كلية الصيدلة / جامعة تكريت

المرحلة الثانية

مادة الفسلجة II

الكورس الثاني

من 1 الى 10

أ.د. جواد علي صالح

أ.م.د. خالد سعود صالح

لجنة عمداء كليات الصيدلة

لجنة توحيد منهاج مادة (Physiology II)

Physiology II

المرحلة الثانية

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تم اعداد ومراجعة هذا المنهج الموحد للامتحان التقويمي لكليات الصيدلة للعام الدراسي 2023-2024 من قبل اساتذة متخصصين لديهم خبرة كبيرة في التدريس والعمل الاكاديمي . لقد بذل الاساتذة قصارى جهودهم في جمع المعلومات وحرصوا على ترتبها وتنظيمها لتكون واضحة يسيرة على طلبتنا الاعزاء . نأمل من طلبتنا الاعزاء الاستفادة منه في طريقهم الى النجاح والتفوق، والله الموفق

Chapter 16

Basic Concepts of Endocrine Regulation

In general, endocrine physiology is concerned with maintaining various aspects of homeostasis. The mediators of such control mechanisms are soluble factors known as hormones. The word hormone was derived from the Greek horman, meaning to set in motion.

The endocrine system differs from other physiological systems in that it cannot be distinctly defined based on anatomical boundaries. It operates as a distributed network comprising glands and circulating messengers, often under the influence of the central nervous system, the autonomic nervous system, or both.

Evolution of Hormones &Their Actions on Target Cells

Hormones comprise steroids, amines, and peptides. Peptide hormones are by far the most numerous. Many hormones can be grouped into families reflecting their structural similarities as well as the similarities of the receptors they activate. However, the number of hormones and their diversity increases as one moves from simple to higher life forms, reflecting the added challenges in providing for homeostasis in more complex organisms. For example, among the peptide hormones, several are heterodimers that share a common α chain, with specificity being conferred by the β-chain. In the specific case of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), there is evidence that the distinctive β-chains arose from a series of duplications of a common ancestral gene. For these and other hormones, moreover, this molecular evolution implies that hormone receptors also need to evolve to allow for the spreading of hormone actions/specificity. This was accomplished by co-evolution of

the basic G-protein–coupled receptors (GPCR) and receptor tyrosine kinases that mediate the effects of peptide and amine hormones that act at the cell surface.

Steroids and thyroid hormones are distinguished by their predominantly intracellular sites of action, since they can diffuse freely through the cell membrane. They bind to a family of largely cytoplasmic proteins known as nuclear receptors. Upon ligand binding, the receptor–ligand complex translocates to the nucleus where it either homodimerizes, or associates with a distinct liganded nuclear receptor to form a heterodimer. In either case, the dimer binds to DNA to either increase or decrease gene transcription in the target tissue.

HORMONE SECRETION

SYNTHESIS & PROCESSING

The regulation of hormone synthesis depends on their chemical nature. For peptide hormones as well as hormone receptors, synthesis is controlled predominantly at the level of transcription. For amine and steroid hormones, synthesis is controlled indirectly by regulating the production of key synthetic enzymes as well as by substrate availability.

Interestingly, the majority of peptide hormones are synthesized initially as much larger polypeptide chains, and then processed intracellularly by specific proteases to yield the final hormone molecule. In some cases, multiple hormones may be derived from the same initial precursor, depending on the specific processing steps present in a given cell type. Presumably, this provides for a level of genetic “economy.” It is also notable that the hormone precursors themselves are typically inactive. This may be a mechanism that provides for an additional measure of regulatory control, or, in the case of thyroid hormones, may dictate the site of highest hormone availability.

The synthesis of all of the proteins/peptides discussed above is subject to the normal mechanisms of transcriptional control in the cell. In addition, there is provision for exquisitely specific regulation by other hormones, since the regulatory regions of many peptide hormone genes contain binding motifs for the nuclear receptors discussed above. For example, thyroid hormone directly suppresses TSH expression via the thyroid hormone receptor. These specific mechanisms to regulate hormone transcription are essential to the function of feedback loops, as will be addressed in greater detail below. In some cases, the abundance of selected hormones may also be regulated via effects on translation. For example, elevated levels of circulating glucose stimulate the translation of insulin mRNA. These effects are mediated by the ability of glucose to increase the interaction of the insulin mRNA with specific RNA-binding proteins, which increase its stability and enhance its translation. The net effect is a more precise and timely regulation of insulin levels, and thus energy metabolism, than could be accomplished with transcriptional regulation alone.

The precursors for peptide hormones are processed through the cellular machinery that handles proteins destined for export, including trafficking through specific vesicles where the propeptide form can be cleaved to the final active hormones. Mature hormones are also subjected to a variety of posttranslational processing steps, such as glycosylation, which can influence their ultimate biological activity and/or stability in circulation. Ultimately, all hormones enter either the constitutive or regulated secretory pathway.

SECRETION

The secretion of many hormones is via a process of exocytosis of stored granules. The exocytotic machinery is activated when the cell type that synthesizes and stores the hormone in question is activated by a specific signal, such as a neurotransmitter

or peptide-releasing factor. One should, however, contrast the secretion of stored hormones with that of those that are continually released by diffusion (eg, steroids). Control of the secretion of the latter molecules occurs via kinetic influences on the synthetic enzymes or carrier proteins involved in hormone production. For example, the steroidogenic acute regulatory protein (StAR) is a labile protein whose expression, activation, and deactivation are regulated by intracellular signaling cascades and their electors, including a variety of protein kinases and phosphatases. StAR traffics cholesterol from the outer to the inner membrane leaflet of the mitochondrion. Because this is a rate-limiting first step in the synthesis of the steroid precursor, pregnenolone, this arrangement permits changes in the rate of steroid synthesis, and thus secretion, in response to homeostatic cues such as trophic hormones, cytokines, and stress (Figure 16–1).

An additional complexity related to hormone secretion relates to the fact that some hormones are secreted in a pulsatile manner. Secretion rates may peak and ebb relative to circadian rhythms, in response to the timing of meals, or as regulated by other pattern generators whose periodicity may range from milliseconds to years. Pulsatile secretion is often related to the activity of oscillators in the hypothalamus that regulate the membrane potential of neurons, in turn secreting bursts of hormone releasing factors into the hypophysial blood flow that then cause the release of pituitary and other downstream hormones in a similar pulsatile manner. There is evidence that these hormone pulses convey different information to the target tissues that they act upon compared to a steady exposure to a single concentration of the hormone. Therapeutically, pulsatile secretion may pose challenges if, due to deficiency, it proves necessary to replace a particular hormone that is normally secreted in this way.

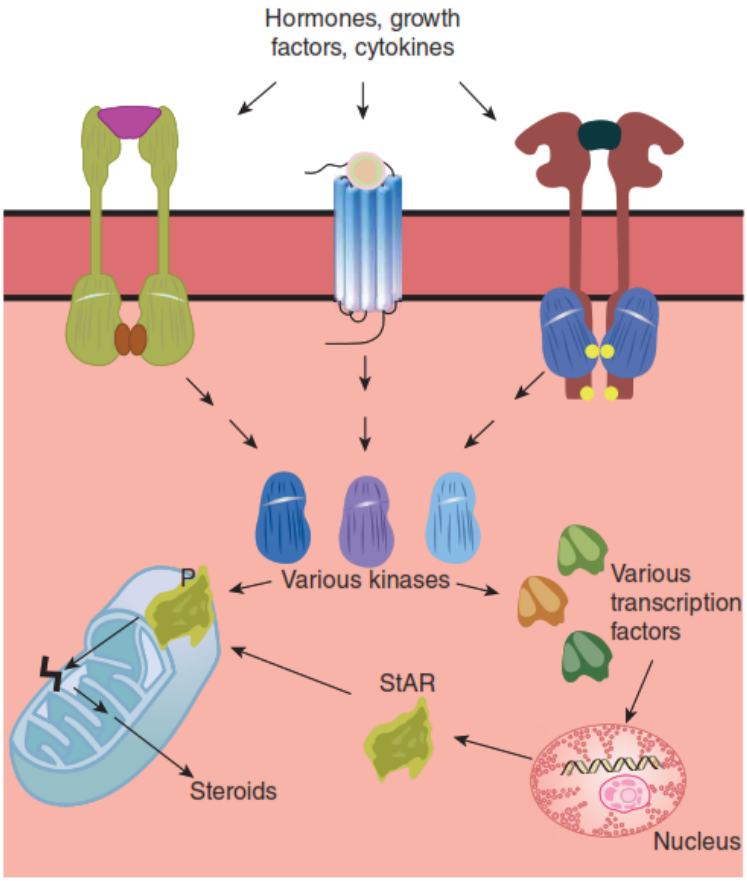


FIGURE 16–1 Regulation of steroid biosynthesis by the steroidogenic acute regulatory protein (StAR). Extracellular signals activate intracellular kinases that, in turn, phosphorylate transcription factors that upregulate StAR expression. StAR is activated by phosphorylation, and facilitates transfer of cholesterol from the outer to inner mitochondrial membrane leaflet. This then allows conversion of cholesterol into pregnenolone, which is the first intermediate in the steroid biosynthetic pathway.

HORMONE TRANSPORT IN THE BLOOD

In addition to the rate of secretion and its nature (steady vs. pulsatile), several factors influence the circulating levels of hormones. These include the rates of hormone degradation and/or uptake, receptor binding and availability of receptors, and the affinity of a given hormone for plasma carriers (Figure 16–2). Stability influences the circulating half-life of a given hormone and has therapeutic

implications for hormone replacement therapy, in addition to those posed by pulsatile secretion as discussed above.

Plasma carriers for specific hormones have several important physiologic functions. First, they serve as a reservoir of inactive hormones and thus provide a hormonal reserve.

Bound hormones are typically prevented from degradation or uptake. Thus, the bound hormone reservoir can allow fluctuations in hormonal levels to be smoothed over time. Plasma carriers also restrict the access of the hormone to some sites. Ultimately, plasma carriers may be vital in modulating levels of the free hormone in question. Typically, it is only the free hormone that is biologically active in target tissues or can mediate feedback regulation (see below) since it is the only form able to access the extravascular compartment.

Catecholamine and most peptide hormones are soluble in plasma and are transported as such. In contrast, steroid hormones are hydrophobic and are mostly bound to large proteins called steroid binding proteins (SBP), which are synthesized in the liver. As a result, only small amounts of the free hormone are dissolved in the plasma. Specifically, sex hormone–binding globulin (SHBG) is a glycoprotein that binds to the sex hormones, testosterone and 17β-estradiol. Progesterone, cortisol, and other corticosteroids are bound by transcortin.

The SBP-hormone complex and the free hormone are in equilibrium in the plasma, and only the free hormone can diffuse across cell membranes. SBP have three main functions: they increase the solubility of lipid-based hormones in the blood; they reduce the rate of hormone loss in the urine by preventing the hormones from being altered in the kidney; and as mentioned above, they provide a source of hormone in the bloodstream that can release free hormone as the equilibrium

changes. It follows that an additional way to regulate the availability of hormones that bind to carrier proteins, such as steroids, is to regulate the expression and secretion of the carrier proteins themselves. This is a critical mechanism that regulates the bioavailability of thyroid hormones, for example.

In a pathophysiologic setting, some medications can alter levels of binding proteins or displace hormones that are bound to them. In addition, some binding proteins are promiscuous and bind multiple hormones (eg, SHBG). These observations may have clinical implications for endocrine homeostasis, since free hormones are needed to feedback and control their rates of synthesis and secretion (see below).

Finally, the anatomic relationship of sites of release and action of hormones may play a key role in their regulation. For example, several hormones are destroyed by passage through the pulmonary circulation or the liver. This may markedly curtail the temporal window within which a given hormone can act.

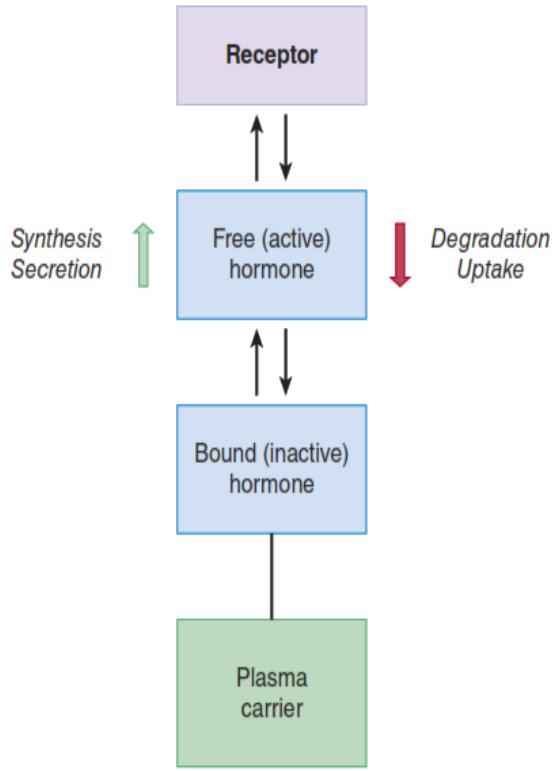


FIGURE 16–2 Summary of factors that determine the level of free hormones circulating in the bloodstream. Factors that increase (green upward arrow) or decrease (red downward arrow) hormone levels are shown. Free hormones also equilibrate with the forms bound to either receptors or plasma carrier proteins.

HORMONE ACTION

Hormones exert a wide range of distinctive actions on a huge number of target cells to effect changes in metabolism, the release of other hormones and regulatory substances, changes in ion channel activity, and cell growth, among others. Ultimately, the concerted action of the hormones of the body ensures the maintenance of homeostasis. Indeed, all hormones affect homeostasis to some degree. However, a subset of the hormones, including thyroid hormone, cortisol, parathyroid hormone, vasopressin, mineralocorticoids, and insulin, are the key contributors to homeostasis (Table 16–1).

Hydrophilic hormones, including peptides and catecholamines, exert their acute effects by binding to cell surface receptors. Most of these are from the GPCR family. Hydrophobic hormones, on the other hand, predominantly exert their actions via nuclear receptors. Two classes of nuclear receptors are important in endocrine physiology.

TABLE 16–1 Major hormonal contributors to homeostasis.

Hormone	Source	Action
Thyroid hormone	Thyroid	Controls basal metabolism in most tissues
Cortisol	Adrenal cortex	Energy metabolism; permissive action for other hormones
Mineralocorticoids	Adrenal cortex	Regulate plasma volume via effects on serum electrolytes
Vasopressin	Posterior pituitary	Regulates plasma osmolality via effects on water excretion
Parathyroid hormone	Parathyroids	Regulates calcium and phosphorus levels
Insulin	Pancreas	Regulates plasma glucose concentration

The first class provides direct stimulation of transcription via induction of the binding of a transcriptional co-activator when the hormonal ligand is bound. In the second class, hormone binding triggers simultaneous dislodging of a transcriptional co-repressor and recruitment of a co-activator. The latter class of receptor allows for a wider dynamic range of regulation of the genes targeted by the hormone in question.

PRINCIPLES OF FEEDBACK CONTROL

A final general principle that is critical for endocrine physiology is that of **feedback regulation**. This holds that the responsiveness of target cells to hormonal action subsequently "feeds back" to control the inciting endocrine organ. Feedback can regulate the further release of the hormone in either a negative feedback or (more rarely) a positive feedback loop. Positive feedback relates to the enhancement or continued stimulation of the original release mechanism/stimulus. Such mechanisms are only seen in settings that need to gather momentum for an eventual outcome, such as parturition. Negative feedback is a far more common control mechanism and involves the inhibition or dampening of the initial hormone release mechanism/stimulus. A general scheme for feedback inhibition of endocrine axes is depicted in Figure 16–3.

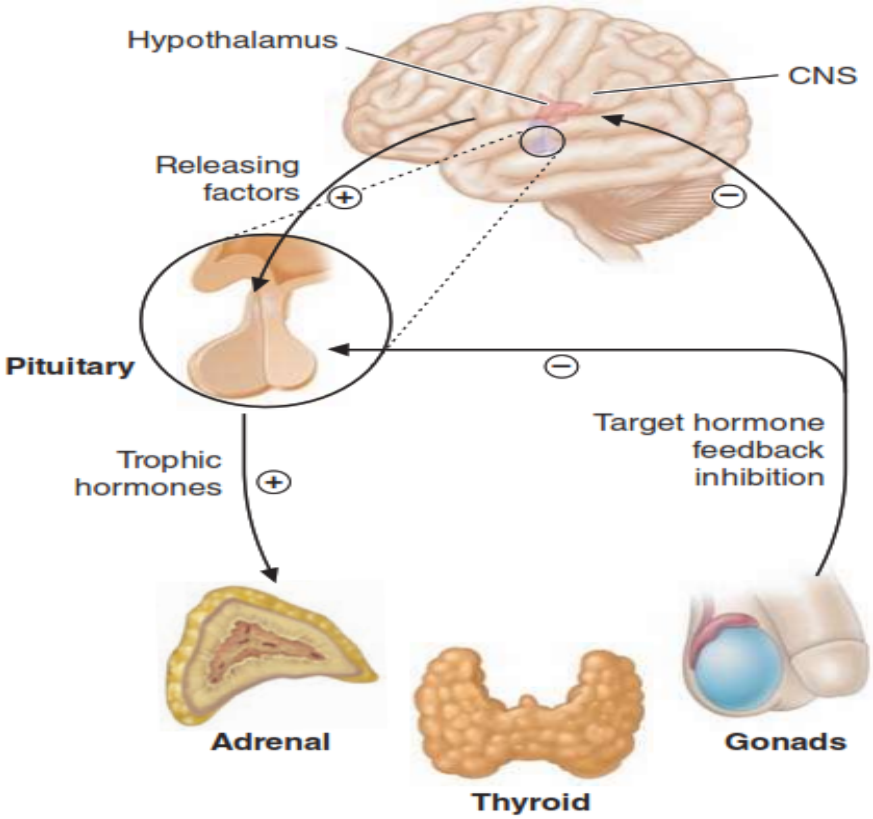


FIGURE 16–3 Summary of feedback loops regulating endocrine axes. CNS, central nervous system.

In general, the endocrine system uses a network of feedback responses to maintain a steady state. Negative feedback control systems such as those described are the most common feedback/homeostatic systems in the body. Feedback control loops also provide for diagnostic strategies in evaluating patients with suspected endocrine disorders. For example, in a patient being evaluated for hypothyroidism, normal levels of TSH tend to rule out a primary defect at the level of the thyroid gland itself, and rather suggest that a defect at the level of the anterior pituitary should be sought. Conversely, if TSH is elevated, it suggests that the normal ability of circulating thyroid hormone to suppress TSH synthesis has been lost, likely due to a reduction in the ability of the thyroid gland to synthesize the hormone.

Chapter 17

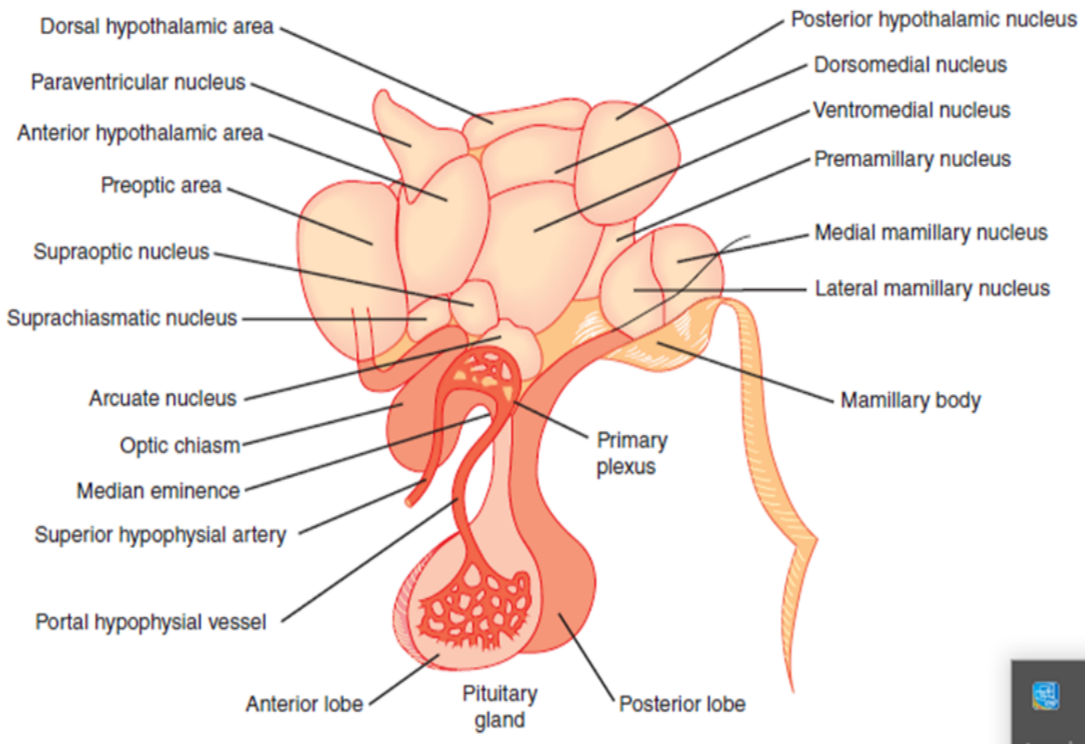
Hypothalamic Regulation of Hormonal Function

Introduction

Many of the complex autonomic mechanisms that maintain the chemical constancy and temperature of the internal environment are integrated in the hypothalamus. The hypothalamus also functions with the limbic system as a unit that regulates emotional and instinctual behavior

Relation to the Pituitary Gland

There are neural connections between the hypothalamus and the posterior lobe of the pituitary gland and vascular connections between the hypothalamus and the anterior lobe. Embryologically, the posterior pituitary arises as an evagination of the floor of the third ventricle. It is made up in large part of the endings of axons that arise from cell bodies in the supraoptic and paraventricular nuclei and pass to the posterior pituitary via the hypothalamohypophysial tract. Most of the supraoptic fibers end in the posterior lobe itself, whereas some of the paraventricular fibers end in the median eminence. The anterior and intermediate lobes of the pituitary arise in the embryo from the Rathke pouch, an evagination from the roof of the pharynx. Sympathetic nerve fiber.



RE 17–1 Human hypothalamus, with a superimposed diagrammatic representation of the portal hypophys

reach the anterior lobe from its capsule, and parasympathetic fibers reach it from the petrosal nerves, but few, if any, nerve fibers pass to it from the hypothalamus. However, the portal hypophysial vessels form a direct vascular link between the hypothalamus and the anterior pituitary. Arterial twigs from the carotid arteries and circle of Willis form a network of fenestrated capillaries called the primary plexus on the ventral surface of the hypothalamus (Figure 17–1). Capillary loops also penetrate the median eminence. The capillaries drain into the sinusoidal portal hypophysial vessels that carry blood down the pituitary stalk to the capillaries of the anterior pituitary. This system begins and ends in capillaries without going through the heart and is therefore a true portal system. In birds and some mammals, including humans, there is no other anterior hypophysial arterial supply other than capsular vessels and anastomotic connections from the capillaries of the posterior pituitary.

