery of the cell) require some stimulus to the cell before the stored prohormone is activated and then released. This stimulus may be hormonal, and in most cases it probably involves a change, for example, in ionic permeability of the cell to Ca^{++} ions. The term 'stimulus-secretion coupling' has been used to describe the latter process, in which divalent metal ions are required for interaction between the vesicle membrane, and the plasma membrane for microfilament and microtubule activation, and also for certain enzymes, all of which are probably involved in the secretion process. The specific endopeptidases (or other enzymes) present with the prohormone (or protein) in the storage vesicle are activated during the secretion process, producing the active form of the hormone before it is actually released from the cell.

The mode of secretion from the cell is called exocytosis. The membrane of an intracellular storage granule fuses with the plasma membrane of the cell which then parts near the point of fusion and the contents of the vesicle are then secreted into extracellular space surrounding the blood vessels. Membrane turnover is increased, and where it has been studied, it appears that the membrane which originally surrounded the vesicle is quickly recycled within the cell and so does not remain a component of the plasma membrane of the cell for long. Large changes in the turnover of membrane phospholipids occur during this period of exocytotic activity, and although particular phospholipids have been shown to be important in different cells, their involvement in the exocytotic process can only be inferred.