The median eminence is generally defined as the portion of the ventral hypothalamus from which the portal vessels arise. This region is outside the blood–brain barrier

THIRST

Decreases in ECF volume also stimulate thirst by a pathway independent of that mediating thirst in response to increased plasma osmolality (Figure 17–4). Thus, hemorrhage causes increased drinking even if there is no change in the osmolality of the plasma. The effect of ECF volume depletion on thirst is mediated in part via the renin–angiotensin system (see Chapter 38). Renin secretion is increased by hypovolemia and results in an increase in circulating angiotensin II. The angiotensin II acts on the subfornical organ, a specialized receptor area in the diencephalon (see Figure 33–7), to stimulate the neural areas concerned with thirst. Some evidences suggest that it acts on the organum vasculosum of the lamina terminalis (OVLT) as well. These areas are highly permeable and are two of the circumventricular organs located outside the blood–brain barrier (see Chapter 33). However, drugs that block the action of angiotensin II do not completely block the thirst response to hypovolemia, and it appears that the baroreceptors in the heart and blood vessels are also involved. The intake of liquids is increased during eating (prandial drinking). The increase has been called a learned or habit response, but it has not been investigated in detail. One factor is an increase in plasma osmolality that occurs as food is absorbed. Another may be an action of one or more gastrointestinal hormones on the hypothalamus

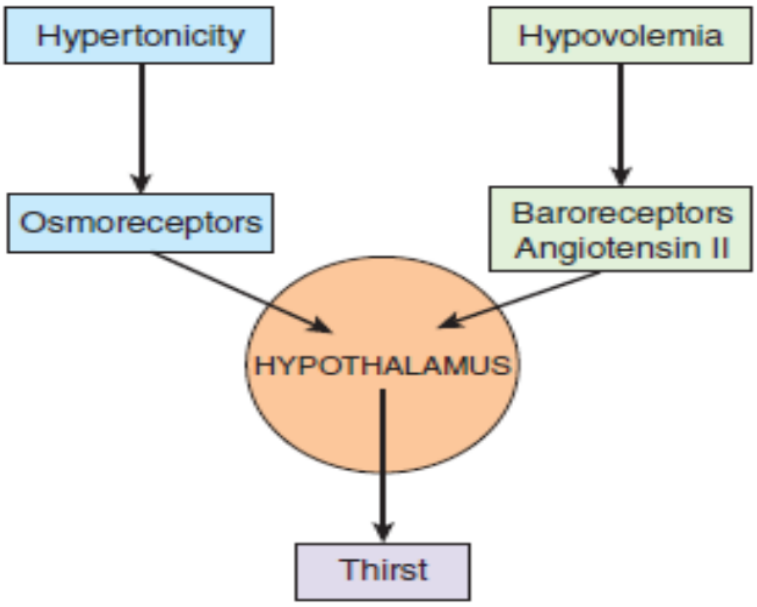


FIGURE 17–4 **Diagrammatic representation of the way in which changes in plasma osmolality and changes in ECF volume affect thirst by separate pathways.**

When the sensation of thirst is obtunded, either by direct damage to the diencephalon or by depressed or altered states of consciousness, patients stop drinking adequate amounts of fluid. Dehydration results if appropriate measures are not instituted to maintain water balance. If the protein intake is high, the products of protein metabolism cause an osmotic diuresis, and the amounts of water required to maintain hydration are large. Most cases of hypernatremia are actually due to simple dehydration in patients with psychoses or hypothalamic disease who do not or cannot increase their water intake when their thirst mechanism is stimulated. Lesions of the anterior communicating artery can also obtund thirst because branches of this artery supply the hypothalamic areas concerned with thirst.

Control of posterior pituitary secretions

- **vasopressin & oxytocin**

In most mammals, the hormones secreted by the posterior pituitary gland are arginine vasopressin (AVP) and oxytocin. In hippopotami and most pigs, arginine in the vasopressin molecule is replaced by lysine to form lysine vasopressin. The posterior pituitaries of some species of pigs and marsupials contain a mixture of arginine and lysine vasopressin. The posterior lobe nano peptides with a disulfide ring at one end

BIOSYNTHESIS, INTRANEURONAL TRANSPORT, & SECRETION

The hormones of the posterior pituitary gland are synthesized in the cell bodies of the magnocellular neurons in the supraoptic and paraventricular nuclei and transported down the axons of these neurons to their endings in the posterior lobe, where they are secreted in response to electrical activity in the endings Oxytocin and vasopressin are typical neural hormones, that is, hormones secreted into the circulation by nerve cells.

vasopressin & oxytocin in other locations

Vasopressin-secreting neurons are found in the suprachiasmatic nuclei, and vasopressin and oxytocin are also found in the endings of neurons that project from the paraventricular nuclei to the brainstem and spinal cord. These neurons appear to be involved in cardiovascular control. In addition, vasopressin and oxytocin are synthesized in the gonads and the adrenal cortex, and oxytocin is present in the thymus. The functions of the peptides in these organs are unsettled

Vasopressin Receptors

There are at least three kinds of vasopressin receptors: V1A, V1B, and V2. All are G-protein–coupled. The V1A and V1B receptors act through phosphatidylinositol hydrolysis to increase intracellular Ca2+ concentrations. The V2 receptors act through Gs to increase cyclic adenosine monophosphate levels.

Effects of Vasopressin

Because one of its principal physiologic effects is the retention of water by the kidney, vasopressin is often called the antidiuretic hormone (ADH). It increases the permeability of the collecting ducts of the kidney so that water enters the hypertonic interstitium of the renal pyramids (see Chapter 37). The urine becomes concentrated and its volume decreases. The overall effect is therefore retention of water in excess of solute; consequently, the effective osmotic pressure of the body fluids is decreased. In the absence of vasopressin, the urine is hypotonic to plasma, urine volume is increased, and there is a net water loss. Consequently, the osmolality of the body fluid rises

Effects of Oxytocin

In humans, oxytocin acts primarily on the breasts and uterus, though it appears to be involved in luteolysis as well. A G-protein–coupled oxytocin receptor has been identified in human myometrium, and a similar or identical receptor is found in mammary tissue and the ovary. It triggers increases in intracellular Ca2+ levels.

Anterior Pituitary Hormones

The anterior pituitary secretes six hormones: adrenocorticotropic hormone (corticotropin, ACTH), thyroid-stimulating hormone (thyrotropin, TSH), growth hormone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and

prolactin (PRL). An additional polypeptide, β-lipotropin (β-LPH), is secreted with ACTH, but its physiologic role is unknown

Nature of Hypothalamic Control

Anterior pituitary secretion is controlled by chemical agents carried in the portal hypophysial vessels from the hypothalamus to the pituitary. These substances used to be called releasing and inhibiting factors, but now they are commonly called hypophysiotropic hormones. The latter term seems appropriate since they are secreted into the bloodstream and act at a distance from their site of origin. Small amounts escape into the general circulation, but they are at their highest concentration in portal hypophysial blood.

Hypophysiotropic Hormones

There are six established hypothalamic releasing and inhibiting hormones (Figure 17–10): corticotropin-releasing hormone (CRH); thyrotropin-releasing hormone (TRH); growth hormone–releasing hormone (GRH); growth hormone–inhibiting hormone (GIH, now generally called somatostatin); luteinizing hormone–releasing hormone (LHRH, now generally known as gonadotropin-releasing hormone [GnRH]); and prolactin-inhibiting hormone (PIH). In addition, hypothalamic extracts contain prolactin-releasing activity, and a prolactin-releasing hormone (PRH) has been postulated to exist. TRH, VIP, and several other

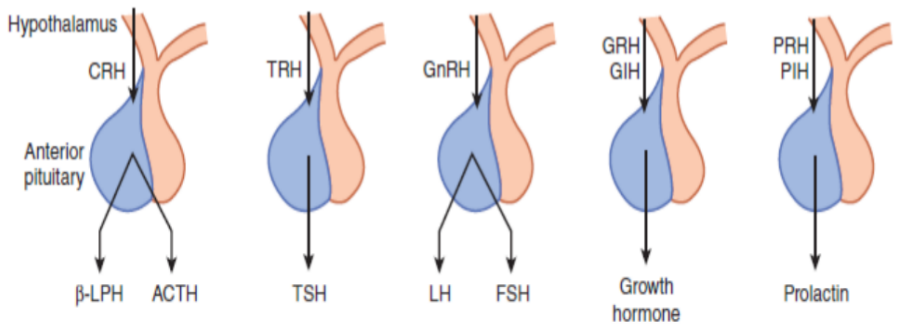


FIGURE 17–10 **Effects of hypophysiotropic hormones on the secretion of anterior pituitary hormones.**

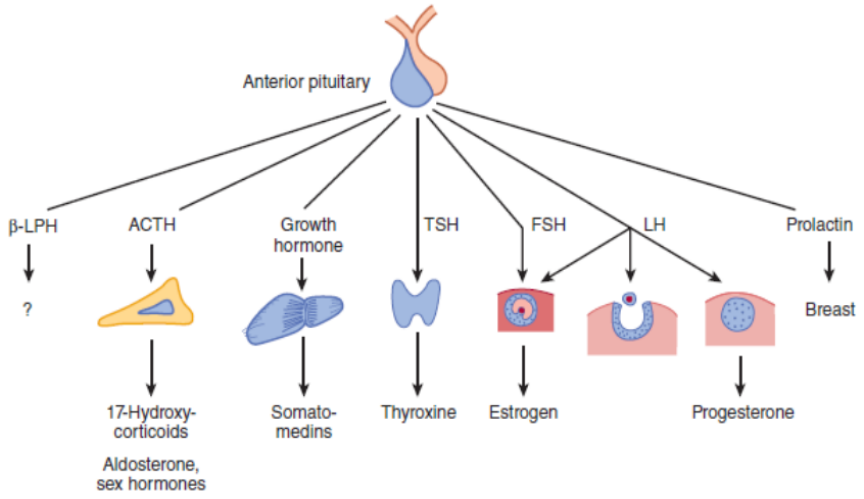


FIGURE 17–9 **Anterior pituitary hormones.** In women, FSH and LH act in sequence on the ovary to produce growth of the ovarian follicle, ovulation, and formation and maintenance of the corpus luteum. Prolactin stimulates lactation. In men, FSH and LH control the functions of the testes. ACTH, adrenocorticotropic hormone; β-LPH, β-lipotropin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

Receptors for most of the hypophysiotropic hormones are coupled to G-proteins. There are two human CRH receptors: hCRH-RI and hCRH-RII. The physiologic role of hCRH-RII is unsettled, though it is found in many parts of the brain. In addition, a CRH-binding protein in the peripheral circulation inactivates CRH. It is also found in the cytoplasm of corticotropes in the anterior pituitary, and in this location it might play a role in receptor internalization. However, the exact physiologic role of this protein is unknown. Other hypophysiotropic hormones do not have known binding proteins

Chapter 18

The Pituitary Gland

Introduction

The pituitary gland, or hypophysis, lies in a pocket of the sphenoid bone at the base of the brain. It is a coordinating center for control of many downstream endocrine glands, some of which are discussed in subsequent chapters. In many ways, it can be considered to consist of at least two (and in some species, three) separate endocrine organs that contain a plethora of hormonally active substances. The anterior pituitary secretes thyroid-stimulating hormone (TSH, thyrotropin), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and growth hormone (see Figure 17–9), and receives almost all of its blood supply from the portal hypophysial vessels that pass initially through the median eminence, a structure immediately below the hypothalamus. This vascular arrangement positions the cells of the anterior pituitary to respond efficiently to regulatory factors released from the hypothalamus. Of the listed hormones, prolactin acts on the breast. The remaining five are, at least in part, tropichormones; that is, they stimulate secretion of hormonally active substances by other endocrine glands or, in the case of growth hormone, the liver and other tissues. The tropic hormones for some endocrine glands are discussed in the chapter on that gland: TSH ; and ACTH . However, the gonadotropins FSH and LH, along with prolactin.

The posterior pituitary in mammals consists predominantly of nerves that have their cell bodies in the hypothalamus, and stores oxytocin and vasopressin in the termini of these neurons, to be released into the bloodstream. The secretion of these hormones, as well as a discussion of the overall role of the hypothalamus and median eminence in regulating both the anterior and posterior pituitary. In some species,

there is also a well-developed intermediate lobe of the pituitary, whereas in humans it is rudimentary. Nevertheless, the intermediate lobe, as well as the anterior pituitary, contains hormonally active of the proopiomelanocortin (POMC) molecule that regulate skin pigmentation, among other functions (see below). To avoid redundancy, this chapter will focus predominantly on growth hormone and its role in growth and facilitating the activity of other hormones, along with a number of general considerations about the pituitary. The melanocyte-stimulating hormones (MSHs) of the intermediate lobe of the pituitary, α-MSH and β-MSH, will also be touched upon.

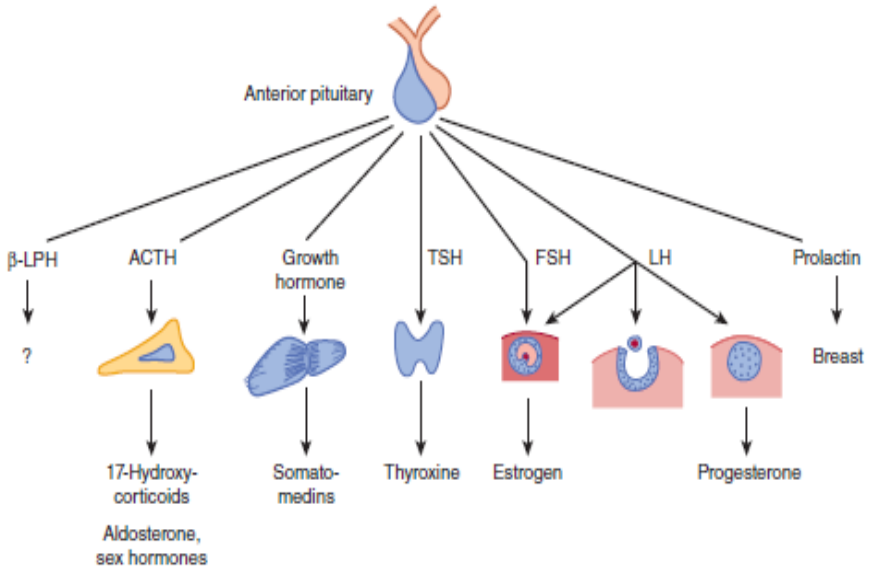


FIGURE 17–9 **Anterior pituitary hormones.** In women, FSH and LH act in sequence on the ovary to produce growth of the ovarian follicle, ovulation, and formation and maintenance of the corpus luteum. Prolactin stimulates lactation. In men, FSH and LH control the functions of the testes. ACTH, adrenocorticotropic hormone; β-LPH, β-lipotropin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

Cell Types in the Anterior Pituitary

Five types of secretory cells have been identified in the anterior pituitary by immunocytochemistry and electron microscopy. The cell types are the somatotropes, which secrete growth hormone; the lactotropes (also called mammotropes), which

secrete prolactin; the corticotropes, which secrete ACTH; the thyrotropes, which secrete TSH; and the gonadotropes, which secrete FSH and LH. The characteristics of these cells are summarized in Table 18–1. Some cells may contain two or more hormones. It is also notable that the three pituitary glycoprotein hormones, FSH, LH, and TSH human chorionic gonadotropin (hCG) has α and β subunits

TABLE 18–1 Hormone-secreting cells of the human anterior pituitary gland.

Cell Type	Hormones Secreted	Percentage of Total Secretory Cells
Somatotrope	Growth hormone	50
Lactotrope	Prolactin	10–30
Corticotrope	ACTH	10
Thyrotrope	TSH	5
Gonadotrope	FSH, LH	20

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

Growth Hormone

- **Biosynthesis & Chemistry**

The long arm of human chromosome 17 contains the growth hormone-hCS cluster that contains five genes: one, hGH-N, codes for the most abundant (“normal”) form of growth hormone; a second, hGH-V, codes for the variant form of growth hormone; two code for human chorionic somatomammotropin (hCS) and the fifth is probably an hCS pseudogene.

Growth hormone that is secreted into the circulation by the pituitary gland consists of a complex mixture of hGH-N, peptides derived from this molecule with varying degrees of posttranslational modifications, such as glycosylation, and a splice variant of hGH-N that lacks amino acids 32–46. The physiologic significance of this

complex array of hormones has yet to be fully understood, particularly since their structural similarities make it difficult to assay for each species separately. Nevertheless, there is emerging evidence that, while the various peptides share a broad range of functions, they may occasionally exert actions in opposition to one another. hGH-V and hCS, on the other hand, are primarily products of the placenta, and as a consequence are only found in appreciable quantities in the circulation during pregnancy

- **Plasma levels, Binding, & Metabolism**

A portion of circulating growth hormone is bound to a plasma protein that is a large fragment of the extracellular domain of the growth hormone receptor. It appears to be produced by cleavage of receptors in humans, and its concentration is an index of the number of growth hormone receptors in the tissues. Approximately 50% of the circulating pool of growth hormone activity is in the bound form, providing a reservoir of the hormone to compensate for the wide fluctuations that occur in secretion

The basal plasma growth hormone level measured by radioimmunoassay in adult humans is normally less than 3 ng/mL. This represents both the protein-bound and free forms. Growth hormone is metabolized rapidly, at least in part in the liver. The half-life of circulating growth hormone in humans is 6–20 min, and the daily growth hormone output has been calculated to be 0.2–1.0 mg/d in adults

Growth Hormone Receptors

The growth hormone receptor is a 620-amino-acid protein with a large extracellular portion, a transmembrane domain, and a large cytoplasmic portion. It is a member of the cytokine receptor superfamily, which is discussed in Chapter 3. Growth hormone has two domains that can bind to its receptor, and when it binds to

one receptor, the second binding site attracts another, producing a homodimer (Figure 18–3). Dimerization is essential for receptor activation.

Growth hormone has widespread effects in the body (see below), so even though it is not yet possible precisely to correlate intracellular and whole-body effects, it is not surprising that, like insulin, growth hormone activates many different intracellular signaling cascades (Figure 18–3). Of particular note is its activation of the JAK2–STAT pathway. JAK2 is a member of the Janus family of cytoplasmic tyrosine kinases. STATs (for signal transducers and activators of transcription) are a family of cytoplasmic transcription factors that, upon phosphorylation by JAK kinases, migrate to the nucleus where they activate various genes. JAK–STAT pathways are known also to mediate the effects of prolactin and various other growth factors

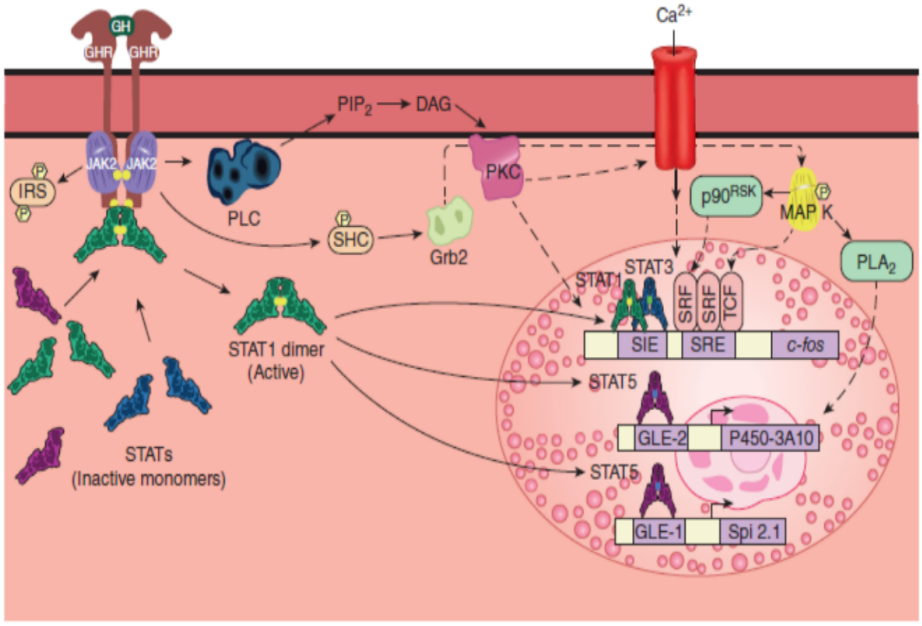


FIGURE 18–3 **Some of the principal signaling pathways activated by the dimerized growth hormone receptor (GHR).** Solid arrows indicate established pathways; dashed arrows indicate probable pathways. The details of the PLC pathway and the pathway from Grb2 to MAP K are discussed in Chapter 2. The small uppercase letter Ps in yellow hexagons represent phosphorylation of the factor indicated. GLE-1 and GLE-2, interferon γ-activated response elements; IRS, insulin receptor substrate; $p90^{RSK}$, an S6 kinase; PLA_2, phospholipase A_2; SIE, Sis-induced element; SRE, serum response element; SRF, serum response factor; TCF, ternary complex factor.

Effects on Growth

In young animals in which the epiphyses have not yet fused to the long bones, growth is inhibited by hypophysectomy and stimulated by growth hormone. Chondrogenesis is accelerated, and as the cartilaginous epiphysial plates widen, they lay down more bone matrix at the ends of long bones. In this way, stature is increased. Prolonged treatment of animals with growth hormone leads to gigantism.

When the epiphyses are closed, linear growth is no longer possible. In this case, an overabundance of growth hormone produces the pattern of bone and soft tissue deformities known in humans as acromegaly. The sizes of most of the viscera are increased. The protein content of the body is increased, and the fat content is decreased

CLINICAL BOX 18–1

Gigantism & Acromegaly

Tumors of the somatotropes of the anterior pituitary (pituitary adenomas) secrete large amounts of growth hormone, leading to **gigantism** in children and to **acromegaly** in adults. If the tumor arises before puberty, the individual may grow to an extraordinary height. After linear growth is no longer possible, on the other hand, the characteristic features of acromegaly arise, including greatly enlarged hands and feet, vertebral changes attributable to osteoarthritis, soft tissue swelling, hirsutism, and protrusion of the brow and jaw. Abnormal growth of internal organs may eventually impair their function such that the condition, which has an insidious onset, can prove fatal if left untreated. Hypersecretion of growth hormone is accompanied by hypersecretion of prolactin in 20–40% of patients with acromegaly. About 25% of patients have abnormal glucose tolerance tests, and 4% develop lactation in the absence of pregnancy. Acromegaly can be caused by extrapituitary as well as intrapituitary growth hormone–secreting tumors and by hypothalamic tumors that secrete GHRH, but the latter are rare.

THERAPEUTIC HIGHLIGHTS

The mainstay of therapy for acromegaly remains the use of somatostatin analogues that inhibit the secretion of growth hormone. A growth hormone receptor antagonist has become available and has been found to reduce plasma IGF-I and produce clinical improvement in cases of acromegaly that do not respond to other treatments. Surgical removal of the pituitary tumor is also helpful in both acromegaly and gigantism, but sometimes challenging to perform due to the tumor's often invasive nature. In any case, adjuvant pharmacologic therapy must often be continued after surgery to control ongoing symptoms.

Effect on Protein & Electrolyte Homeostasis

Growth hormone is a protein anabolic hormone and produces a positive nitrogen and phosphorus balance, a rise in plasma phosphorus, and a fall in blood urea nitrogen and amino acid levels. In adults with growth hormone deficiency, recombinant human growth hormone produces an increase in lean body mass and a decrease in body fat, along with an increase in metabolic rate and a fall in plasma cholesterol. Gastrointestinal absorption of Ca^{2+} is increased. Na^+ and K^+ excretion is reduced by an action independent of the adrenal glands, probably because these electrolytes are diverted from the kidneys to the growing tissues. On the other hand, excretion of the amino acid 4-hydroxyproline is increased during this growth, reflective of the ability of growth hormone to stimulate the synthesis of soluble collagen

Effects on Carbohydrate & Fat metabolism

The actions of growth hormone on carbohydrate metabolism are discussed in Chapter 24. At least some forms of growth hormone are diabetogenic because they increase hepatic glucose output and exert an anti-insulin effect in muscle. Growth hormone is also ketogenic and increases circulating free fatty acid (FFA) levels. The increase in plasma FFA, which takes several hours to develop, provides a ready source of energy for the tissues during hypoglycemia, fasting, and stressful stimuli. Growth hormone does not stimulate β cells of the pancreas directly, but it increases the ability of the pancreas to respond to insulinogenic stimuli such as arginine and glucose. This is an additional way growth hormone promotes growth, since insulin has a protein anabolic effect

Somatomedins

The effects of growth hormone on growth, cartilage, and protein metabolism depend on an interaction between growth hormone and somatomedins, which are

polypeptide growth factors secreted by the liver and other tissues. The first of these factors isolated was called sulfation factor because it stimulated the incorporation of sulfate into cartilage. However, it also stimulated collagen formation, and its name was changed to somatomedin. It then became clear that there are a variety of different somatomedins and that they are members of an increasingly large family of growth factors that affect many different tissues and organs.

The principal (and in humans probably the only) circulating somatomedins are insulin-like growth factor I (IGF-I, somatomedin C) and IGF-II. These factors are closely related to insulin, except that their C chains are not separated and they have an extension of the A chain called the D domain. The hormone relaxin is also a member of this family. Humans have two related relaxin isoforms, and both resemble IGF-II humans a variant form of IGF-I lacking three amino terminal amino acid residues has been found in the brain, and there are several variant forms of human IGF-II .

The mRNAs for IGF-I and IGF-II are found in the liver, other proteins to intracellular organelles. Secretion of IGF-I is independent of growth hormone before birth but is stimulated by growth hormone after birth, and it has pronounced growth-stimulating activity. Its concentration in plasma rises during childhood and peaks at the time of puberty, then declines to low levels in old age. IGF-II is largely independent of growth hormone and plays a role in the growth of the fetus before birth. In human fetuses in which it is overexpressed, several organs, especially the tongue, other muscles, kidneys, heart, and liver, develop out of proportion to the rest of the body. In adults, the gene for IGF-II is expressed only in the choroid plexus and meninges

Chapter 19
Thyroid Gland

Introduction

The thyroid gland is one of the larger endocrine glands of the body. The gland has two primary functions. The first is to secrete the thyroid hormones, which maintain the level of metabolism in the tissues that is optimal for their normal function. Thyroid hormones stimulate O2 consumption by most of the cells in the body, help regulate lipid and carbohydrate metabolism, and thereby influence body mass and mentation. Consequences of thyroid gland dysfunction depend on the life stage at which they occur. The thyroid is not essential for life, but its absence or hypofunction during fetal and neonatal life results in severe mental retardation and dwarfism. In adults, hypothyroidism is accompanied by mental and physical slowing and poor resistance to cold. Conversely, excess thyroid secretion leads to body wasting, nervousness, tachycardia, tremor, and excess heat production. Thyroid function is controlled by the thyroid-stimulating hormone (TSH, thyrotropin) of the anterior pituitary. The secretion of this hormone is in turn increased by thyrotropin-releasing hormone (TRH) from the hypothalamus and is also subject to negative feedback control by high circulating levels of thyroid hormones acting on the anterior pituitary and the hypothalamus. The second function of the thyroid gland is to secrete calcitonin, a hormone that regulates circulating levels of calcium.

FORMATION & SECRETION OF THYROID HORMONE

Thyroglobulin is a glycoprotein made up of two subunits and has a molecular weight of 660 kDa. It contains 10% carbohydrate by weight. It also contains 123 tyrosine residues, but only 4–8 of these are normally incorporated into thyroid

hormones. Thyroglobulin is synthesized in the thyroid cells and secreted into the colloid by exocytosis of granules. The oxidation and reaction of iodide with the secreted thyroglobulin is mediated by **thyroid peroxidase,** a membrane-bound enzyme found in the thyrocyte apical membrane. The thyroid hormones so produced remain part of the thyroglobulin molecule until needed. As such, colloid represents a reservoir of thyroid hormones, and humans can ingest a diet completely devoid of iodide for up to 2 months before a decline in circulating thyroid hormone levels is seen. When there is a need for thyroid hormone secretion, colloid is internalized by the thyrocytes by endocytosis, and directed toward lysosomal degradation Thyroid hormone synthesis is a multistep process. Thyroid peroxidase generates reactive iodine species that can attack thyroglobulin. The first product is monoiodotyrosine (MIT). MIT is next iodinated on the carbon 5 position to form diiodotyrosine (DIT). Two DIT molecules then undergo an oxidative condensation to form T4 with the elimination of the alanine side chain from the molecule that forms the outer ring. There are two theories of how this **coupling reaction** occurs. One holds that the coupling occurs with both DIT molecules attached to thyroglobulin (intramolecular coupling). The other holds that the DIT that forms the outer ring is first detached from thyroglobulin (intermolecular coupling). In either case, thyroid peroxidase is involved in coupling as well as iodination. T3 is formed by condensation of MIT with DIT. A small amount of RT3 is also formed, probably by condensation of DIT with MIT. In the normal human thyroid, the average distribution of iodinated compounds is 3% MIT, 33% DIT, 35% T4, and 7% T3. Only traces of RT3 and other components are present. The human thyroid secretes about 80 μg (103 nmol) of T4, 4 μg (7 nmol) of T3, and 2 μg (3.5 nmol) of RT3 per day

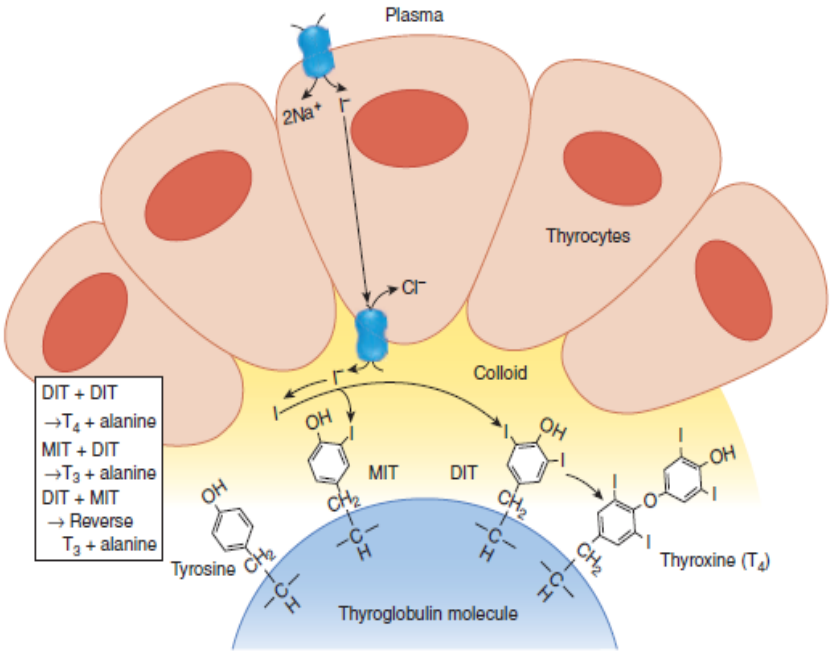


FIGURE 19–6 **Outline of thyroid hormone biosynthesis.** Iodide (I^-) is transported vectorially from the plasma across the epithelial cells of the thyroid gland by specific transporters. The iodide is converted to iodine, which reacts with tyrosine residues exposed on the surface of thyroglobulin molecules resident in the colloid. Iodination of tyrosine takes place at the apical border of the thyroid cells while the tyrosine moieties remain bound to thyroglobulin via peptide linkages.

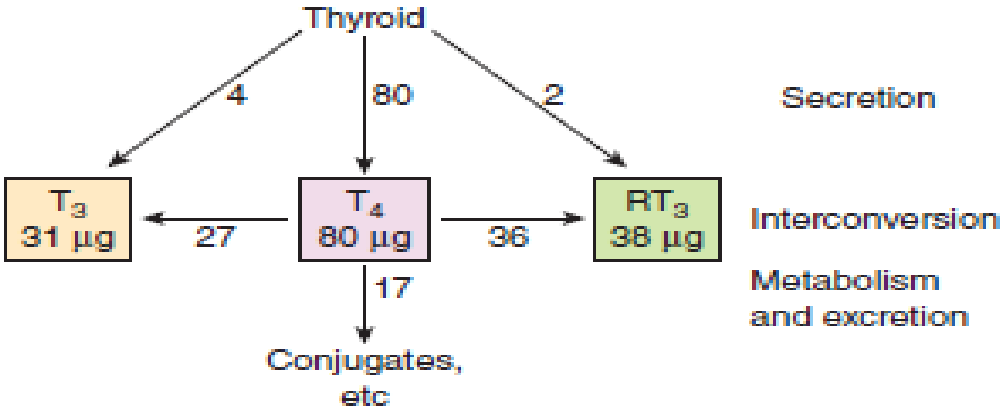


FIGURE 19–7 **Secretion and interconversion of thyroid hormones in normal adult humans.** Figures are in micrograms per day. Note that most of the T_3 and RT_3 are formed from T_4 deiodination in the tissues and only small amounts are secreted by the thyroid. T_4 is also conjugated for subsequent excretion from the body.

protein binding

The normal total **plasma T**4 level in adults is approximately 8 µg/dL (103 nmol/L), and the **plasma T**3 level is approximately 0.15 µg/dL (2.3 nmol/L). T4 and T3 are relatively lipophilic; thus, their free forms in plasma are in equilibrium with a much larger pool of protein-bound thyroid hormones in plasma and in tissues. Free thyroid hormones are added to the circulating pool by the thyroid. It is the free thyroid hormones in plasma that are physiologically active and that feed back to inhibit pituitary secretion of TSH (**Figure 19–8**).

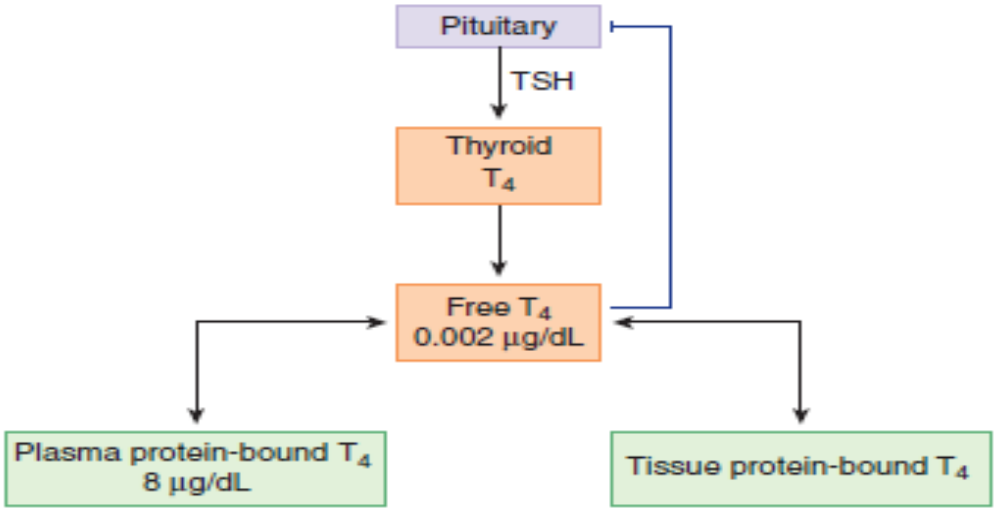


FIGURE 19–8 Regulation of thyroid hormone synthesis. T_4 is secreted by the thyroid in response to TSH. Free T_4 secreted by the thyroid into the circulation is in equilibrium with T_4 bound to both plasma and tissue proteins. Free T_4 also feeds back to inhibit TSH secretion by the pituitary.

The plasma proteins that bind thyroid hormones are **albumin,** a prealbumin called **transthyretin** (formerly called **thyroxine-binding prealbumin),** and a globulin known as **thyroxine-binding globulin (TBG).** Of the three proteins, albumin has the largest **capacity** to bind T4 (ie, it can bind the most T4 before becoming

saturated) and TBG has the smallest capacity. However, the **affinities** of the proteins for T4 (ie, the avidity with which they bind T4 under physiologic conditions) are such that most of the circulating T4 is bound to TBG (**Table 19–1**), with over a third of the binding sites on the protein occupied. Smaller amounts of T4 are bound to transthyretin and albumin. The half-life of transthyretin is 2 days, that of TBG is 5 days, and that of albumin is 13 days.

TABLE 19–1 Binding of thyroid hormones to plasma proteins in normal adult humans.

Protein	Plasma Concentration (mg/dL)	Amount of Circulating Hormone Bound (%)	
		T_4	T_3
Thyroxine-binding globulin (TBG)	2	67	46
Transthyretin (thyroxine-binding prealbumin, TBPA)	15	20	1
Albumin	3500	13	53

Metabolism of Thyroid Hormones

T4 and T3 are deiodinated in the liver, the kidneys, and many other tissues. These deiodination reactions serve not only to catabolize the hormones, but also to provide a local supply specifically of T3, which is believed to be the primary mediator of the physiologic effects of thyroid secretion. One third of the circulating T4 is normally converted to T3 in adult humans, and 45% is converted to RT3. As shown in Figure 19–7, only about 13% of the circulating T3 is secreted by the thyroid while 87% is formed by deiodination of T4; similarly, only 5% of the circulating RT3 is secreted by the thyroid and 95% is formed by deiodination of T4

Regulation of Thyroid Secretion

Thyroid function is regulated primarily by variations in the circulating level of pituitary TSH (Figure 19–8). TSH secretion is increased by the hypothalamic hormone TRH and inhibited in a negative feedback manner by circulating free T4 and T3. The effect of T4 is enhanced by production

Effects of TSH on the Thyroid

When the pituitary is removed, thyroid function is depressed and the gland atrophies; when TSH is administered, thyroid function is stimulated. Within a few minutes after the injection of TSH, there are increases in iodide binding, synthesis of T3, T4, and iodotyrosines, secretion of thyroglobulin into the colloid, and endocytosis of colloid. Iodide trapping is increased in a few hours; blood flow increases; and, with long-term TSH treatment, the cells hypertrophy and the weight of the gland increases. Whenever TSH stimulation is prolonged, the thyroid becomes detectably enlarged. Enlargement of the thyroid is called a **goit**

Reduced Thyroid Function

The syndrome of adult **hypothyroidism** is generally called **myxedema,** although this term is also used to refer specifically to the skin changes in the syndrome. Hypothyroidism may be the end result of a number of diseases of the thyroid gland, or it may be secondary to pituitary or hypothalamic failure. In the latter two conditions, the thyroid remains able to respond to TSH. Thyroid function may be reduced by a number of conditions (Table 19–3). For example, when the dietary iodine intake falls below 50 µg/day, thyroid hormone synthesis is inadequate and secretion declines. As a result of increased TSH secretion, the thyroid hypertrophies, producing an **iodine deficiency goiter** that may become very large. Such "endemic goiters" have been substantially reduced by the practice of adding iodide to table salt. Drugs may also inhibit thyroid function. Most do so either by interfering with the iodide-trapping mechanism or by blocking the organic binding of iodine. In either case, TSH secretion is stimulated by the decline in circulating thyroid hormones, and a goiter is produced. Paradoxically, another substance that inhibits thyroid function under certain conditions is iodide itself. In normal individuals, large doses of iodide act directly on the thyroid to produce a mild and transient inhibition of organic binding of iodide and hence of hormone synthesis. This inhibition is known as the **Wolff-Chaikoff effect.**

In completely athyreotic adults, the BMR falls to about 40%. The hair is coarse and sparse, the skin is dry and yellowish (carotenemia), and cold is poorly tolerated. Mentation is slow, memory is poor, and in some patients there are severe mental symptoms ("myxedema madness"). Plasma cholesterol is elevated. Children who are hypothyroid from birth or before are called **cretins.** They are dwarfed and mentally retarded. Worldwide, congenital hypothyroidism is one of the most common causes of preventable mental retardation. The main causes are included in Table 19–3. They include not only maternal iodine deficiency and various congenital abnormalities of the fetal hypothalamo–pituitary–thyroid axis, but also maternal antithyroid antibodies that cross the placenta and damage the fetal thyroid. T_4 crosses the placenta, and unless the mother is hypothyroid, growth and development are normal until birth. If treatment is started at birth, the prognosis for normal growth and development is good, and mental retardation can generally be avoided; for this reason, screening tests for congenital hypothyroidism are becoming routine. When the mother is hypothyroid as well, as in the case of iodine deficiency, the mental deficiency is more severe and less responsive to treatment after birth. It has been estimated that 20 million people in the world now have various degrees of brain damage caused by iodine deficiency in utero.

Uptake of tracer doses of radioactive iodine can be used to assess thyroid function (contrast this with the use of large doses to ablate thyroid tissue in cases of hyperthyroidism (Clinical Box 19–2).

THERAPEUTIC HIGHLIGHTS

The treatment of hypothyroidism depends on the underlying mechanisms. Iodide deficiency can be addressed by adding it to the diet, as is done routinely in developed countries with the use of iodized salt. In congenital hypothyroidism, levothyroxine—a synthetic form of the thyroid hormone T_4—can be given. It is important that this take place as soon as possible after birth, with levels regularly monitored, to minimize long-term adverse effects.

CLINICAL BOX 19–2

Hyperthyroidism

The symptoms of an overactive thyroid gland follow logically from the actions of thyroid hormone discussed in this chapter. Thus, hyperthyroidism is characterized by nervousness; weight loss; hyperphagia; heat intolerance; increased pulse pressure; a fine tremor of the outstretched fingers; warm, soft skin; sweating; and a BMR from +10 to as high as +100. It has various causes (Table 19–4); however, the most common cause is **Graves disease (Graves hyperthyroidism),** which accounts for 60–80% of the cases. This is an autoimmune disease, more common in women, in which antibodies to the TSH receptor stimulate the receptor. This produces marked T_4 and T_3 secretion and enlargement of the thyroid gland (goiter). However, due to the feedback effects of T_4 and T_3, plasma TSH is low, not high. Another hallmark of Graves disease is the occurrence of swelling of tissues in the orbits, producing protrusion of the eyeballs **(exophthalmos).** This occurs in 50% of patients and often precedes the development of obvious hyperthyroidism. Other antithyroid antibodies are present in Graves disease, including antibodies to thyroglobulin and thyroid peroxidase. In Hashimoto thyroiditis, autoimmune antibodies and infiltrating cytotoxic T cells ultimately destroy the thyroid, but during the early stage the inflammation of the gland causes excess thyroid hormone secretion and thyrotoxicosis similar to that seen in Graves disease.

THERAPEUTIC HIGHLIGHTS

Some of the symptoms of hyperthyroidism can be controlled by the **thioureylenes.** These are a group of compounds related to thiourea, which inhibit the iodination of monoiodotyrosine and block the coupling reaction. The two used clinically are propylthiouracil and methimazole. Iodination of tyrosine is inhibited because propylthiouracil and methimazole compete with tyrosine residues for iodine and become iodinated. In addition, propylthiouracil but not methimazole inhibits D_2 deiodinase, reducing the conversion of T_4 to T_3 in many extrathyroidal tissues. In severe cases, hyperthyroidism can also be treated by the infusion of radioactive iodine, which accumulates in the gland and then partially destroys it. Surgery is also considered if the thyroid becomes so large that it affects swallowing and/or breathing.

TABLE 19–4 Causes of hyperthyroidism.

Thyroid overactivity
Graves disease
Solitary toxic adenoma
Toxic multinodular goiter
Early stages of Hashimoto thyroiditis[a]
TSH-secreting pituitary tumor
Mutations causing constitutive activation of TSH receptor
Other rare causes
Extrathyroidal
Administration of T_3 or T_4 (factitious or iatrogenic hyperthyroidism)
Ectopic thyroid tissue

Effects of Thyroid Hormones

Some of the widespread effects of thyroid hormones in the body are secondary to stimulation of O2 consumption **(calorigenic action),** although the hormones also affect growth and development in mammals, help regulate lipid metabolism, and increase the absorption of carbohydrates from the intestine (**Table 19–5**). They also increase the dissociation of oxygen from hemoglobin by increasing red cell 2,3-diphosphoglycerate (DPG)

Mechanism of action

Thyroid hormones enter cells and T3 binds to TR in the nuclei. T4 can also bind, but not as avidly. The hormone–receptor complex then binds to DNA via zinc fingers and increases (or in some cases, decreases) the expression of a variety of different genes that code for proteins that regulate cell function. Thus, the nuclear receptors for thyroid hormones are members of the superfamily of hormone-sensitive nuclear transcription factors.

TABLE 19–5 Physiologic effects of thyroid hormones.

Target Tissue	Effect	Mechanism
Heart	Chronotropic and inotropic	Increased number of β-adrenergic receptors Enhanced responses to circulating catecholamines Increased proportion of α-myosin heavy chain (with higher ATPase activity)
Adipose tissue	Catabolic	Stimulated lipolysis
Muscle	Catabolic	Increased protein breakdown
Bone	Developmental	Promote normal growth and skeletal development
Nervous system	Developmental	Promote normal brain development
Gut	Metabolic	Increased rate of carbohydrate absorption
Lipoprotein	Metabolic	Formation of LDL receptors
Other	Calorigenic	Stimulated oxygen consumption by metabolically active tissues (exceptions: testes, uterus, lymph nodes, spleen, anterior pituitary) Increased metabolic rate

Chapter 20

The Adrenal Medulla & Adrenal Cortex:

There are two endocrine organs in the adrenal gland, one surrounding the other. The main secretions of the inner **adrenal medulla** are the catecholamines **epinephrine, norepinephrine,** and **dopamine;** the outer **adrenal cortex secretes steroid hormones.** The adrenal cortex secretes **glucocorticoids,** steroids with widespread effects on the metabolism of carbohydrate and protein; and a **mineralocorticoid** essential to the maintenance of Na+ balance and extracellular fluid (ECF) volume. It is also a secondary site of **androgen** synthesis, secreting sex hormones such as testosterone, which can exert effects on reproductive function.

The adrenal medulla, which constitutes 28% of the mass of the adrenal gland, two cell types can be distinguished morphologically: an epinephrine-secreting type and a norepinephrine-secreting type. In humans, 90% of the cells are the epinephrine-secreting type and 10% are the norepinephrine-secreting type. In adult mammals, the adrenal cortex is divided into three zones ,the outer **zona glomerulosa , then zona fasciculate and zona reticularis.** All three cortical zones secrete corticosterone, but the active enzymatic mechanism for aldosterone biosynthesis is limited to the zona glomerulosa, whereas the enzymatic mechanisms for forming cortisol and sex hormones are found in the two inner zones.

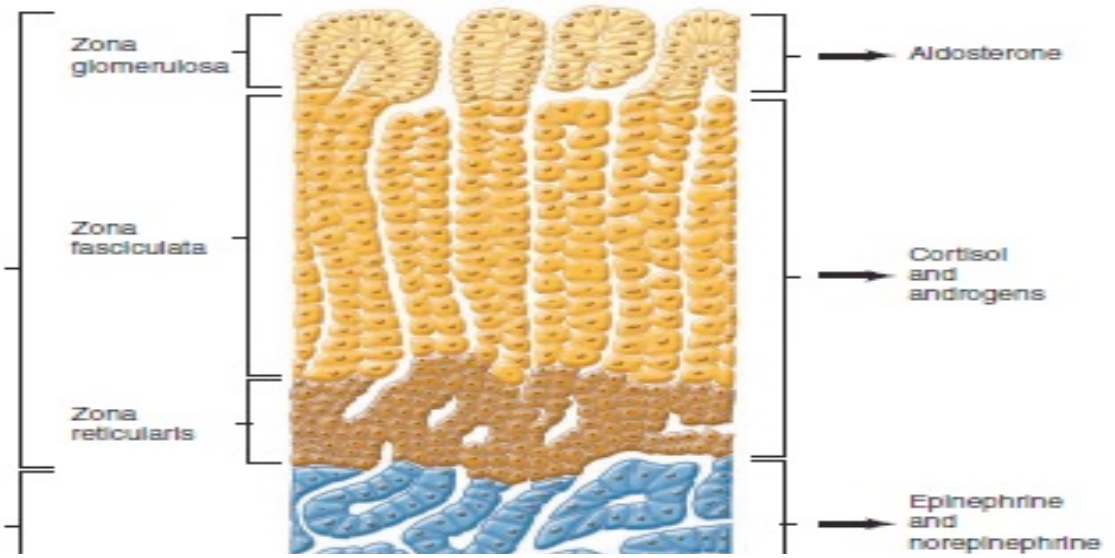


FIGURE 1: Section through an adrenal gland showing both the medulla and the zones of the cortex, as well as the hormones they secrete.

ADRENAL MEDULLA: STRUCTURE & FUNCTION OF MEDULLARY HORMONES:

CATECHOLAMINES

Norepinephrine, epinephrine, and small amounts of dopamine are synthesized by the adrenal medulla. Norepinephrine is formed by hydroxylation and decarboxylation of tyrosine, and epinephrine by methylation of norepinephrine. In plasma, about 95% of the dopamine and 70% of the norepinephrine and epinephrine are conjugated to sulfate. Sulfate conjugates are inactive and their function is unsettled. The catecholamines have a half-life of about 2 min in the circulation.

EFFECTS OF EPINEPHRINE & NOREPINEPHRINE:

The norepinephrine and epinephrine exert metabolic effects that include glycogenolysis in liver and skeletal muscle, mobilization of free fatty acids (FFA), increased plasma lactate, and stimulation of the metabolic rate. The effects of norepinephrine and epinephrine are brought about by actions on two classes of

receptors: α- and β-adrenergic receptors. In addition, the catecholamines increase the secretion of insulin and glucagon via β-adrenergic mechanisms and inhibit the secretion of these hormones via α-adrenergic mechanisms. Norepinephrine and epinephrine both increase the force and rate of contraction of the isolated heart. These responses are mediated by β1-receptors. Norepinephrine produces vasoconstriction in most if not all organs via α1-receptors, but epinephrine dilates the blood vessels in skeletal muscle and the liver via β2-receptors.

EFFECTS OF DOPAMINE:

The physiologic function of the dopamine in the circulation is unknown. However, injected dopamine produces renal vasodilation, probably by acting on a specific dopaminergic receptor. It produces vasoconstriction, probably by releasing norepinephrine, and it has a positive inotropic effect on the heart by an action on β1-adrenergic receptors. Dopamine is made in the renal cortex. It causes natriuresis and may exert this effect by inhibiting renal Na, K, ATPase.

REGULATION OF ADRENAL MEDULLARY SECRETION

Certain drugs act directly on the adrenal medulla, but physiologic stimuli affect medullary secretion through the nervous system. Catecholamine secretion is low in basal states, but the secretion of epinephrine and, to a lesser extent, that of norepinephrine is reduced even further during sleep. Increased adrenal medullary secretion is part of the diffuse sympathetic discharge provoked in emergency situations, which Cannon called the “emergency function of the sympathoadrenal system.” The ways in which this discharge prepares the individual for flight or fight and the increases in plasma catecholamines under various conditions.

ADRENAL CORTEX: STRUCTURE & BIOSYNTHESIS OF ADRENOCORTICAL HORMONES

CLASSIFICATION & STRUCTURE

The hormones of the adrenal cortex are derivatives of cholesterol. Like cholesterol, bile acids, vitamin D, and ovarian and testicular steroids, they contain the cyclopentanoperhydrophenanthrene nucleus.

SECRETED STEROIDS:

Innumerable steroids have been isolated from adrenal tissue, but the only steroids normally secreted in physiologically significant amounts are the mineralocorticoid **aldosterone,** the glucocorticoids **cortisol** and **corticosterone,** and the androgens **dehydroepiandrosterone (DHEA)** and **androstenedione**.

Deoxycorticosterone is a mineralocorticoid that is normally secreted in about the same amount as aldosterone but has only 3% of the mineralocorticoid activity of aldosterone

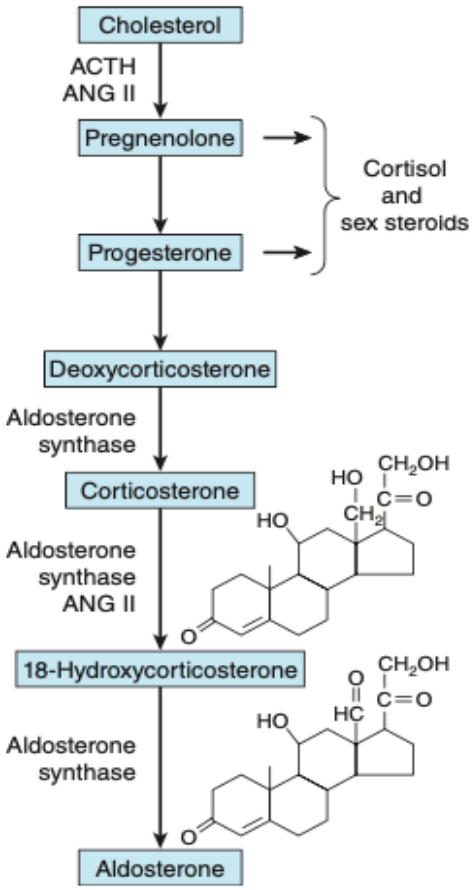


FIGURE 20–8 **Hormone synthesis in the zona glomerulosa.**

STEROID BIOSYNTHESIS: The precursor of all steroids is cholesterol. Some of the cholesterol is synthesized from acetate, but most of it is taken up from LDL in the circulation. **Cholesterol ester hydrolase** catalyzes the formation of free cholesterol in the lipid droplets. The cholesterol is transported to mitochondria by a sterol carrier protein. In the mitochondria, it is converted to pregnenolone. Pregnenolone moves to the smooth endoplasmic reticulum, where some of it is dehydrogenated to form progesterone. ACTH binds to high-affinity receptors on the plasma membrane of adrenocortical cells. This activates adenylyl cyclase via Gs. The resulting reactions lead to a prompt increase in the formation of pregnenolone and its derivatives. Over longer periods, ACTH also increases the synthesis of the P450s involved in the synthesis of glucocorticoids.

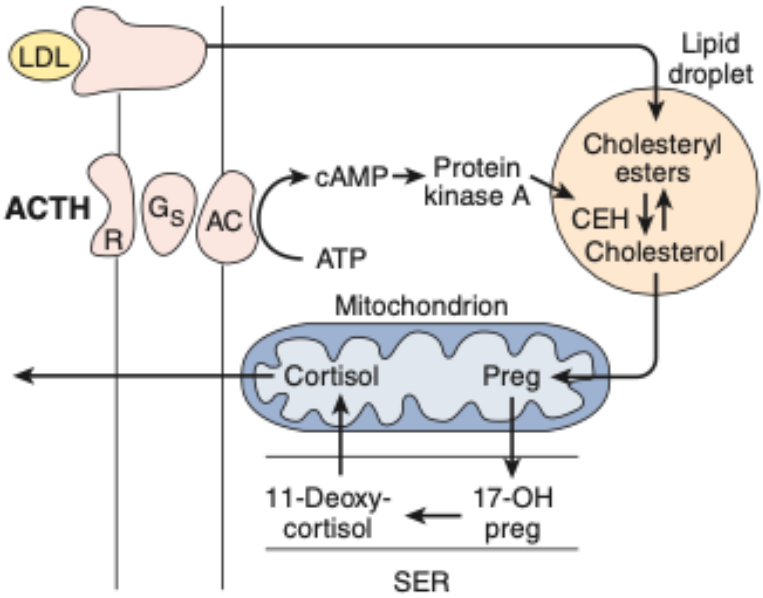


FIGURE 20–9 Mechanism of action of ACTH on cortisol-secreting cells in the inner two zones of the adrenal cortex. When ACTH binds to its receptor (R), adenylyl cyclase (AC) is activated via Gs. The resulting increase in cAMP activates protein kinase A, and the kinase phosphorylates cholesteryl ester hydrolase (CEH), increasing its activity. Consequently, more free cholesterol is formed and converted to pregnenolone. Note that in the subsequent steps in steroid biosynthesis, products are shuttled between the mitochondria and the smooth endoplasmic reticulum (SER). Corticosterone is also synthesized and secreted.

TRANSPORT, METABOLISM, & EXCRETION OF ADRENOCORTICAL HORMONES:

GLUCOCORTICOID BINDING

Cortisol is bound in the circulation to an α globulin called transcortin or corticosteroid-binding globulin (CBG). CBG is synthesized in the liver and its production is increased by estrogen. CBG levels are elevated during pregnancy and depressed in cirrhosis, nephrosis, and multiple myeloma. When the CBG level rises, more cortisol is bound, and initially the free cortisol level drops. This stimulates

ACTH secretion, and more cortisol is secreted. Changes in the opposite direction occur when the CBG level falls.

A minor degree of binding to albumin also takes place. The half-life of cortisol in the circulation is therefore longer (about 60–90 min). Bound steroids are physiologically inactive. In addition, relatively little free cortisol & corticosterone are found in the urine because of protein binding. The bound cortisol functions as a circulating reservoir of hormone that keeps a supply of free cortisol available to the tissue.

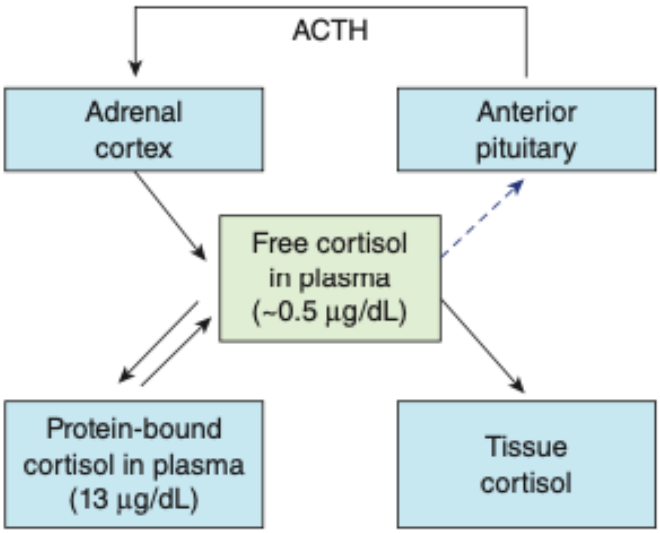


FIGURE 20–10 The interrelationships of free and bound cortisol. The dashed arrow indicates that cortisol inhibits ACTH secretion. The value for free cortisol is an approximation; in most studies, it is calculated by subtracting the protein-bound cortisol from the total plasma cortisol.

METABOLISM & EXCRETION OF GLUCOCORTICOIDS

Cortisol is metabolized in the liver, which is the principal site of glucocorticoid catabolism. Most of the cortisol is reduced to dihydrocortisol and then to

tetrahydrocortisol, which is conjugated to glucuronic acid . Cortisone is an active glucocorticoid because it is converted to cortisol, and it is well known because of its extensive use in medicine. It is not secreted in appreciable quantities by the adrenal glands. Little, if any, of the cortisone formed in the liver enters the circulation, because it is promptly reduced and conjugated to form tetrahydrocortisone glucuronides.

ALDOSTERONE

Aldosterone is bound to protein to only a slight extent, and its half-life is short (about 20 min). The amount secreted is small when compared with a cortisol level (bound and free). Much of the aldosterone is converted in the liver to the tetrahydroglucuronide derivative, but some is changed in the liver and in the kidneys to an 18-glucuronide.

17-KETOSTEROIDS

The major adrenal androgen is the 17-ketosteroid dehydroepiandrosterone, although androstenedione is also secreted. The 11-hydroxy derivative of androstenedione and the 17-ketosteroids formed from cortisol and cortisone by side chain cleavage in the liver. Testosterone is also converted to a 17-ketosteroid. Because the daily 17-ketosteroid excretion in normal adults is 15 mg in men and 10 mg in women, about two-thirds of the urinary ketosteroids in men are secreted by the adrenal or formed from cortisol in the liver and about one-third are of testicular origin.

EFFECTS OF ADRENAL ANDROGENS & ESTROGENS

ANDROGENS

Androgens are the hormones that exert masculinizing effects and they promote protein anabolism and growth. Testosterone from the testes is the most active

androgen and the adrenal androgens have less than 20% of its activity. Secretion of the adrenal androgens is controlled acutely by ACTH and not by gonadotropins. In normal males, so it is clear that these hormones exert very little masculinizing effect when secreted in normal amounts. However, they can produce appreciable masculinization when secreted in excessive amounts. In adult males, excess adrenal androgens merely accentuate existing.

ESTROGENS

The adrenal androgen androstenedione is converted to testosterone and to estrogens (aromatized) in fat and other peripheral tissues. This is an important source of estrogens in men and postmenopausal women.

PHYSIOLOGIC EFFECTS OF GLUCOCORTICOIDS

MECHANISM OF ACTION

The multiple effects of glucocorticoids are triggered by binding to glucocorticoid receptors, and the steroid–receptor complexes act as transcription factors that promote the transcription of certain segments of DNA.

EFFECTS ON INTERMEDIARY METABOLISM: .They include increased protein catabolism and increased hepatic glycogenesis and gluconeogenesis. Glucose-6-phosphatase activity is increased, and the plasma glucose level rises. Glucocorticoids exert an anti-insulin action in peripheral tissues and make diabetes worse. However, the brain and the heart are spared, so the increase in plasma glucose provides extra glucose to these vital organs. In diabetics, glucocorticoids raise plasma lipid levels and increase ketone body formation.

EFFECTS ON ACTH SECRETION

Glucocorticoids inhibit ACTH secretion, which represents a negative feedback response on the pituitary.

EFFECTS ON THE NERVOUS SYSTEM

Changes in the nervous system in adrenal insufficiency that are reversed only by glucocorticoids include the appearance of electroencephalographic waves slower than the normal β rhythm, and personality changes. The latter, which are mild, include irritability, apprehension, and inability to concentrate.

EFFECTS ON WATER METABOLISM

Adrenal insufficiency is characterized by an inability to excrete a water load, causing the possibility of water intoxication. Only glucocorticoids repair this deficit. In patients with adrenal insufficiency who have not received glucocorticoids, glucose infusion may cause high fever ("glucose fever") followed by collapse and death.

EFFECTS ON THE BLOOD CELLS & LYMPHATIC ORGANS: Glucocorticoids decrease the number of circulating eosinophils by increasing their sequestration in the spleen and lungs. Glucocorticoids also lower the number of basophils in the circulation and increase the number of neutrophils, platelets, and red blood cells .

RESISTANCE TO STRESS

The term **stress** as used in biology has been defined as any change in the environment that changes or threatens to change an existing optimal steady state. Most, if not all, of these stresses activate processes at the molecular, cellular, or systemic level that tend to restore the previous state, that is, they are homeostatic

reactions. Some, but not all, of the stresses stimulate ACTH secretion. The increase in ACTH secretion is essential for survival when the stress is severe. Most of the stressful stimuli that increase ACTH secretion also activate the sympathetic nervous system, and part of the function of circulating glucocorticoids may be maintenance of vascular reactivity to catecholamines.

It should also be noted that the increase in ACTH, which is beneficial in the short term, becomes harmful and disruptive in the long term, causing among other things, the abnormalities of Cushing syndrome

PHARMACOLOGIC & PATHOLOGIC EFFECTS OF GLUCOCORTICOIDS

CUSHING SYNDROME

The clinical picture produced by prolonged increases in plasma glucocorticoids was described by Harvey Cushing and is called **Cushing syndrome** . Patients with Cushing syndrome are protein-depleted as a result of excess protein catabolism. The skin and subcutaneous tissues are therefore thin and the muscles are poorly developed. The hair is thin and scraggly. Many patients with the disease have some increase in facial hair and acne, but this is caused by the increased secretion of adrenal androgens and often accompanies the increase in glucocorticoid secretion. Body fat is redistributed in a characteristic way. The extremities are thin, but fat collects in the abdominal wall, face, and upper back, where it produces a “buffalo hump.”

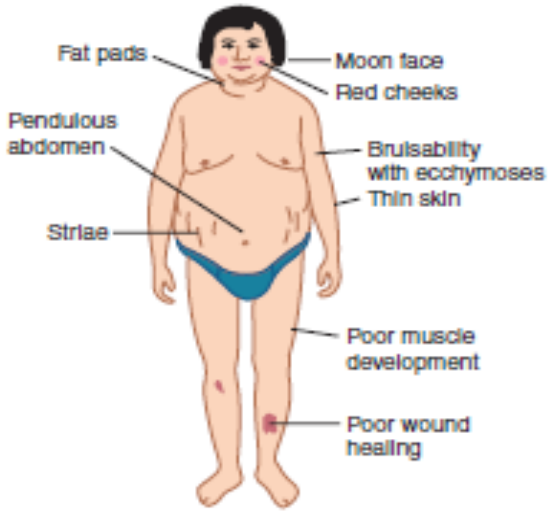


FIGURE 20–13 Typical findings in Cushing syndrome.

The salt and water retention plus the facial obesity cause the characteristic plethoric, rounded "moon-faced" appearance, and there may be significant K+ depletion and weakness. About 85% of patients with Cushing syndrome are hypertensive. The hypertension may be due to increased deoxycorticosterone secretion, increased angiotensinogen secretion, or a direct glucocorticoid effect on blood vessels .

ANTI-INFLAMMATORY & ANTI-ALLERGIC EFFECTS OF GLUCOCORTICOIDS

Glucocorticoids inhibit the inflammatory response to tissue injury. The glucocorticoids also suppress manifestations of allergic disease that are due to the release of histamine from mast cells and basophils. Both of these effects require high levels of circulating glucocorticoids and cannot be produced by administering steroids without producing the other manifestations of glucocorticoid excess.

REGULATION OF GLUCOCORTICOID SECRETION

ROLE OF ACTH

Both basal secretion of glucocorticoids and the increased secretion provoked by stress depend on ACTH from the anterior pituitary, its half-life in the circulation in humans is about 10 min. ACTH not only produces prompt increases in glucocorticoid secretion but also increases the sensitivity of the adrenal to subsequent doses of ACTH. ACTH are necessary to restore normal adrenal responses to ACTH.

CIRCADIAN RHYTHM

ACTH is secreted in irregular bursts throughout the day and plasma cortisol tends to rise and fall in response to these bursts . In humans, the bursts are most frequent in the early morning, and about 75% of the daily production of cortisol occurs between 4:00 AM and 10:00 AM. The bursts are least frequent in the evening. This **diurnal (circadian) rhythm** in ACTH secretion is present in patients with adrenal insufficiency receiving constant doses of glucocorticoids

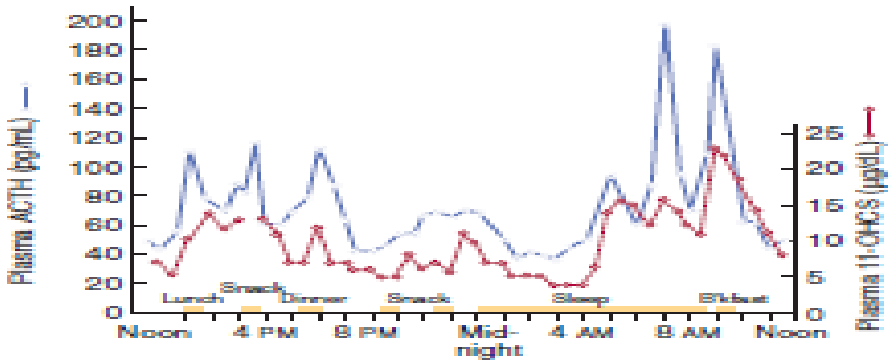


FIGURE 20–15 Fluctuations in plasma ACTH and glucocorticoids throughout the day in a normal girl (age 16). Tl

GLUCOCORTICOID FEEDBACK

Free glucocorticoids inhibit ACTH secretion, and the degree of pituitary inhibition is proportional to the circulating glucocorticoid level. The inhibitory effect is exerted at both the pituitary and the hypothalamic levels. A drop in resting corticoid levels stimulates ACTH secretion, and in chronic adrenal insufficiency the rate of ACTH synthesis and secretion is markedly increased.

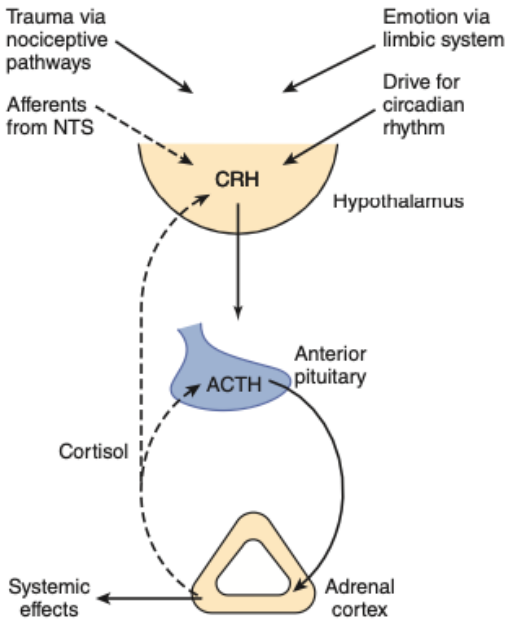


FIGURE 20–17 Feedback control of the secretion of cortisol and other glucocorticoids via the hypothalamic-pituitary-adrenal axis. The dashed arrows indicate inhibitory effects and the solid arrows indicate stimulating effects. NTS, nucleus tractus solitarius.

EFFECTS OF MINERALOCORTICOIDS:

ACTIONS

Aldosterone and other steroids with mineralocorticoid activity increase the reabsorption of Na+ from the urine, sweat, saliva, and the contents of the colon. Thus, mineralocorticoids cause retention of Na+ in the ECF. This expands ECF volume. Under the influence of aldosterone, increased amounts of Na+ are in effect

exchanged for K+ and H+ in the renal tubules, producing a K+ diuresis and an increase in urine acidity.

MECHANISM OF ACTION

Like many other steroids, aldosterone binds to a cytoplasmic receptor, and the receptor–hormone complex moves to the nucleus where it alters the transcription of mRNAs. The aldosterone-stimulated proteins have two effects—a rapid effect, to increase the activity of epithelial sodium channels (ENaCs) by increasing the insertion of these channels into the cell membrane from a cytoplasmic pool; and a slower effect to increase the synthesis of ENaCs.

REGULATION OF ALDOSTERONE SECRETION

STIMULI

The principal conditions that increase aldosterone secretion are summarized in **Table 20–6**. Some of them also increase glucocorticoid secretion; others selectively affect the output of aldosterone. The primary regulatory factors involved are ACTH from the pituitary, renin from the kidney via angiotensin II, and a direct stimulatory effect on the adrenal cortex of a rise in plasma K+ concentration.

TABLE 20–6 Conditions that increase aldosterone secretion.

Glucocorticoid secretion also increased
Surgery
Anxiety
Physical trauma
Hemorrhage
Glucocorticoid secretion unaffected
High potassium intake
Low sodium intake
Constriction of inferior vena cava in thorax
Standing
Secondary hyperaldosteronism (in some cases of heart failure, cirrhosis, and nephrosis)

EFFECT OF ACTH

When first administered, ACTH stimulates the output of aldosterone as well as that of glucocorticoids and sex hormones. Although the amount of ACTH required to increase aldosterone output is somewhat greater than the amount that stimulates maximal glucocorticoid secretion.

EFFECTS OF ANGIOTENSIN II & RENIN

The angiotensin II is formed in the body from angiotensin I, which is liberated by the action of renin on circulating angiotensinogen. Injections of angiotensin II stimulate adrenocortical secretion and, in small doses, affect primarily the secretion of aldosterone. Hemorrhage stimulates ACTH and renin secretion. Like hemorrhage, standing and constriction of the thoracic inferior vena cava decrease intrarenal arterial pressure. Dietary sodium restriction also increases aldosterone secretion via the renin–angiotensin system .Such restriction reduces ECF volume, but aldosterone and renin secretion are increased before any consistent decrease in blood pressure takes place.

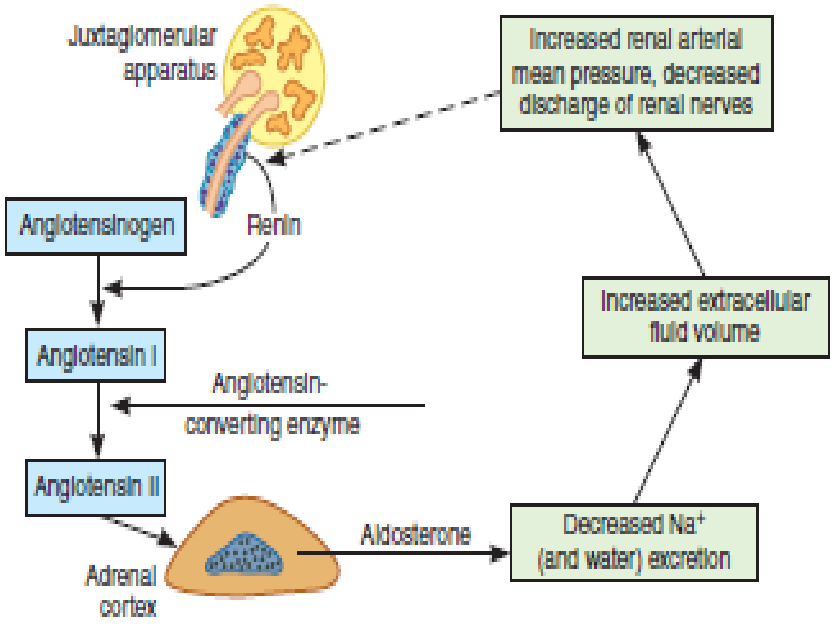


FIGURE 20–22 **Feedback mechanism regulating aldosterone secretion.** The dashed arrow indicates inhibition.

ROLE OF MINERALOCORTICOIDS IN THE REGULATION OF SALT BALANCE

Variations in aldosterone secretion is only one of many factors affecting Na+ excretion. Other major factors include the glomerular filtration rate, ANP, the presence or absence of osmotic diuresis, and changes in tubular reabsorption of Na+ independent of aldosterone. It takes some time for aldosterone to act. When one rises from the supine to the standing position, aldosterone secretion increases and Na+ is retained from the urine. However, the decrease in Na+ excretion develops too rapidly to be explained solely by increased aldosterone secretion. The primary function of the aldosterone-secreting mechanism is the defense of intravascular volume, but it is only one of the homeostatic mechanisms involved in this regulation.

Chapter 21

Hormonal Control of Calcium & Phosphate Metabolism & the Physiology of Bone

Introduction

Calcium is an essential intracellular signaling molecule and also plays a variety of extracellular functions, thus the control of body calcium concentrations is vitally important. The components of the system that maintains calcium homeostasis include cell types that sense changes in extracellular calcium and release calcium-regulating hormones, and the targets of these hormones, including the kidneys, bones, and intestine, that respond with changes in calcium mobilization, excretion, or uptake. Three hormones are primarily concerned with the regulation of calcium homeostasis. Parathyroid hormone (PTH) is secreted by the parathyroid glands. Its main action is to mobilize calcium from bone and increase urinary phosphate excretion. 1,25-Dihydroxycholecalciferol is a steroid hormone formed from vitamin D by successive hydroxylations in the liver and kidneys. Its primary action is to increase calcium absorption from the intestine. Calcitonin, a calcium-lowering hormone that in mammals is secreted primarily by cells in the thyroid gland, inhibits bone resorption. Although the role of calcitonin seems to be relatively minor, all three hormones probably operate in concert to maintain the constancy of the calcium level in the body fluids. Phosphate homeostasis is likewise critical to normal body function, particularly given its inclusion in adenosine triphosphate (ATP), its role as a biological buffer, and its role as a modifier of proteins, thereby altering their functions. Many of the systems that regulate calcium homeostasis also contribute to that of phosphate, albeit sometimes in a reciprocal manner.

CALCIUM & PHOSPHORUS METABOLISM

Calcium

The body of a young adult human contains about 1100 g (27.5 moles) of calcium. Ninety-nine percent of the calcium is in the skeleton. Plasma calcium, normally at a concentration of around 10 mg/dL (5 mEq/L, 2.5 mmol/L), is partly bound to protein and partly diffusible (Table 21–1).

TABLE 21–1 Distribution (mg/dL) of calcium in normal human plasma.

Total diffusible		**5.36**
Ionized (Ca^{2+})	4.72	
Complexed to HCO_3^-, citrate, etc	0.64	
Total nondiffusible (protein-bound)		**4.64**
Bound to albumin	3.68	
Bound to globulin	0.96	
Total plasma calcium		**10.00**

It is the free, ionized calcium (Ca^{2+}) in the body fluids that is a vital second messenger and is necessary for blood coagulation, muscle contraction, and nerve function. A decrease in extracellular Ca^{2+} exerts a net excitatory effect on nerve and muscle cells in vivo. The result is hypocalcemic tetany, which is characterized by extensive spasms of skeletal muscle, involving especially the muscles of the extremities and the larynx. Laryngospasm can become so severe that the airway is obstructed and fatal asphyxia is produced. Ca^{2+} also plays an important role in blood clotting, but in vivo, fatal tetany would occur before compromising the clotting reaction.

Because the extent of Ca^{2+} binding by plasma proteins is proportional to the plasma protein level, it is important to know the plasma protein level when evaluating the total plasma calcium. Other electrolytes and pH also affect the free Ca^{2+} level. Thus, for example, symptoms of tetany appear at higher total calcium levels if the patient hyperventilates, thereby increasing plasma pH. Plasma proteins are more ionized when the pH is high, providing more protein anions to bind with Ca^{2+}.

The calcium in bone is of two types: a readily exchangeable reservoir and a much larger pool of stable calcium that is only slowly exchangeable. Two independent but interacting homeostatic systems affect the calcium in bone. One is the system that regulates plasma Ca^{2+}, providing for the movement of about 500 mmol of Ca^{2+} per day into and out of the readily exchangeable pool in the bone (Figure 21–1). The other system involves bone remodeling by the constant interplay of bone resorption and deposition. However, the Ca^{2+} interchange between plasma and this stable pool of bone calcium is only about 7.5 mmol/d. The overall transportation process of Ca^{2+} across the brush border of intestinal epithelial cells to the bloodstream is regulated by 1,25-dihydroxycholecalciferol.

Plasma Ca^{2+} is filtered in the kidneys, but 98–99% of the filtered Ca^{2+} is reabsorbed. About 60% of the reabsorption occurs in the proximal tubules and the remainder in the ascending limb of the loop of Henle and the distal tubule. Distal tubular reabsorption is regulated by PTH.

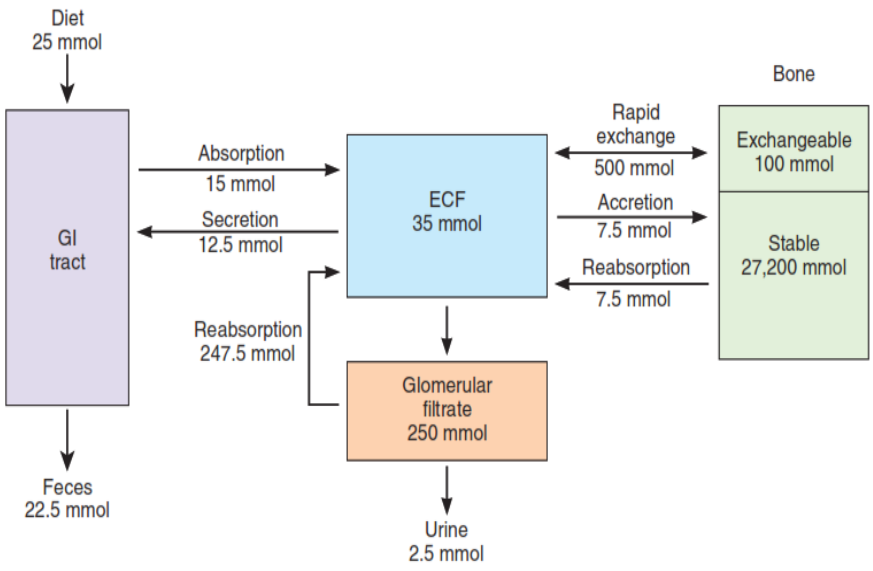


FIGURE 21–1 Calcium metabolism in an adult human. A typical daily dietary intake of 25 mmol Ca^{2+} (1000 mg) moves through many body compartments. Note that the majority of body calcium is in bones, in a pool that is only slowly exchangeable with the extracellular fluid (ECF).

PHOSPHORUS

Phosphate is found in ATP, cyclic adenosine monophosphate (cAMP), 2,3-diphosphoglycerate, many proteins, and other vital compounds in the body. Phosphorylation and dephosphorylation of proteins are involved in the regulation of cell function. Therefore, it is not surprising that, like calcium, phosphate metabolism is closely regulated. Total body phosphorus is 500–800 g (16.1–25.8 moles), 85–90% of which is in the skeleton. Total plasma phosphorus is about 12 mg/dL, with two-thirds of this total in organic compounds and the remaining inorganic phosphorus (Pi) mostly in PO_4^{3-}, HPO_4^{2-}, and $H_2PO_4^-$. The amount of phosphorus normally entering bone is about 3 mg (97 μmol)/kg/d, with an equal amount leaving via reabsorption.

Pi in the plasma is filtered in the glomeruli, and 85–90% of the filtered Pi is reabsorbed. Active transport in the proximal tubule accounts for most of the reabsorption and involves two related sodium-dependent Pi cotransporters, NaPi-IIa and NaPi-IIc. NaPi-IIa is powerfully inhibited by PTH, which causes its internalization and degradation and thus a reduction in renal Pi reabsorption. Pi is

absorbed in the duodenum and small intestine. Many stimuli that increase Ca^{2+} absorption, including 1,25-dihydroxycholecalciferol, also increase Pi absorption.

VITAMIN D & THE HYDROXYCHOLECALCIFEROLS

CHEMISTRY

The active transport of Ca^{2+} and PO_4^{3-} from the intestine is increased by a metabolite of vitamin D. The term "vitamin D" is used to refer to a group of closely related sterols produced by the action of ultraviolet light on certain provitamins (Figure 21–2). Vitamin D3, which is also called cholecalciferol, is produced in the skin of mammals from 7-dehydrocholesterol by the action of sunlight. The reaction involves the rapid formation of previtamin D3, which is then converted more slowly to vitamin D3. Vitamin D3 and its hydroxylated derivatives are transported in the plasma bound to a globulin, vitamin D-binding protein (DBP). Vitamin D3 is also ingested in the diet.

Vitamin D3 is metabolized by enzymes that are members of the cytochrome P450 (CYP) superfamily. In the liver, vitamin D3 is converted to 25-hydroxycholecalciferol (calcidiol, 25-OHD3). The 25-hydroxycholecalciferol is converted in the cells of the proximal tubules of the kidneys to the more active metabolite 1,25-dihydroxycholecalciferol, which is also called calcitriol or 1,25-(OH)2D3. 1,25-Dihydroxycholecalciferol is also made in the placenta, in keratinocytes in the skin, and in macrophages. The normal plasma level of 25-hydroxycholecalciferol is about 30 ng/mL, and that of 1,25-dihydroxycholecalciferol is about 0.03 ng/mL (approximately 100 pmol/L). The less active metabolite 24,25-dihydroxycholecalciferol is also formed in the kidneys (Figure 21–2).

In addition to increasing Ca^{2+} absorption from the intestine, 1,25-dihydroxycholecalciferol facilitates Ca^{2+} reabsorption in the kidneys (proximal tubules), increases the synthetic activity of osteoblasts, and is necessary for normal

calcification of matrix. The stimulation of osteoblasts brings about a secondary increase in the activity of osteoclasts.

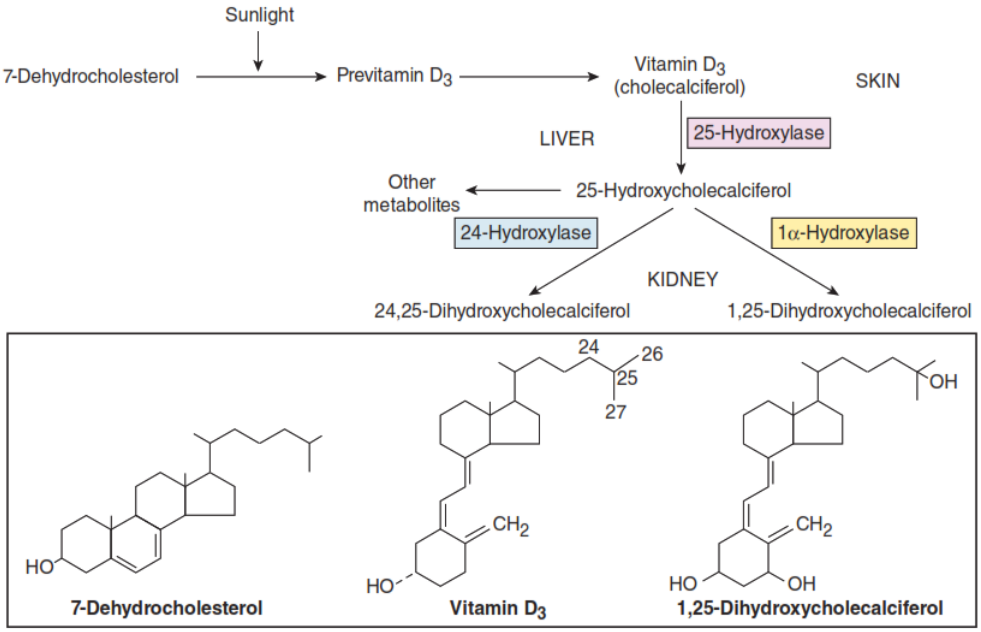


FIGURE 21–2 **Formation and hydroxylation of vitamin D_3.** 25-Hydroxylation takes place in the liver, and the other hydroxylations occur primarily in the kidneys. The structures of 7-dehydrocholesterol, vitamin D_3, and 1,25-dihydroxycholecalciferol are also shown in the boxed area.

REGULATION OF SYNTHESIS

The formation of 25-hydroxycholecalciferol does not appear to be stringently regulated. However, the formation of 1,25-dihydroxycholecalciferol in the kidneys, which is catalyzed by the renal 1α-hydroxylase, is regulated in a feedback manner by plasma Ca^{2+} and PO_4^{3+} (Figure 21–3). When the plasma Ca^{2+} level is high, little 1,25-dihydroxycholecalciferol is produced, and the kidneys produce the relatively inactive metabolite 24,25-dihydroxycholecalciferol instead. This effect of Ca^{2+} on production of 1,25-dihydroxycholecalciferol is the mechanism that brings about adaptation of Ca^{2+} absorption from the intestine. Conversely, expression of 1α-hydroxylase is stimulated by PTH, and when the plasma Ca^{2+} level is low, PTH secretion is increased. The production of 1,25-dihydroxycholecalciferol is also increased by low plasma PO_4^{3-} levels and inhibited by high plasma PO_4^{3-} levels, by a direct inhibitory effect of PO_4^{3-} on the 1α-hydroxylase. Additional control of 1,25-

dihydroxycholecalciferol formation results from a direct negative feedback effect of the metabolite on 1α-hydroxylase, a positive feedback action on the formation of 24,25-dihydroxycholecalciferol, and a direct action on the parathyroid gland to inhibit PTH expression.

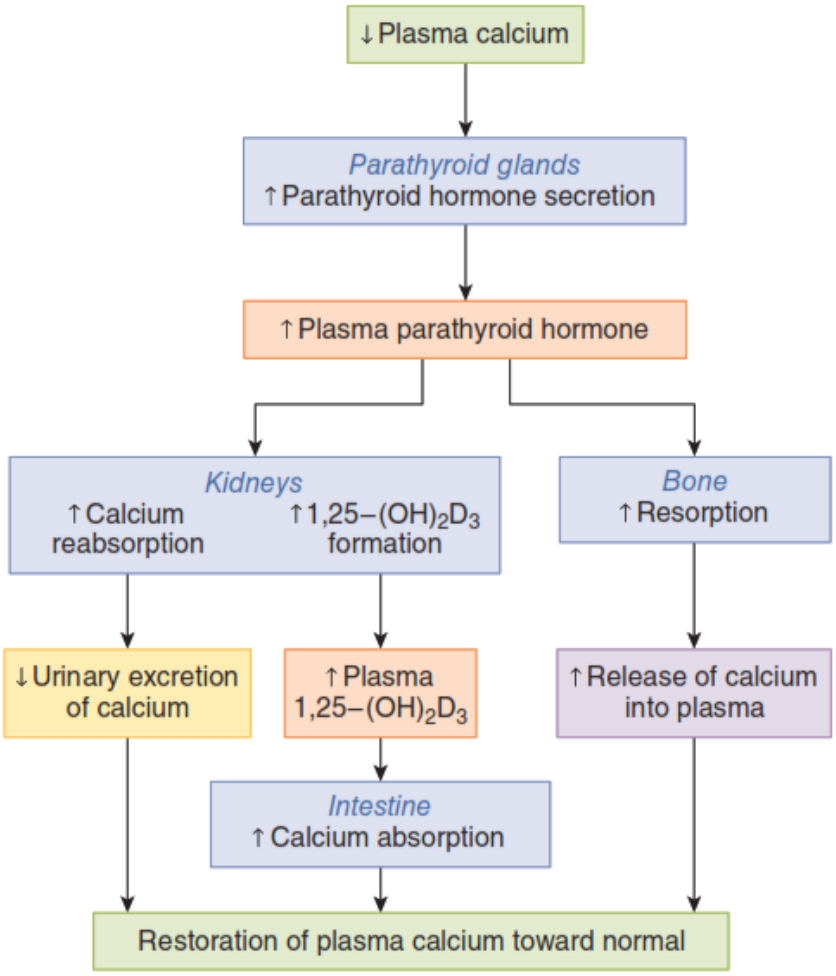


FIGURE 21–3 Effects of PTH and 1,25-dihydroxycholecalciferol on whole body calcium homeostasis. A reduction in plasma calcium stimulates parathyroid hormone secretion. PTH in turn causes calcium conservation and production of 1,25-dihydroxycholecalciferol in the kidneys, the latter of which increases calcium uptake in the intestine. PTH also releases calcium from the readily exchangeable pool in the bone. All of these actions act to restore normal plasma calcium. (Reproduced with permission from Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology*, 10th ed. New York, NY: McGraw-Hill; 2006.)

THE PARATHYROID GLANDS

ANATOMY

Humans usually have four parathyroid glands: two embedded in the superior poles of the thyroid and two in its inferior poles (Figure 21–4). Each parathyroid gland is a richly vascularized disk, about 3 × 6 × 2 mm, containing two distinct types of cells (Figure 21–5). The abundant chief cells, which contain a prominent Golgi apparatus plus endoplasmic reticulum and secretory granules, synthesize and secrete PTH. The less abundant and larger oxyphil cells contain oxyphil granules and large numbers of mitochondria in their cytoplasm. In humans, few oxyphil cells are seen before puberty, and thereafter they increase in number with age.

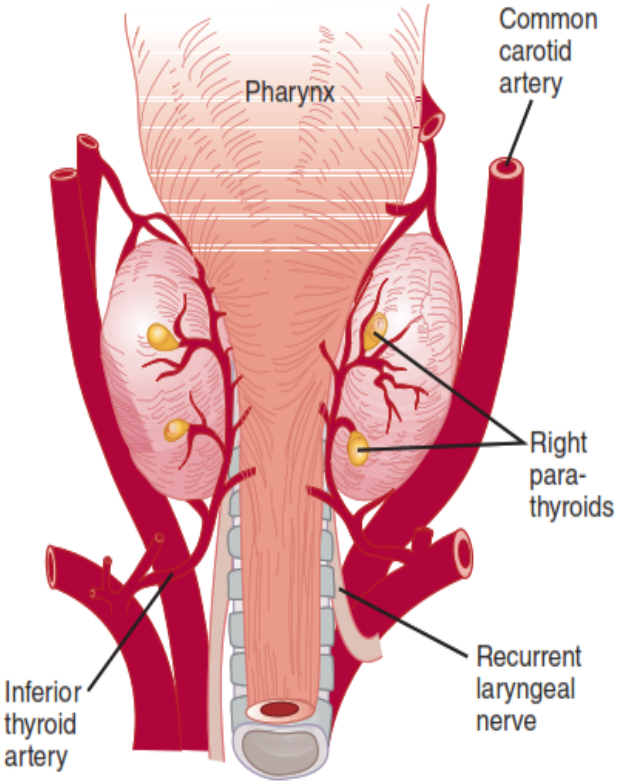


FIGURE 21–4 The human parathyroid glands, viewed from behind. The glands are small structures adherent to the posterior surface of the thyroid gland.

SYNTHESIS & METABOLISM OF PTH

Human PTH is a linear polypeptide with a molecular weight of 9500 that contains 84 amino acid residues. It is synthesized as part of a larger molecule containing 115 amino acid residues (preproPTH). On entry of preproPTH into the endoplasmic reticulum, a leader sequence is removed from the amino terminal to form the 90-amino-acid polypeptide proPTH. Six additional amino acid residues are removed from the amino terminal of proPTH in the Golgi apparatus, and the 84-amino-acid polypeptide PTH is packaged in secretory granules and released as the main secretory product of the chief cells.

The normal plasma level of intact PTH is 10–55 pg/mL. The half-life of PTH is approximately 10 min, and the secreted polypeptide is rapidly cleaved by the Kupfer cells in the liver into fragments that are probably biologically inactive. PTH and these fragments are then cleared by the kidneys.

ACTIONS

PTH acts directly on bone to increase bone resorption and mobilize Ca^{2+}. In addition to increasing plasma Ca^{2+}, PTH increases phosphate excretion in the urine and thereby depresses plasma phosphate levels. This phosphaturic action is due to a decrease in reabsorption of phosphate via effects on NaPi-IIa in the proximal tubules. PTH also increases reabsorption of Ca^{2+} in the distal tubules, although Ca^{2+} excretion in the urine is often increased in hyperparathyroidism because the increase in the load of filtered calcium overwhelms the effect on reabsorption. PTH also increases the formation of 1,25-dihydroxycholecalciferol, and this increases Ca^{2+} absorption from the intestine. On a longer time scale, PTH stimulates both osteoblasts and osteoclasts.

REGULATION OF SECRETION

Circulating Ca^{2+} acts directly on the parathyroid glands in a negative feedback manner to regulate the secretion of PTH. When the plasma Ca^{2+} level is high, PTH

secretion is inhibited and Ca^{2+} is deposited in the bones. When it is low, secretion is increased and Ca^{2+} is mobilized from the bones.

1,25-Dihydroxycholecalciferol acts directly on the parathyroid glands to decrease preproPTH mRNA. Increased plasma phosphate stimulates PTH secretion by lowering plasma levels of free Ca^{2+} and inhibiting the formation of 1,25-dihydroxycholecalciferol. Magnesium is required to maintain normal parathyroid secretory responses. Impaired PTH release along with diminished target organ responses to PTH account for the hypocalcemia that occasionally occurs in magnesium deficiency.

CALCITONIN

ORIGIN, SECRETION & METABOLISM

Calcitonin is a Ca^{2+}-lowering hormone. In mammals, calcitonin is produced by the parafollicular cells of the thyroid gland, which are also known as the clear or C cells. Calcitonin secretion is increased when the thyroid gland is exposed to a plasma calcium level of approximately 9.5 mg/dL. Above this level, plasma calcitonin is directly proportional to plasma calcium. β-Adrenergic agonists, dopamine, and estrogens also stimulate calcitonin secretion. Gastrin, cholecystokinin (CCK), glucagon, and secretin have also been reported to stimulate calcitonin secretion, with gastrin being the most potent stimulus. Thus, the plasma calcitonin level is elevated in Zollinger–Ellison syndrome and in pernicious anemia. However, the dose of gastrin needed to stimulate calcitonin secretion is supraphysiologic and not seen after eating in normal individuals, so dietary calcium in the intestine probably does not induce secretion of a calcium-lowering hormone prior to the calcium being absorbed. In any event, the actions of calcitonin are short-lived because it has a half-life of less than 10 min in humans.

ACTIONS

Receptors for calcitonin are found in bones and the kidneys. Calcitonin lowers circulating calcium and phosphate levels. It exerts its calcium-lowering effect by inhibiting bone resorption. This action is direct, and calcitonin inhibits the activity of osteoclasts in vitro. It also increases Ca^{2+} excretion in the urine.

The exact physiologic role of calcitonin is uncertain. The calcitonin content of the human thyroid is low, and after thyroidectomy, bone density and plasma Ca^{2+} level are normal as long as the parathyroid glands are intact. In addition, after thyroidectomy, there are only transient abnormalities of Ca^{2+} homeostasis when a Ca^{2+} load is injected. This may be explained in part by secretion of calcitonin from tissues other than the thyroid. However, there is general agreement that the hormone has little long-term effect on the plasma Ca^{2+} level in adult animals and humans. Further, unlike PTH and 1,25-dihydroxycholecalciferol, calcitonin does not appear to be involved in phosphate homeostasis. Moreover, patients with medullary carcinoma of the thyroid have a very high circulating calcitonin level but no symptoms directly attributable to the hormone, and their bones are essentially normal. No syndrome due to calcitonin deficiency has been described. More hormone is secreted in young individuals, and it may play a role in skeletal development. In addition, it may protect the bones of the mother from excess calcium loss during pregnancy. Bone formation in the infant and lactation are major drains on Ca^{2+} stores, and plasma concentrations of 1,25-dihydroxycholecalciferol are elevated in pregnancy. They would cause bone loss in the mother if bone resorption were not simultaneously inhibited by an increase in the plasma calcitonin level.

SUMMARY OF CALCIUM HOMEOSTATIC MECHANISMS

The actions of the three principal hormones that regulate the plasma concentration of Ca^{2+} can now be summarized. PTH increases plasma Ca^{2+} by mobilizing this ion from bone. It increases Ca^{2+} reabsorption in the kidney, but this may be offset by the

increase in filtered Ca^{2+}. It also increases the formation of 1,25-dihydroxycholecalciferol. 1,25-Dihydroxycholecalciferol increases Ca^{2+} absorption from the intestine and increases Ca^{2+} reabsorption in the kidneys. Calcitonin inhibits bone resorption and increases the amount of Ca^{2+} in the urine.

EFFECTS OF OTHER HORMONES & HUMORAL AGENTS ON CALCIUM METABOLISM

Calcium metabolism is affected by various hormones in addition to 1,25-dihydroxycholecalciferol, PTH, and calcitonin. Glucocorticoids lower plasma Ca^{2+} levels by inhibiting osteoclast formation and activity, but over long periods they cause osteoporosis by decreasing bone formation and increasing bone resorption. They decrease bone formation by inhibiting protein synthesis in osteoblasts. They also decrease the absorption of Ca^{2+} and PO_4^{3-} from the intestine and increase the renal excretion of these ions. The decrease in plasma Ca^{2+} concentration also increases the secretion of PTH, and bone resorption is facilitated. Growth hormone increases Ca^{2+} excretion in the urine, but it also increases intestinal absorption of Ca^{2+}, and this effect may be greater than the effect on excretion, with a resultant positive calcium balance. Insulin-like growth factor I (IGF-I) generated by the action of growth hormone stimulates protein synthesis in bone. As noted previously, thyroid hormones may cause hypercalcemia, hypercalciuria, and, in some instances, osteoporosis. Estrogens prevent osteoporosis by inhibiting the stimulatory effects of certain cytokines on osteoclasts. Insulin increases bone formation, and there is significant bone loss in untreated diabetes.

BONE PHYSIOLOGY

Bone is a special form of connective tissue with a collagen framework impregnated with Ca^{2+} and PO_4^{3-} salts, particularly hydroxyapatites, which have the general formula $Ca_{10}(PO_4)_6(OH)_2$. Bone is also involved in overall Ca^{2+} and $PO4^{3-}$ homeostasis. It protects vital organs, and the rigidity it provides permits locomotion

and the support of loads against gravity. Old bone is constantly being resorbed and new bone formed, permitting remodeling that allows it to respond to the stresses and strains that are put upon it. It is a living tissue that is well vascularized and has a total blood flow of 200–400 mL/min in adult humans.

STRUCTURE

There are two types of bone: compact or cortical bone, which makes up the outer layer of most bones (Figure 21–8) and accounts for 80% of the bone in the body; and trabecular or spongy bone inside the cortical bone, which makes up the remaining 20% of bone in the body. In compact bone, the surface-to-volume ratio is low, and bone cells lie in lacunae. They receive nutrients by way of canaliculi that ramify throughout the compact bone (Figure 21–8). Trabecular bone is made up of spicules or plates, with a high surface to volume ratio and many cells sitting on the surface of the plates. Nutrients diffuse from bone extracellular fluid (ECF) into the trabeculae, but in compact bone, nutrients are provided via haversian canals (Figure 21–8), which contain blood vessels. Around each haversian canal, collagen is arranged in concentric layers, forming cylinders called osteons or haversian systems.

The protein in bone matrix is over 90% type I collagen, which is also the major structural protein in tendons and skin. This collagen, which weight for weight is as strong as steel, is made up of a triple helix of three polypeptides bound tightly together. Two of these are identical α1 polypeptides encoded by one gene, and one is an α2 polypeptide encoded by a different gene. Collagens make up a family of structurally related proteins that maintain the integrity of many different organs. Over 40 collagen genes that contribute to at least 28 distinct trimeric collagens have so far been identified.

BONE GROWTH

During fetal development, most bones are modeled in cartilage and then transformed into bone by ossification (enchondral bone formation). The exceptions

are the clavicles, the mandibles, and certain bones of the skull in which mesenchymal cells form bone directly (intramembranous bone formation).

During growth, specialized areas at the ends of each long bone (epiphyses) are separated from the shaft of the bone by a plate of actively proliferating cartilage, the epiphysial plate (Figure 21–9). The bone increases in length as this plate lays down new bone on the end of the shaft. The width of the epiphysial plate is proportional to the rate of growth. The width is affected by several hormones, but most markedly by the pituitary growth hormone and IGF-I.

Linear bone growth can occur as long as the epiphyses are separated from the shaft of the bone, but such growth ceases after the epiphyses unite with the shaft (epiphysial closure). The cartilage cells stop proliferating, become hypertrophic, and secrete vascular endothelial growth factor (VEGF), leading to vascularization and ossification. The epiphyses of the various bones close in an orderly temporal sequence, the last epiphyses closing after puberty. The normal age at which each of the epiphyses closes is known, and the "bone age" of a young individual can be determined by radiographing the skeleton and noting which epiphyses are open and which are closed.

The periosteum is a dense fibrous, vascular, and innervated membrane that covers the surface of bones. This layer consists of an outer layer of collagenous tissue and an inner layer of fine elastic fibres that can include cells that have the potential to contribute to bone growth. The periosteum covers all surfaces of the bone except for those capped with cartilage (eg, at the joints) and serves as a site of attachment of ligaments and tendons. As one ages, the periosteum becomes thinner and loses some of its vasculature. This renders bones more susceptible to injury and disease.

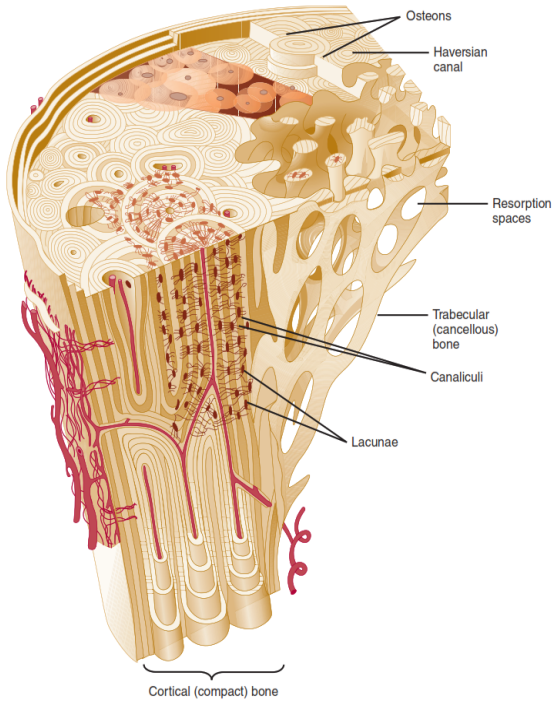


FIGURE 21–8 Structure of compact and trabecular bone. The compact bone is shown in horizontal section (top) and vertical section (bottom). (Reproduced with permission from Williams PL et al [editors]: *Gray's Anatomy,* 37th ed. Churchill Livingstone; 1989.)

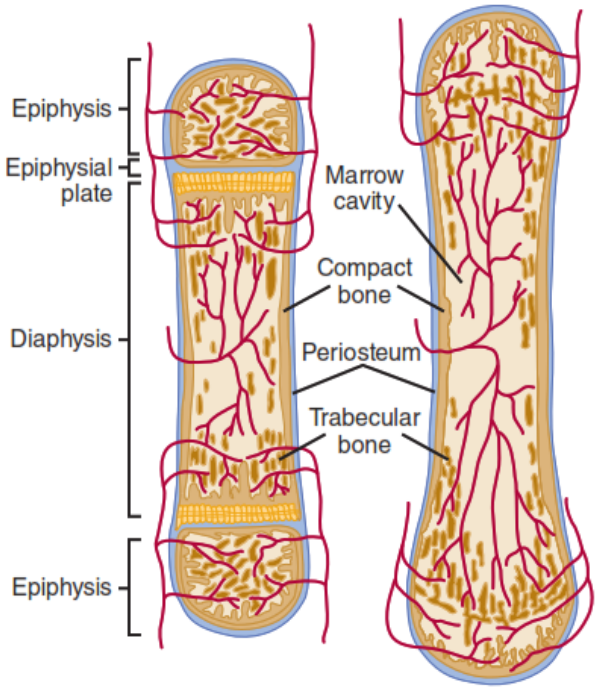


FIGURE 21–9 Structure of a typical long bone before (left) and after (right) epiphysial closure. Note the rearrangement of cells and growth of the bone as the epiphysial plate closes (see text for details).

BONE FORMATION & RESORPTION

The cells responsible for bone formation are osteoblasts and the cells responsible for bone resorption are osteoclasts.

Osteoblasts are modified fibroblasts. Their early development from the mesenchyme is the same as that of fibroblasts, with extensive growth factor regulation. Later, ossification-specific transcription factors, such as runt-related transcription factor 2 (Runx2; also known as core binding factor subunit alpha-1), contribute to their differentiation.

Osteoclasts, on the other hand, are members of the monocyte family. Osteoclasts erode and absorb previously formed bone. They become attached to bone via integrins in a membrane extension called the sealing zone. This creates an isolated area between the bone and a portion of the osteoclast. Proton pumps (ie, H^+-dependent ATPases) then move from endosomes into the cell membrane apposed to the isolated area, and they acidify the area to approximately pH 4.0. The acidic pH dissolves hydroxyapatite, and acid proteases secreted by the cell break down collagen, forming a shallow depression in the bone (Figure 21–10). The products of digestion are then endocytosed and move across the osteoclast by transcytosis, with release into the interstitial fluid. The collagen breakdown products have pyridinoline structures, and pyridinolines can be measured in the urine as an index of the rate of bone resorption.

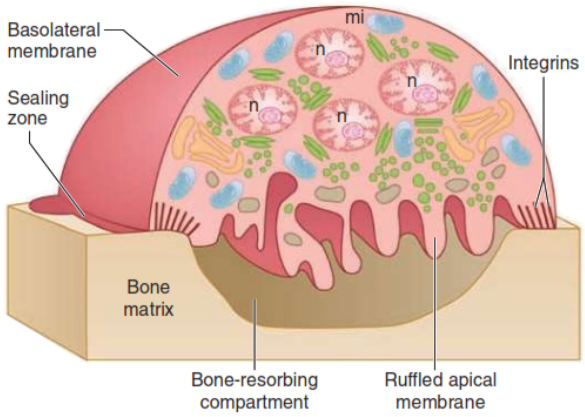


FIGURE 21–10 **Osteoclast resorbing bone.** The edges of the cell are tightly sealed to bone, permitting secretion of acid from the ruffled apical membrane and consequent erosion of the bone underneath the cell. Note the multiple nuclei (n) and mitochondria (mi). (Used with permission of R. Baron.)

Throughout life, bone is being constantly resorbed and new bone is being formed. The calcium in bone turns over at a rate of 100% per year in infants and 18% per year in adults. Bone remodeling is mainly a local process carried out in small areas by populations of cells called bone-remodeling units. First, osteoclasts resorb bone, and then osteoblasts lay down new bone in the same general area. This cycle takes about 100 days. Modeling drifts also occur in which the shapes of bones change as bone is resorbed in one location and added in another. Osteoclasts tunnel into cortical bone followed by osteoblasts, whereas trabecular bone remodeling occurs on the surface of the trabeculae. About 5% of the bone mass is being remodeled by about 2 million bone-remodeling units in the human skeleton at any one time. The renewal rate for bone is about 4% per year for compact bone and 20% per year for trabecular bone. The remodeling is related in part to the stresses and strains imposed on the skeleton by gravity.

Chapter 22

Reproductive Development & Function of the Female Reproductive System

Introduction

In most species of mammals, the multiple differences between the male and the female depend primarily on a single chromosome (the Y chromosome) and a single pair of endocrine structures, namely the testes in the male and the ovaries in the female. The differentiation of the primitive gonads into testes or ovaries in utero is genetically determined in humans, but the formation of male genitalia depends on the presence of a functional, secreting testis; in the absence of testicular tissue, development is female. Evidence indicates that male sexual behavior and, in some species, the male pattern of gonadotropin secretion are due to the action of male hormones on the brain in early development. After birth, the gonads remain quiescent until adolescence, when they are activated by gonadotropins from the anterior pituitary. Hormones secreted by the gonads at this time cause the appearance of features typical of the adult male or female and the onset of the sexual cycle in the female. In human females . ovarian function regresses after a number of years and sexual cycles cease (the menopause). In males, gonadal function slowly declines with advancing age, but the ability to produce viable gametes persists. In both sexes, the gonads have a dual function: the production of germ cells (gametogenesis) and the secretion of sex hormones. The androgens are steroid sex hormones that are masculinizing in their action; the estrogens are those that are feminizing. Both types of hormones are normally secreted in both sexes. The ovaries secrete large amounts of estrogens and small amounts of androgens, a pattern that is reversed in males. Androgens are secreted from the adrenal cortex in both sexes, and some of the androgens are converted to estrogens in fat and other extragonadal and extra-adrenal

tissues. The ovaries also secrete progesterone, a steroid that has special functions in preparing the uterus for pregnancy. Particularly during pregnancy, the ovaries secrete the polypeptide hormone relaxin, which loosens the ligaments of the pubic symphysis and softens the cervix, facilitating delivery of the fetus. In both sexes, the gonads secrete other polypeptides, including inhibin B, a polypeptide that inhibits follicle-stimulating hormone (FSH) secretion. The secretory and gametogenic functions of the gonads are both dependent on the secretion of the anterior pituitary gonadotropins, FSH, and luteinizing hormone (LH). The sex hormones and inhibin B feed back to inhibit gonadotropin secretion. In males, gonadotropin secretion is noncyclic; but in postpubertal females an orderly, sequential secretion of gonadotropins is necessary for the occurrence of menstruation, pregnancy, and lactation.

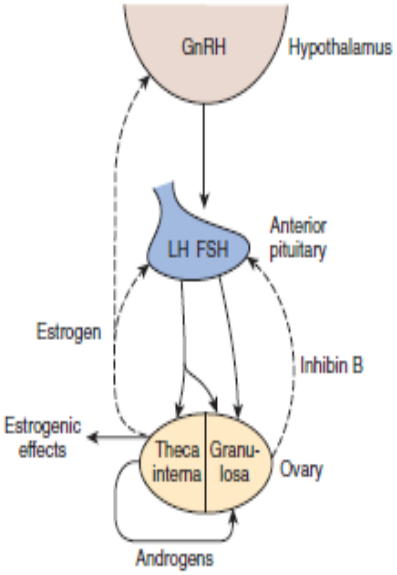


FIGURE 22–19 Feedback regulation in female

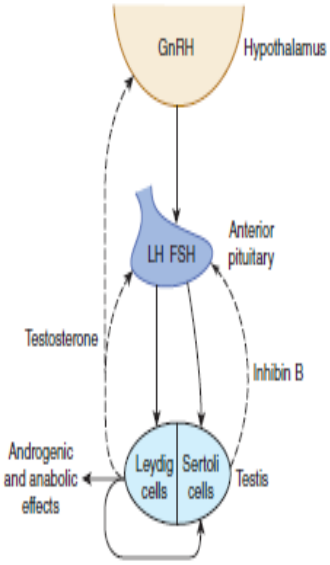


FIGURE 23–10 Feedback regulation in male

SEX DIFFERENTIATION and DEVELOPMENT

The Sex Chromosomes

Sex is determined genetically by two chromosomes, called the sex chromosomes, to distinguish them from the somatic chromosomes (autosomes). In humans and many other mammals, the sex chromosomes are called X and Y. The Y chromosome is necessary and sufficient for the production of testes, and the testis-determining gene product is called SRY (for sex-determining region of the Y chromosome). SRY is a DNA-binding regulatory protein. It bends the DNA and acts as a transcription factor that initiates transcription of a cascade of genes necessary for testicular differentiation, including the gene for müllerian inhibiting substance (MIS). The gene for SRY is located near the tip of the short arm of the human Y chromosome. Diploid male cells contain an X and a Y chromosome (XY pattern), whereas female cells contain two X chromosomes (XX pattern). As a consequence of meiosis during gametogenesis, each normal ovum contains a single X chromosome, but half of the normal sperm contain an X chromosome and half contain a Y chromosome (Figure 22–1). When a sperm containing a Y chromosome fertilizes an ovum, an XY pattern results and the zygote develops into a genetic male. When fertilization occurs with an X-containing sperm, an XX pattern and a genetic female results.

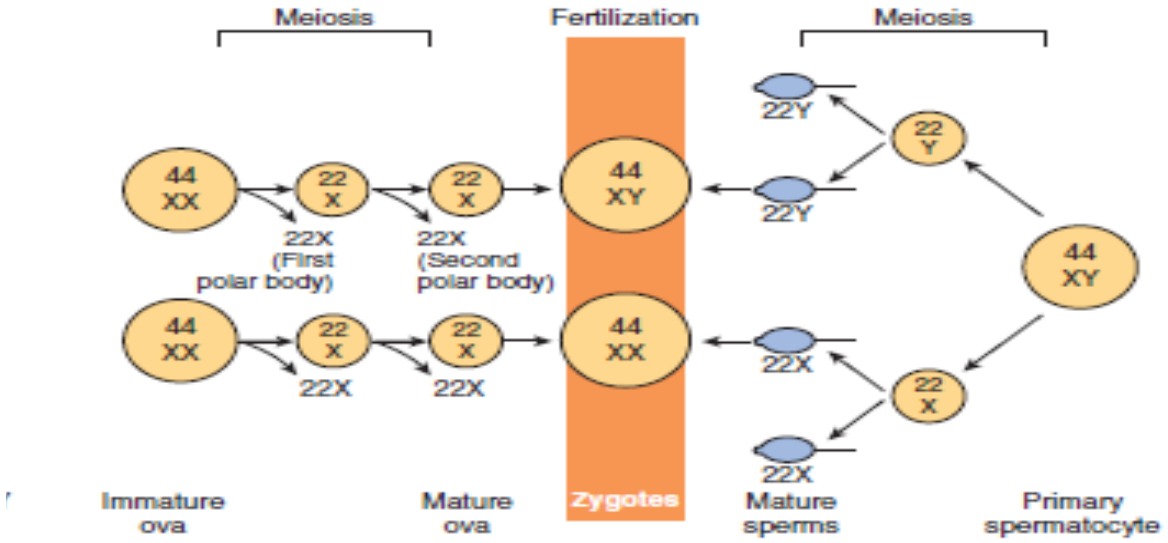


FIGURE 22–1 Basis of genetic sex determination.

In the two-stage meiotic division in the female, only one cell survives as the mature ovum. In the male, the meiotic division results in the formation of four sperms, two containing the X and two the Y chromosome. Fertilization thus produces a male zygote with 22 pairs of autosomes plus an X and a Y or a female zygote with 22 pairs of autosomes and two X chromosomes .

Development of the Gonads

On each side of the embryo, a primitive gonad arises from the genital ridge, a condensation of tissue near the adrenal gland. The gonad develops a cortex and a medulla. Until the sixth week of development, these structures are identical in both sexes. In genetic males, the medulla develops during the seventh and eighth weeks into a testis, and the cortex regresses. Leydig and Sertoli cells appear, and testosterone and MIS are secreted. The MIS causes regression of mullerian duct . In genetic females, the cortex develops into an ovary and the medulla regresses. the müllerian duct system then develops into uterine tubes (oviducts) and a uterus. The embryonic ovary does not secrete hormones. Hormonal treatment of the mother has no effect on gonadal (as opposed to ductal and genital) differentiation in humans.

PUBERTY

A burst of testosterone secretion occurs in male fetuses before birth. In the neonatal period there is another burst, with unknown function, but thereafter the Leydig cells become quiescent. There follows in all mammals a period in which the gonads of both sexes are quiescent until they are activated by gonadotropins from the pituitary to bring about the final maturation of the reproductive system. (**Figure 22–8**).

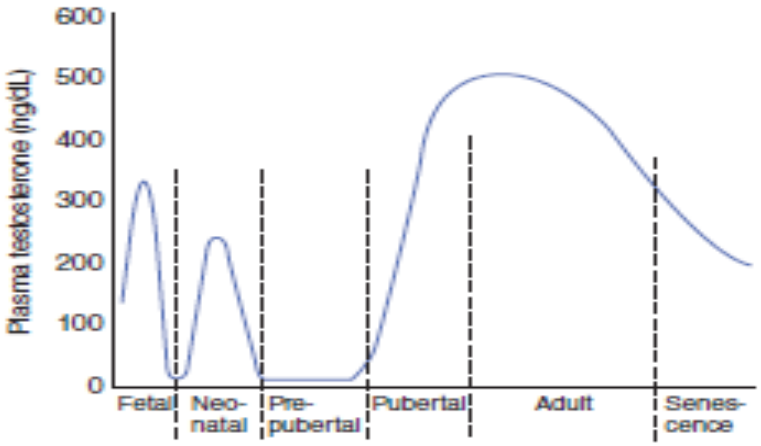


FIGURE 22–8 **Plasma testosterone levels at various ages in human males.**

This period of final maturation is known as adolescence. It is often also called puberty, although puberty, strictly defined, is the period when the endocrine and gametogenic functions of the gonads have first developed to the point where reproduction is possible. In girls, the first event is thelarche, the development of breasts, followed by pubarche, the development of axillary and pubic hair, and then by menarche, the first menstrual period. Initial menstrual periods are generally anovulatory, and regular ovulation appears about a year later. In contrast to the situation in adulthood, removal of the gonads during the period from soon after birth to puberty causes only a small increase in gonadotropin secretion, so gonadotropin secretion is not being held in check by the gonadal hormones. In children between the ages of 7 and 10, a slow increase in estrogen and androgen secretion precedes the more rapid rise in the early teens . The age at the time of puberty is variable.

puberty generally occurs between the ages of 8 and 13 in girls and 9 and 14 in boys. Another event that occurs in humans at the time of puberty is an increase in the secretion of adrenal androgens. The onset of this increase is called adrenarche. It occurs at age 8–10 years in girls and age 10–12 years in boys. (DHEA) values peak at about age 25 in women and slightly later than that in men. They then decline slowly to low values in old age. The rise appears to be due to an increase in the activity of 17α-hydroxylase.

Control of the Onset of Puberty

The gonads of children can be stimulated by gonadotropins; their pituitaries contain gonadotropins and their hypothalami contain gonadotropin-releasing Dehydroepiandrosterone hormone (GnRH) Thus, it seems clear that pulsatile secretion of GnRH brings on puberty. During the period from birth to puberty, a neural mechanism is operating to prevent the normal pulsatile release of GnRH. The nature of the mechanism inhibiting the GnRH pulse generator is unknown. However, one or more genes produce products that stimulate secretion of GnRH, and inhibition of these genes before puberty is an interesting possibility (**Clinical Box 22–2**).

CLINICAL BOX 22–2

Leptin: It has been argued for some time that a critical body weight must normally be reached for puberty to occur. Thus, for example, young women who engage in strenuous athletics lose weight and stop menstruating, as do girls with anorexia nervosa. If these girls start to eat and gain weight, they menstruate again, that is, they "go back through puberty." It now appears that leptin, the satiety-producing hormone secreted by fat cells, may be the link between body weight and puberty. Obese ob/ob mice that cannot make leptin are infertile, and their fertility is restored by injections of leptin. Leptin treatment also induces precocious puberty in immature female mice.

However, the way that leptin fits into the overall control of puberty remains to be determined

MENOPAUSE

The human ovaries become unresponsive to gonadotropins with advancing age, and their function declines, so that sexual cycles disappear **(menopause).** This unresponsiveness is associated with and probably caused by decline in the number of primordial follicles,

which becomes precipitous at the time of menopause.

1. The ovaries no longer secrete progesterone and 17β-estradiol in appreciable quantities, and estrogen is formed only in small amounts by aromatization of androstenedione in peripheral tissues.
2. The uterus and the vagina gradually become atrophic.
3. As the negative feedback effect of estrogens and progesterone is reduced, secretion of FSH is increased, and plasma FSH increases to high levels, LH levels are moderately high.

In women, a period called perimenopause precedes menopause and can last up to 10 years. During perimenopause FSH levels will increase before an increase in LH is observed due to a decrease in estrogen, progesterone, and inhibins and the menses become irregular. This usually occurs between the ages of 45 and 55. The average age at onset of the menopause is 52 years.

The loss of ovarian function causes many symptoms such as sensations of warmth spreading from the trunk to the face (hot flushes; also called hot flashes) and night sweats. In addition, the onset of menopause increases the risk of many diseases such as osteoporosis, ischemic heart disease, and renal disease. Hot flushes are said to occur in 75% of menopausal women and may continue intermittently for as long as 40 years. They also occur when early menopause is produced by bilateral

ovariectomy, and they are prevented by estrogen treatment. Their cause is unknown. However, they coincide with surges of LH secretion. LH is secreted in episodic bursts at intervals of 30–60 min or more **(circhoral secretion),** and in the absence of gonadal hormones these bursts are large. Each hot flush begins with the start of a burst. However, LH itself is not responsible for the symptoms, because they can continue after removal of the pituitary. Instead, it appears that some estrogen-sensitive event in the hypothalamus initiates both the release of LH and the episode of flushing. Although the function of the testes tends to decline slowly with advancing age, the evidence is unclear whether there is a "male menopause" **(andropause)** similar to that occurring in women.

THE FEMALE REPRODUCTIVE SYSTEM

THE MENSTRUAL CYCLE

The reproductive system of women, unlike that of men, shows regular cyclic changes that teleologically may be regarded as periodic preparations for fertilization and pregnancy. In humans and other primates, the cycle is a **menstrual** cycle, and its most conspicuous feature is the periodic vaginal bleeding that occurs with the shedding of the uterine mucosa **(menstruation).** The length of the cycle is notoriously variable in women, but an average figure is 28 days from the start of one menstrual period to the start of the next. By common usage, the days of the cycle are identified by number, starting with the first day of menstruation.

Ovarian Cycle

1.The follicular phase :

From the time of birth, there are many primordial follicles under the ovarian capsule. Each contains an immature ovum. At the start of each cycle, several of these follicles enlarge, and a cavity forms around the ovum (antrum formation). This cavity is filled with follicular fluid. grow rapidly on about the 6th day and becomes the dominant

follicle, while the others regress, forming atretic follicles. The atretic process involves apoptosis. It is uncertain how one follicle is selected to be the dominant follicle in this follicular phase of the menstrual cycle, but it seems to be related to the ability of the follicle to secrete the estrogen inside it that is needed for final maturation. The structure of a maturing ovarian (graafian) follicle is shown in (Figure 22–11).

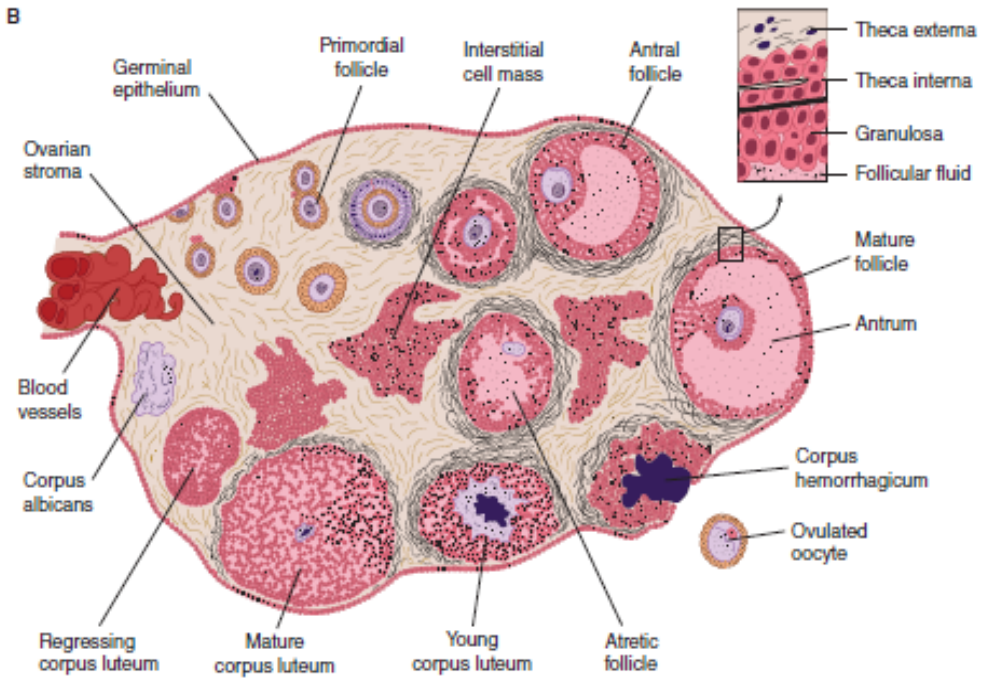


FIGURE 22–11 Functional anatomy of the female reproductive tract

The primary source of circulating estrogen is the granulosa cells of the ovaries; however, the cells of the theca interna of the follicle are necessary for the production of estrogen as they secrete androgens that are aromatized to estrogen by the granulosa cells.

2.The ovulatory phase:

At about the 14th day of the cycle, the distended follicle ruptures, and the ovum is extruded into the abdominal cavity. This is the process of ovulation. The ovum is

picked up by the fimbriated ends of the uterine tubes (oviducts). It is transported to the uterus and, unless fertilization occurs, out through the vagina.

3.The luteal phase:

The follicle that ruptures at the time of ovulation promptly fills with blood, forming what is sometimes called a corpus hemorrhagicum. Minor bleeding from the follicle into the abdominal cavity may cause peritoneal irritation and fleeting lower abdominal pain ("mittelschmerz"). The granulosa and theca cells of the follicle lining promptly begin to proliferate, and the clotted blood is rapidly replaced with yellowish, lipid-rich luteal cells, forming the corpus luteum. This initiates the luteal phase of the menstrual cycle, during which the luteal cells secrete estrogen and progesterone. Growth of the corpus luteum depends on its developing an adequate blood supply, and there is evidence that vascular endothelial growth factor (VEGF) is essential for this process. If pregnancy occurs, the corpus luteum persists and usually there are no more periods until after delivery. If pregnancy does not occur, the corpus luteum begins to degenerate about 4 days before the next menses (24th day of the cycle) and is eventually replaced by scar tissue, forming a corpus albicans. The ovarian cycle in other mammals is similar, except that in many species more than one follicle ovulates and multiple births are the rule. Corpora lutea form in some submammalian species but not in others. In humans, no new ova are formed after birth. During fetal development, the ovaries contain over 7 million primordial follicles. However, many undergo atresia (involution) before birth and others are lost after birth. At the time of birth, there are 2 million ova . Atresia continues during development, and the number of ova in both of the ovaries at the time of puberty is less than 300,000. Only one of these ova per cycle (or about 500 in the course of a normal reproductive life) normally reaches maturity; the remainder degenerate. Just before ovulation.

Uterine Cycle :

At the end of menstruation, all but the deep layers of the endometrium have sloughed. A new endometrium then regrows under the influence of estrogens from the developing follicle. The endometrium increases rapidly in thickness from the 5th to the 14th days of the menstrual cycle. As the thickness increases, the uterine glands are drawn out so that they lengthen (Figure 22–12), but they do not become convoluted or secrete to any degree.

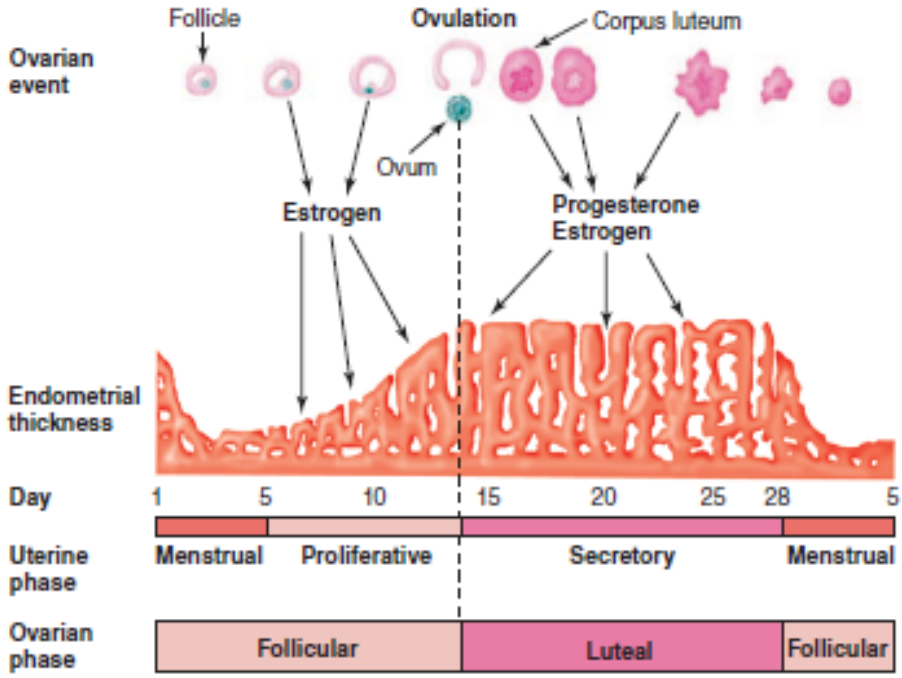


FIGURE 22–12 Relationship between ovarian and uterine changes during the menstrual cycle.

These endometrial changes are called proliferative, and this part of the menstrual cycle is sometimes called the proliferative phase. It is also called the preovulatory or follicular phase of the cycle. After ovulation, the endometrium becomes more highly vascularized and slightly edematous under the influence of estrogen and progesterone from the corpus luteum. The glands become coiled and tortuous and they begin to secrete a clear fluid. Consequently, this phase of the cycle is called the secretory or luteal phase. When the corpus luteum regresses, hormonal support for the endometrium is withdrawn. The endometrium becomes thinner, which adds to

the coiling of the spiral arteries. Foci of necrosis appear in the endometrium, and these coalesce. In addition, spasm and degeneration of the walls of the spiral arteries take place, leading to spotty hemorrhages that become confluent and produce the menstrual flow. The vasospasm is probably produced by locally released prostaglandins. Large quantities of prostaglandins are present in the secretory endometrium and in menstrual blood, From the point of view of endometrial function, the proliferative phase of the menstrual cycle represents restoration of the epithelium from the preceding menstruation, and the secretory phase represents preparation of the uterus for implantation of the fertilized ovum. The length of the secretory phase is remarkably constant at about 14 days, and the variations seen in the length of the menstrual cycle are due for the most part to variations in the length of the proliferative phase. When fertilization fails to occur during the secretory phase, the endometrium is shed and a new cycle starts.

Normal Menstruation :

Menstrual blood is predominantly arterial, with only 25% of the blood being of venous origin. It contains tissue debris, prostaglandins, and relatively large amounts of fibrinolysin from endometrial tissue. The fibrinolysin lyses clots, so that menstrual blood does not normally contain clots unless the flow is excessive. The usual duration of the menstrual flow is 3–5 days, but flows as short as 1 day and as long as 8 days can occur in normal women. The amount of blood lost may range normally from slight spotting to 80 mL; the average amount lost is 30 mL. Loss of more than 80 mL is abnormal. Obviously, the amount of flow can be affected by various factors, including the thickness of the endometrium, medication, and diseases that affect the clotting mechanism.

Anovulatory Cycles

In some instances, ovulation fails to occur during the menstrual cycle. Such anovulatory cycles are common for the first 12–18 months after menarche and again

before the onset of the menopause. When ovulation does not occur, no corpus luteum is formed and the effects of progesterone on the endometrium are absent. Estrogens continue to cause growth, however, and the proliferative endometrium becomes thick enough to break down and begins to slough. The time it takes for bleeding to occur is variable, but it usually occurs in less than 28 days from the last menstrual period. The flow is also variable and ranges from scanty to relatively profuse.

Indicators of Ovulation

A convenient and reasonably reliable indicator of the time of ovulation is a change—usually a rise—in the basal body temperature (**Figure 22–14**). The rise starts 1–2 days after ovulation. Women interested in obtaining an accurate temperature chart should use a digital thermometer and take their temperatures (oral or rectal) in the morning before getting out of bed. The cause of the temperature change at the time of ovulation is probably the increase in progesterone secretion, since progesterone is thermogenic.

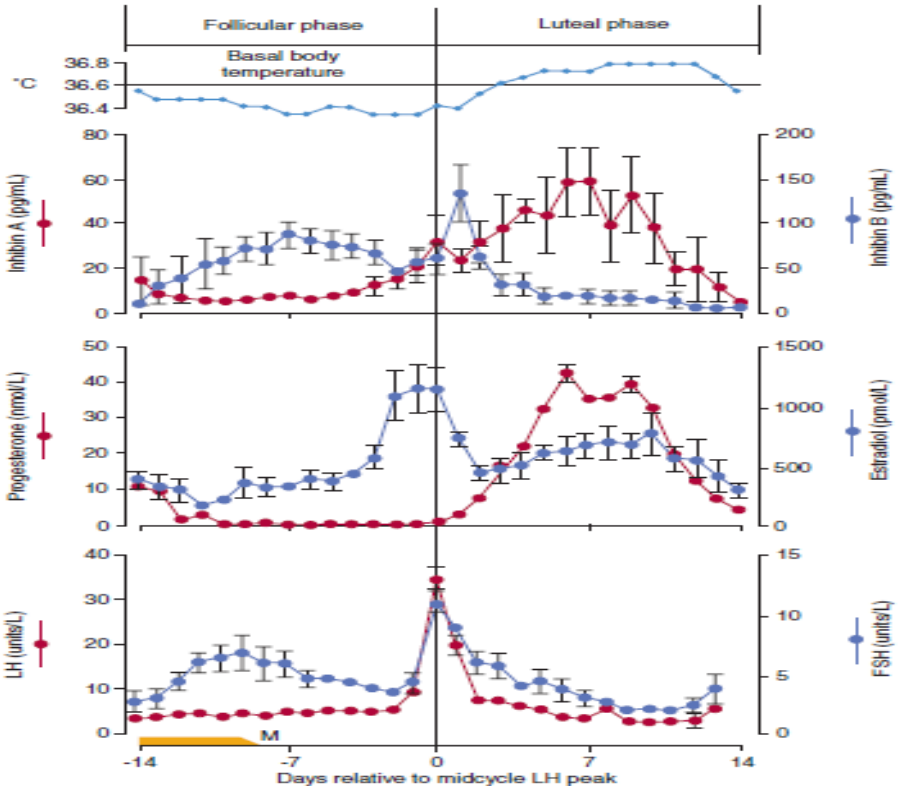


FIGURE 22–14 Basal body temperature and plasma hormone concentrations (mean ± standard error) during the normal human menstrual cycle.

A surge in LH secretion triggers ovulation, and ovulation normally occurs about 9 h after the peak of the LH surge at midcycle (Figure 22–14). The ovum lives for approximately 72 h after it is extruded from the follicle, but it is fertilizable for a much shorter time than this. the most fertile period is clearly the 48 h before ovulation. However, for those interested in the "rhythm method" of contraception, it should be noted that there are rare but documented cases in the literature of pregnancy resulting from isolated coitus on every day of the cycle.

OVARIAN HORMONES

Estrogens :

The naturally occurring estrogens are **17β-estradiol, estrone,** and **estriol**. They are steroids secreted primarily by the granulosa cells of the ovarian follicles, the corpus luteum, and the placenta. Their biosynthesis depends on the enzyme **aromatase** (CYP19), which converts testosterone to estradiol and androstenedione to estrone . The latter reaction also occurs in fat, liver, muscle, and the brain. Theca interna cells have many LH receptors, and LH acts via cAMP to increase conversion of cholesterol to androstenedione. The theca interna cells supply androstenedione to the granulosa cells. The granulosa cells make estradiol when provided with androgens and it appears that the estradiol they form in primates is secreted into the follicular fluid. Granulosa cells have many FSH receptors, and FSH facilitates their secretion of estradiol by acting via cAMP to increase their aromatase activity. Mature granulosa cells also acquire LH receptors, and LH also stimulates estradiol production.Two percent of the circulating estradiol is free, and the remainder is bound to protein: 60% to albumin and 38% to the same gonadal steroid-binding globulin (GBG) that binds testosterone.In the liver, estradiol, estrone, and estriol are converted to glucuronide and sulfate conjugates. All these compounds, along with

other metabolites, are excreted in the urine. Appreciable amounts are secreted in the bile and reabsorbed into the bloodstream (enterohepatic circulation).

Estrogens Secretion :

estrogen comes from the ovary, and two peaks of secretion occur: one just before ovulation and one during the midluteal phase. The estradiol secretion rate is 36 μg/day (133 nmol/day) in the early follicular phase, 380 μg/day just before ovulation, and 250 μg/day during the midluteal phase (After menopause, estrogen secretion declines to low levels. As noted previously, the estradiol production rate in men is about 50 μg/day (184 nmol/day).

Effects on the Female Genitalia:

Estrogens facilitate the growth of the ovarian follicles and increase the motility of the uterine tubes. They increase uterine blood flow and have important effects on the smooth muscle of the uterus. Under the influence of estrogens, the muscle becomes more active and excitable, and action potentials in the individual fibers become more frequent. The “estrogen-dominated” uterus is also more sensitive to oxytocin.

Effects on Endocrine Organs:

Estrogens decrease FSH secretion. Under some circumstances, they inhibit LH secretion (negative feedback); in other circumstances, they increase LH secretion (positive feedback). Women are sometimes given large doses of estrogens for 4–6 days to prevent conception after coitus during the fertile period (postcoital or “morning-after” contraception). However, in this instance, pregnancy is probably prevented by interference with implantation of the ovum rather than changes in gonadotropin secretion.

Effects on the Breasts:

Estrogens produce duct growth in the breasts and are largely responsible for breast enlargement at puberty in girls; they have been called the growth hormones of the breast. They are responsible for the pigmentation of the areolas, although pigmentation usually becomes more intense during the first pregnancy than it does at puberty

Female Secondary Sex Characteristics:

The body changes that develop in girls at puberty—in addition to enlargement of breasts, uterus, and vagina—are due in part to estrogens, which are the "feminizing hormones," and in part simply to the absence of testicular androgens. Women have narrow shoulders and broad hips, thighs that converge, and arms that diverge (wide **carrying angle**). This body configuration, plus the female distribution of fat in the breasts and buttocks, is seen also in castrate males. In women, the larynx retains its prepubertal proportions and the voice stays high-pitched. Women have less body hair and more scalp hair, and the pubic hair generally has a characteristic flat-topped pattern (female escutcheon). However, growth of pubic and axillary hair in both sexes is due primarily to androgens rather than estrogens.

Mechanism of Action:

There are two principal types of nuclear estrogen receptors: estrogen receptor α (ERα). After binding estrogen, they form homodimers and bind to DNA, altering its transcription. Some tissues contain one type or the other, but overlap also occurs, with some tissues containing both ERα and ERβ. ERα is found primarily in the uterus, kidneys, liver, and heart, whereas ERβ is found primarily in the ovaries, prostate, lungs, gastrointestinal tract, hemopoietic system, and central nervous system (CNS). Most of the effects of estrogens are genomic, that is, due to actions on the nucleus, but some are so rapid that it is difficult to believe they are mediated via production of mRNAs. These include effects on neuronal discharge in the brain and, possibly, feedback effects on gonadotropin secretion.

Progesterone

Progesterone is a steroid secreted by the corpus luteum, the placenta, and (in small amounts) the follicle. It is an important intermediate in steroid biosynthesis in all tissues that secrete steroid hormones, and small mounts apparently enter the circulation from the testes and adrenal cortex. About 2% of the circulating progesterone is free whereas 80% is bound to albumin and 18% is bound to corti-costeroid-binding globulin. Progesterone has a short half-life and is converted in the liver to pregnanediol, which is conjugated to glucuronic acid and excreted in the urine.

Secretion

In men, the plasma progesterone level is approximately 0.3 ng/mL (1 nmol/L). In women, the level is approximately 0.9 ng/mL (3 nmol/L) during the follicular phase of the menstrual cycle. The difference is due to secretion of small amounts of progesterone by cells in the ovarian follicles; theca cells provide pregnenolone to the granulosa cells, which convert it to progesterone. Late in the follicular**.** phase, progesterone secretion begins to increase. During the luteal phase, the corpus luteum produces large quantities of progesterone and plasma progesterone is markedly increased to a peak value of approximately 18 ng/mL (60 nmol/L). The stimulating effect of LH on progesterone secretion by the corpus luteum is due to activation of adenylyl cyclase and involves a subsequent step that is dependent on protein synthesis .

Actions

The principal target organs of progesterone are the uterus, the breasts, and the brain. Progesterone is responsible for the progestational changes in the endometrium and the cyclical changes in the cervix and vagina .It has an antiestrogenic effect on the myometrial cells, decreasing their excitability, their sensitivity to oxytocin, and their spontaneous electrical activity while

increasing their membrane potential. It also decreases the number of estrogen receptors in the endometrium and increases the rate of conversion of 17β-estradiol to less active estrogens. In the breast, progesterone stimulates the development of lobules and alveoli. It induces differentiation of estrogen-prepared ductal tissue and supports the secretory function of the breast during lactation. The feedback effects of progesterone are complex and are exerted at both the hypothalamic and pituitary levels. Large doses of progesterone inhibit LH secretion and potentiate the inhibitory effect of estrogens, preventing ovulation. Progesterone is thermogenic and is probably responsible for the rise in basal body temperature at the time of ovulation. It stimulates respiration, and the alveolar PCO2 Large doses of progesterone produce natriuresis, probably by blocking the action of aldosterone on the kidney. The hormone does not have a significant anabolic effect.

Relaxin

Relaxin is a polypeptide hormone that is produced in the corpus luteum, uterus, placenta, and mammary glands in women and in the prostate gland in men. During pregnancy, it relaxes the pubic symphysis and other pelvic joints and softens and dilates the uterine cervix. Thus, it facilitates delivery. It also inhibits uterine contractions and may play a role in the development of the mammary glands. In nonpregnant women, relaxin is found in the corpus luteum and the endometrium during the secretory but not the proliferative phase of the menstrual cycle. Its function in nonpregnant women is unknown. In men, it is found in semen, where it may help maintain sperm motility and aid in sperm penetration of the ovum.

Feedback regulation of ovarian function

During the early part of the follicular phase, inhibin B is low and FSH is modestly elevated, fostering follicular growth. LH secretion is held in check by the negative

feedback effect of the rising plasma estrogen level. At 36–48 h before ovulation, the estrogen feedback effect becomes positive, and this initiates the burst of LH secretion (LH surge) that produces ovulation. Ovulation occurs about 9 h after the LH peak. FSH secretion also peaks, despite a small rise in inhibin**.** probably because of the strong stimulation of gonadotropes by GnRH. During the luteal phase, the secretion of LH and FSH is low because of the elevated levels of estrogen, progesterone, and inhibin **Figure 22–19**.

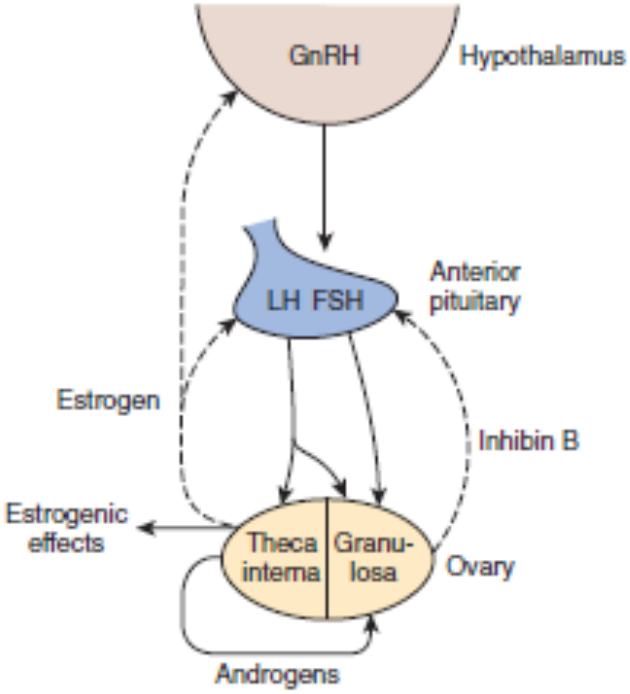


FIGURE 22–19 Feedback regulation of ovarian function.

It should be emphasized that a moderate, constant level of circulating estrogen exerts a negative feedback effect on LH secretion, whereas during the cycle, an elevated estrogen level exerts a positive feedback effect and stimulates LH secretion. but exactly how negative feedback is switched to positive feedback and then back to negative feedback in the luteal phase remains unknown.

PREGNANCY:

Fertilization & Implantation : In humans, **fertilization** of the ovum by the sperm usually occurs in the ampulla of the uterine tube. Fertilization involves (1) chemoattraction of the sperm to the ovum by substances produced by the ovum; (2) adherence to the **zona pellucida,** the membranous structure surrounding the ovum; (3) penetration of the zona pellucida and the acrosome reaction; and (4) adherence of the sperm head to the cell membrane of the ovum, with breakdown of the area of fusion and release of the sperm nucleus into the cytoplasm of the ovum (**Figure 22–20**).

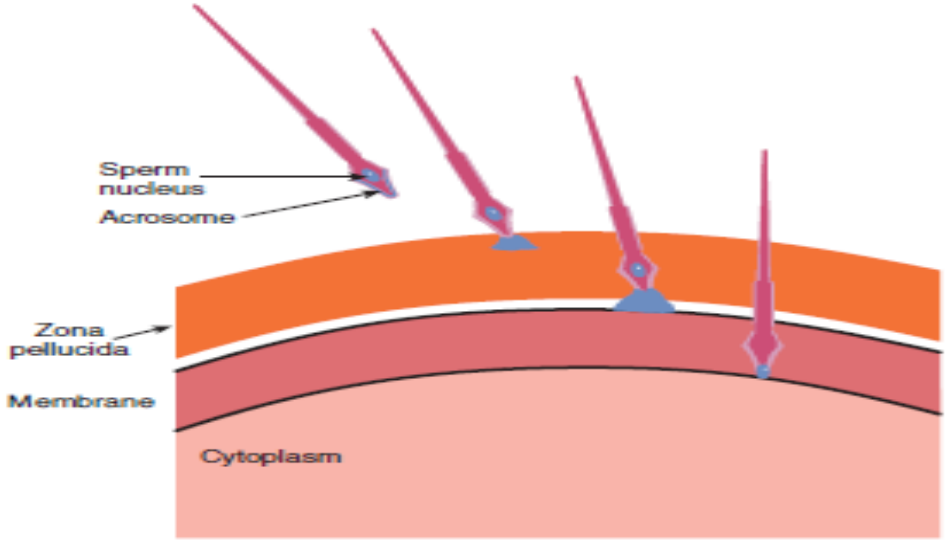


FIGURE 22–20 Sequential events in fertilization in mammals.

Millions of sperm are deposited in the vagina during intercourse. Eventually, 50–100 sperm reach the ovum, and many of them contact the zona pellucida. Sperm bind to a receptor in the zona, and this is followed by the **acrosomal reaction,** that is, the breakdown of the acrosome, the lysosome-like organelle on the head of the sperm. Various enzymes are released, including the trypsin-like protease **acrosin.** Acrosin facilitates but is not required for the penetration of the sperm through the zona pellucida. When one sperm reaches the membrane of the ovum, fusion to the ovum membrane is mediated by **fertilin,** a protein on the surface of the sperm head

.The fusion provides the signal that initiates development. In addition, the fusion sets off a reduction in the membrane potential of the ovum that prevents polyspermy, the fertilization of the ovum by more than one sperm. This transient potential change is followed by a structural change in the zona pellucida that provides protection against polyspermy on a more long-term basis.The developing embryo, now called a **blastocyst,** moves down the tube into the uterus. This journey takes about 3 days, during which the blastocyst reaches the 8- or 16-cell stage. Once in contact with the endometrium, the blastocyst becomes surrounded by an outer layer of **syncytiotrophoblast,** a multi-nucleate mass with no discernible cell boundaries, and an inner layer of **cytotrophoblast** made up of individual cells. The syncytiotrophoblast erodes the endometrium, and the blastocyst burrows into it **(implantation).** The implantation site is usually on the dorsal wall of the uterus. A placenta then develops, and the trophoblast remains associated with it.

Endocrine Changes

In all mammals, the corpus luteum in the ovary at the time of fertilization fails to regress and instead enlarges in response to stimulation by gonadotropic hormones secreted by the placenta. The placental gonadotropin in humans is called **human chorionic gonadotropin (hCG).** The enlarged **corpus luteum of pregnancy** secretes estrogens, progesterone, and relaxin. Progesterone and relaxin help maintain pregnancy by inhibiting myometrial contractions; progesterone prevents prosta-glandin production by the uterus, which stops contractions from occurring. In humans, the placenta produces sufficient estrogen and progesterone from maternal and fetal precursors to take over the function of the corpus luteum after the sixth week of pregnancy. The function of the corpus luteum begins to decline after 8 weeks of pregnancy, but it persists throughout pregnancy. hCG secretion decreases after an initial marked rise, but estrogen and progesterone secretion increase until just before parturition .

Human Chorionic Gonadotropin

hCG is a glycoprotein that contains galactose and hexosamine. It is produced by the syncytiotrophoblast. Like the pituitary glycoprotein hormones, it is made up of α and β subunits. hCG-α is identical to the α subunit of LH, FSH, and TSH. The molecular weight of hCG-α is 18,000, and that of hCG-β is 28,000. hCG is primarily luteinizing and luteotropic and has little FSH activity. It can be measured by radioimmunoassay and detected in the blood as early as 6 days after conception.

Its presence in the urine in early pregnancy is the basis of the various laboratory tests for pregnancy, and it can sometimes be detected in the urine as early as 14 days after conception.

Human Chorionic Somatomammotropin

The syncytiotrophoblast also secretes large amounts of a protein hormone that is lactogenic and has a small amount of growth-stimulating activity. The structure of hCS is very similar to that of human growth hormone, and it appears that these two hormones and prolactin evolved from a common progenitor hormone. Large quantities of hCS are found in maternal blood, but very little reaches the fetus. Secretion of growth hormone from the maternal pituitary is not increased during pregnancy and may actually be decreased by hCS. However, hCS has most of the actions of growth hormone and apparently functions as a "maternal growth hormone of pregnancy" to bring about the nitrogen, potassium, and calcium retention, lipolysis, and decreased glucose utilization seen in this state. These latter two actions divert glucose to the fetus.. Low hCS levels are a sign of placental insufficiency.

Parturition

The duration of pregnancy in humans averages 270 days from fertilization (284 days from the first day of the menstrual period preceding conception). Irregular uterine contractions increase in frequency in the last month of pregnancy.The difference between the body of the uterus and the cervix becomes evident at the time of

delivery. The cervix, which is firm in the nonpregnant state and throughout pregnancy until near the time of delivery, softens and dilates, while the body of the uterus contracts and expels the fetus. There is still considerable uncertainty about the mechanisms responsible for the onset of labor. One factor is the increase in circulating estrogens produced by increased circulating DHEAS. This makes the uterus more excitable, increases the number of gap junctions between myometrial cells, and causes production of more prostaglandins, which in turn cause uterine contractions. In humans, CRH secretion by the fetal hypothalamus increases and is supplemented by increased placental production of CRH. This increases circulating adrenocorticotropic hormone (ACTH) in the fetus, and the resulting increase in cortisol hastens the maturation of the respiratory system. Thus, in a sense, the fetus picks the time to be born by increasing CRH secretion. The number of oxytocin receptors in the myometrium and the decidua (the endometrium of pregnancy) increases more than 100-fold during pregnancy and reaches a peak during early labor. Estrogens increase the number of oxytocin receptors, and uterine distension late in pregnancy may also increase their formation. Once labor is started, the uterine contractions dilate the cervix, and this dilation in turn sets up signals in afferent nerves that increase oxytocin secretion (**Figure 22–22**).

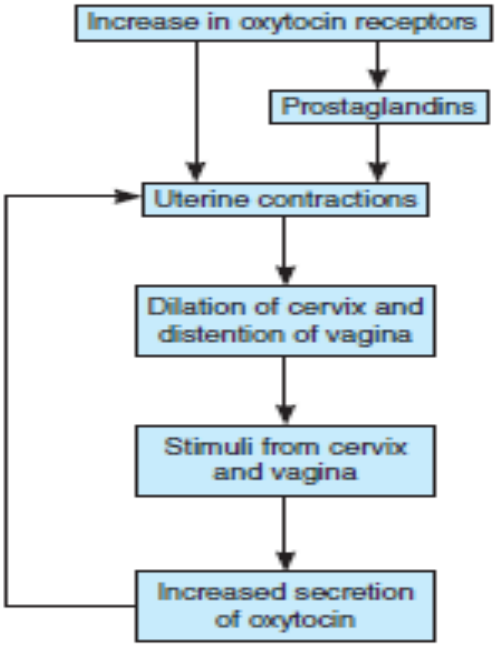


FIGURE 22–22 Role of oxytocin in parturition.

The plasma oxytocin level rises and more oxytocin becomes available to act on the uterus. Thus, a positive feedback loop is established that aids delivery and terminates on expulsion of the products of conception. Oxytocin increases uterine contractions in two ways: (1) It acts directly on uterine smooth muscle cells to make them contract and (2) it stimulates the formation of prostaglandins in the decidua. The prostaglandins enhance the oxytocin-induced contractions. During labor, spinal reflexes and voluntary contractions of the abdominal muscles ("bearing down") also aid in delivery.

LACTATION

Development of the Breasts :

In general, estrogens are primarily responsible for proliferation of the mammary ducts and progesterone for the development of the lobules. During pregnancy, prolactin levels increase steadily until term, and levels of estrogens and progesterone are elevated as well, producing full lobuloalveolar development.

Secretion & Ejection of Milk:

prolactin cause the formation of milk droplets and their secretion into the ducts. Oxytocin causes contraction of the myoepithelial cells lining the duct walls, with consequent ejection of the milk through the nipple in addition on the placenta secret human chorionic somatomammotropin (hcs) which has mild lactogenic properties .

Initiation of Lactation after Delivery:

The breasts enlarge during pregnancy in response to high circulating levels of estrogens, progesterone, prolactin, and possibly hCG. Some milk is secreted into the ducts as early as the 5th month, but the amounts are small compared with the surge of milk secretion that follows delivery. In most animals, milk is secreted within an hour after delivery, but in women it takes 1–3 days for the milk to "come in."After expulsion of the placenta at parturition, the levels of circulating estrogens and progesterone abruptly decline. The drop in circulating estrogen initiates lactation. Prolactin and estrogen synergize in producing breast growth, but estrogen antagonizes the milk-producing effect of prolactin on the breast. Indeed, in women who do not wish to breastfeed their babies, estrogens may be administered to stop lactation. Suckling not only evokes reflex oxytocin release and milk ejection, it also maintains and augments the secretion of milk because of the stimulation of prolactin secretion it produces. The first fluid secreted is the colostrum with contain the same conc. Of protein and lactose but no fat as in milk .

Effect of Lactation on Menstrual Cycles

Women who do not breastfeed their infants usually have their first menstrual period 6 weeks after delivery. However, women who breastfeed regularly have amenorrhea for 25–30 weeks. Breastfeeding stimulates prolactin secretion, and evidence suggests that prolactin inhibits GnRH secretion, inhibits the action of GnRH on the pituitary, and antagonizes the action of gonadotropins on the ovaries. Ovulation is

inhibited, and the ovaries are inactive, so estrogen and progesterone output falls to low levels. Consequently, only 5–10% of women become pregnant again during the suckling period, and breastfeeding has long been known to be an important, if only partly effective, method of birth control. Furthermore, almost 50% of the cycles in the first 6 months after resumption of menses are anovulatory .

Chapter 23

Function of the male Reproductive System

Introduction

The physiology of the mature male reproductive system is related to the gonads . the male gonads have a dual function: the production of germ cells (gametogenesis) and the secretion of sex hormones. The androgens are the steroid sex hormones that are masculinizing in their action. The testes secrete large amounts of androgens, principally testosterone, but they also secrete small amounts of estrogens. Unlike that observed in females, male gonadotropin secretion is noncyclical, and once mature, male gonadal function slowly declines with advancing age, but the ability to produce viable gametes persists.

THE MALE REPRODUCTIVE SYSTEM

The testes are the male source of DNA which is packed in the head of the sperm and it is the main source of male hormones. There are two testes each is ovoid and encloses by a capsule of connective tissue & smooth muscle called tonica albuginea . Thin partitions of connective T. extend from tonica Albuginea across the testes dividing them into partitions called lobules . The lobules are the center of testicular activity because the lobules in the two testes contain about 500m of convoluted seminiferous tubules. The testes are made up of loops of convoluted seminiferous tubules, in the walls of which the spermatozoa are formed from the primitive germ cells (spermatogenesis). Both ends of each loop drain into a network of ducts in the head of the epididymis. From there, spermatozoa pass through the tail of the epididymis into the vas deferens. They enter through the ejaculatory ducts into the urethra in the body of the prostate at the time of ejaculation (Figure 23–1).

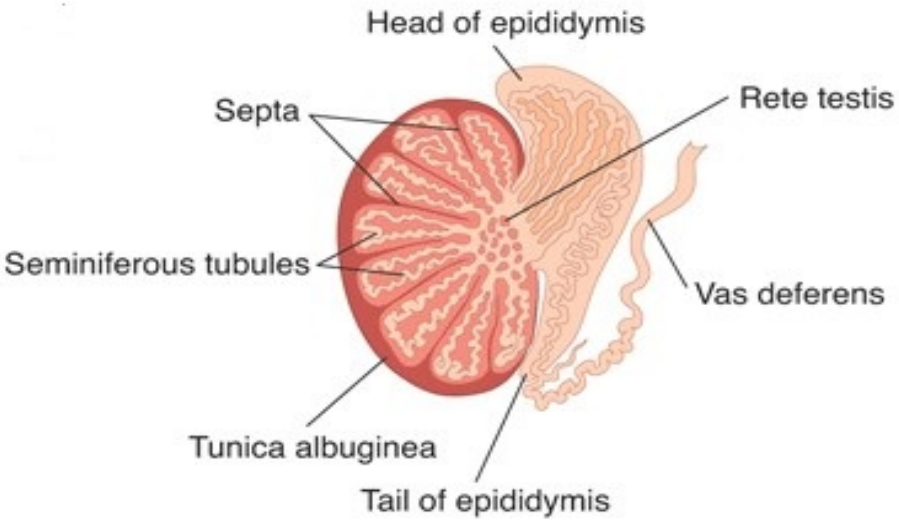


FIGURE 23–1 Male reproductive system.

Between the tubules in the testes are nests of cells containing lipid granules, the interstitial cells of Leydig (Leydig cells; 23–3) which secrete testosterone into the bloodstream.

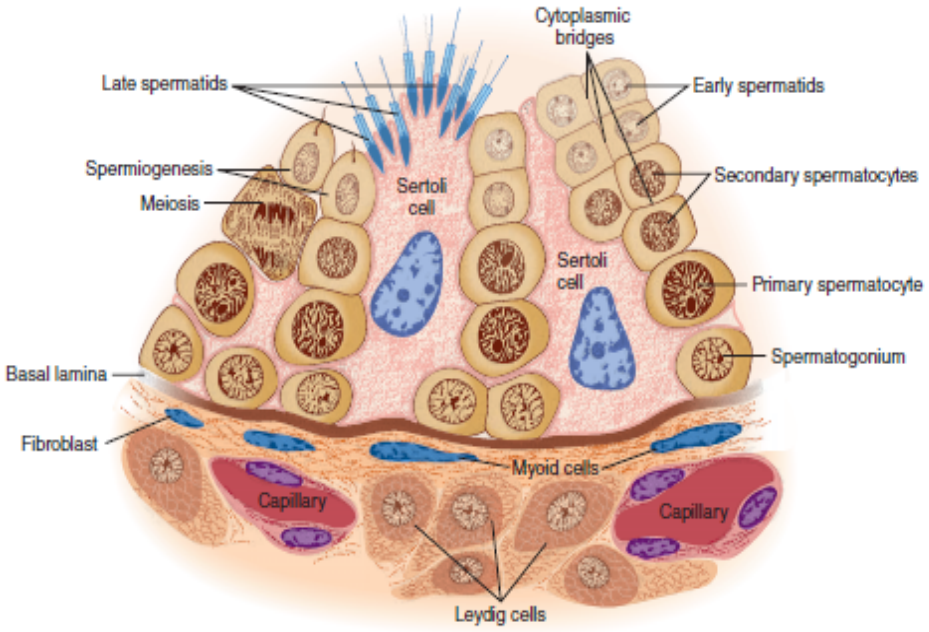


FIGURE 23–3 Seminiferous epithelium.

The spermatic arteries to the testes are tortuous, and blood in them runs parallel but in the opposite direction to blood in the pampiniform plexus of spermatic veins. This anatomic arrangement may permit countercurrent exchange of heat and testosterone.

GAMETOGENESIS & EJACULATION

Blood-Testis Barrier

The walls of the seminiferous tubules are lined by primitive germ cells and **Sertoli cells,** large, complex glycogen-containing cells that stretch from the basal lamina of the tubule to the lumen (Figure 23–3). Germ cells must stay in contact with Sertoli cells to survive; this contact is maintained by cytoplasmic bridges. Tight junctions between adjacent Sertoli cells near the basal lamina form a **blood-testis barrier** that prevents many large molecules from passing from the interstitial tissue and the part of the tubule near the basal lamina (basal compartment) to the region near the tubular lumen (adluminal compartment) and the lumen. However, steroids penetrate this barrier with ease, and evidence suggests that some proteins also pass from the Sertoli cells to the Leydig cells, and vice versa, to function in a paracrine manner. In addition, maturing germ cells must pass through the barrier as they move to the lumen. This appears to occur without disruption of the barrier by coordinated break-down of the tight junctions above the germ cells and formation of new tight junctions below them.The fluid in the lumen of the seminiferous tubules is quite different from plasma; it contains very little protein and glucose but is rich in androgens, estrogens, K+, inositol, and glutamic and aspartic acids. Maintenance of its composition depends on the blood-testis barrier. The barrier also protects the germ cells from bloodborne noxious agents, prevents antigenic products of germ cell division and maturation from entering the circulation and generating an autoimmune response, and may help establish an osmotic gradient that facilitates movement of fluid into the tubular lumen.

Spermatogenesis

Spermatogonia, the primitive germ cells next to the basal lamina of the seminiferous tubules, mature into **primary spermatocytes** (Figure 23–3). This process begins during adolescence. The primary spermatocytes undergo meiotic division, reducing the number of chromosomes. In this two-stage process, they divide into **secondary spermatocytes** and then into **spermatids,** which contain the haploid number of 23 chromosomes. The spermatids mature into **spermatozoa (sperm).** The formation of a mature sperm from a primitive germ cell by spermatogenesis in humans spans approximately 74 days.

Each sperm is an intricate motile cell, rich in DNA, with a head that is made up mostly of chromosomal material (**Figure 23–4**).

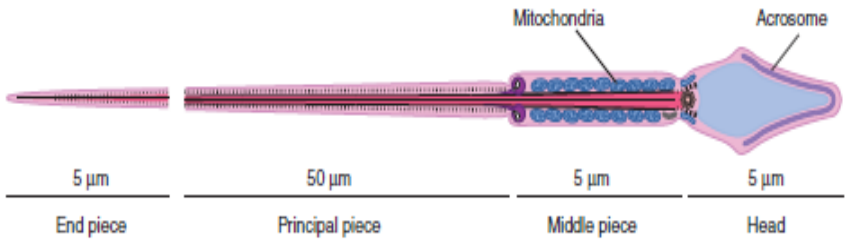


FIGURE 23–4 Human spermatozoon, profile view.

Covering the head like a cap is the **acrosome,** a lysosome-like organelle rich in enzymes involved in sperm penetration of the ovum and other events associated with fertilization. The motile tail of the sperm is wrapped in its proximal portion by a sheath holding numerous mitochondria. Spermatids mature into spermatozoa in deep folds of the cytoplasm of the Sertoli cells (Figure 23–3). Mature spermatozoa are released from the Sertoli cells and become free in the lumens of the tubules.

The Sertoli cells secrete :**Androgen-Binding Protein (ABP) , Inhibin and MIS.** They do not synthesize androgens, but they contain aromatase (CYP19), the enzyme responsible for conversion of androgens to estrogens, and they can produce

estrogens. ABP probably functions to maintain a high, stable supply of androgen in the tubular fluid. Inhibin inhibits follicle-stimulating hormone (FSH) secretion. FSH and androgens maintain the gametogenic function of the testis. The stages from spermatogonia to spermatids appear to be androgen-independent. However, the maturation from spermatids to spermatozoa depends on androgen acting on the Sertoli cells in which the developing spermatozoa are embedded. FSH acts on the Sertoli cells to facilitate the last stages of spermatid maturation. In addition, it promotes the production of ABP.

Further Development of Spermatozoa

Spermatozoa leaving the testes are not fully mobile. They continue their maturation and acquire motility during their passage through the epididymis. Motility is obviously important in vivo, but fertilization occurs in vitro if an immotile spermatozoon from the head of the epididymis is microinjected directly into an ovum. The ability to move forward **(progressive motility),** which is acquired in the epididymis, involves activation of a unique set of proteins from the **CatSper** family, which are localized to the principal piece of the sperm tail. CatSpers form an alkaline-sensitive Ca2+ channel that becomes more active as the sperm go from the acidic vagina (pH ~5) to the cervical mucus (pH ~8). Sperm from knockout mice that do not express CatSper1-4 have altered motility and are infertile, emphasizing the important role of these proteins. In addition, spermatozoa express olfactory receptors, and ovaries produce odorant-like molecules. Recent evidence indicates that these molecules and their receptors interact, fostering movement of the spermatozoa toward the ovary (chemotaxis). Ejaculation of the spermatozoon involves contractions of the vas deferens mediated in part by P2X receptors, ligand-gated cation channels that respond to ATP and fertility is reduced in mice in which these receptors are knocked out. Once ejaculated into the female, the spermatozoa move up the uterus to the isthmus of the uterine tubes, where they slow down and

undergo **capacitation.** This further maturation process involves two components: increasing the motility of the spermatozoa and facilitating their preparation for the acrosome reaction.

Effect of Temperature

Spermatogenesis requires a temperature considerably lower than that of the interior of the body. The testes are normally maintained at a temperature of about 32°C. They are kept cool by air circulating around the scrotum and probably by heat exchange in a countercurrent manner between the spermatic arteries and veins. Situations that increase heat around the testes in humans (eg, hot baths [43–45°C for 30 min/d] and insulated athletic supporters) can reduce sperm counts In addition, evidence suggests a seasonal effect in men, with sperm counts being greater in the winter regardless of the temperature to which the scrotum is exposed.

Semen

The fluid that is ejaculated at the time of orgasm, the **semen,** contains sperm and the secretions of the seminal vesicles, prostate, Cowper glands, and, probably, the urethral glands (**Table 23–1**). An average volume per ejaculate is 2.5–3.5 mL after several days of abstinence from sexual activity. The volume of semen and the sperm count decrease rapidly with repeated ejaculation. Even though it takes only one sperm to fertilize the ovum, each milliliter of semen normally contains about 100 million sperm. Reduction in sperm production is associated with infertility: 50% of men with counts of 20–40 million/mL and essentially all of those with counts under 20 million/mL are sterile. The presence of many morphologically abnormal or immotile spermatozoa also correlates with infertility. The **prostaglandins** in semen, which come from the seminal vesicles, are at high concentrations, but their function in semen is unknown. Human sperm move at a speed of about 3 mm/min through the female genital tract. Sperm reach the uterine tubes 30–60 min after copulation.

Contractions of the female organs may facilitate the transport of the sperm to the uterine tubes.

TABLE 23–1 Composition of human semen.

Color: White, opalescent	
Specific gravity: 1.028	
pH: 7.35–7.50	
Sperm count: Average about 100 million/mL, with fewer than 20% abnormal forms	
Other components: Fructose (1.5–6.5 mg/mL) Phosphorylcholine Ergothioneine Ascorbic acid Flavins Prostaglandins	From seminal vesicles (contributes 60% of total volume)
Spermine Citric acid Cholesterol, phospholipids Fibrinolysin, fibrinogenase Zinc Acid phosphatase	From prostate (contributes 20% of total volume)
Phosphate Bicarbonate Hyaluronidase	Buffers

Erection

Erection is initiated by dilation of the arterioles of the penis. As the erectile tissue of the penis fills with blood, the veins are compressed, blocking outflow and adding to the turgor of the organ. The integrating centers in the lumbar segments of the spinal cord are activated by impulses in afferents from the genitalia and descending tracts that mediate erection in response to erotic psychological stimuli. The efferent parasympathetic fibers are in the pelvic splanchnic nerves **(nervi erigentes).** The fibers presumably release acetylcholine and the vasodilator vasoactive intestinal polypeptide (VIP) as cotransmitters . NO as a vasodilator plays a prominent role in

the production of erection. Normally, erection is terminated by sympathetic vasoconstrictor impulses to the penile arterioles.

Ejaculation

Ejaculation is a two-part spinal reflex that involves **emission,** the movement of the semen into the urethra; and **ejaculation** proper, the propulsion of the semen out of the urethra at the time of orgasm. The afferent pathways are mostly fibers from touch receptors in the glans penis that reach the spinal cord through the internal pudendal nerves. Emission is a sympathetic response, integrated in the upper lumbar segments of the spinal cord and effected by contraction of the smooth muscle of the vasa deferentia and seminal vesicles in response to stimuli in the hypogastric nerves. The semen is propelled out of the urethra by contraction of the bulbocavernosus muscle, a skeletal muscle. The spinal reflex centers for this part of the reflex are in the upper sacral and lowest lumbar segments of the spinal cord.

ENDOCRINE FUNCTION OF THE TESTES

Testosterone

Testosterone, the principal hormone of the testes is a steroid ,It is synthesized from cholesterol in the Leydig cells and is also formed from androstenedione secreted by the adrenal cortex. (**Figure 23–5**)

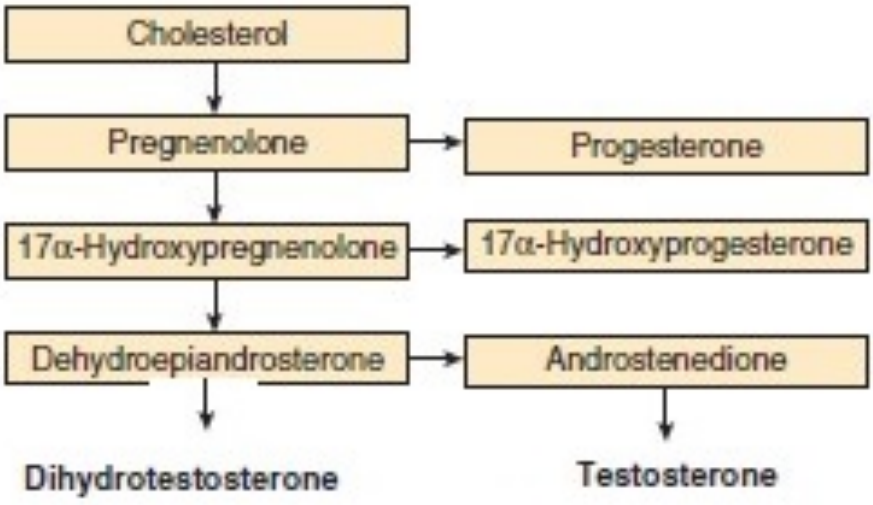


FIGURE 23–5 Biosynthesis of testosterone

The secretion of testosterone is under the control of LH, and the mechanism by which LH stimulates Leydig cells involves increased formation of cyclic adenosine monophosphate (cAMP) via the G-protein–coupled LH receptor and Gs. Cyclic AMP increases the formation of cholesterol from cholesterol esters and the conversion of cholesterol to pregnenolone via the activation of protein kinase A.

Secretion

The testosterone secretion rate is 4–9 mg/d (13.9–31.33 μmol/d) in normal adult males. Small amounts of testosterone are also secreted in females, with the major source being the ovary, but possibly from the adrenal as well.

Transport & Metabolism

Ninety-eight percent of the testosterone in plasma is bound to protein: 65% is bound to a β-globulin called gonadal steroid–binding globulin (GBG) or sex steroid–binding globulin, and 33% to albumin .GBG also binds estradiol. The plasma testosterone level (free and bound) is 300–1000 ng/dL (10.4–34.7 nmol/L) in adult men, compared with 30–70 ng/dL (1.04–2.43 nmol/L) in adult women. It declines somewhat with age in men.

A small amount of circulating testosterone is converted to estradiol, but most of the testosterone is converted to 17-ketosteroids, principally androsterone and its isomer etiocholanolone and excreted in the urine.

Actions

In addition to their actions during development, testosterone and other androgens exert an inhibitory feedback effect on pituitary LH secretion; develop and maintain the male secondary sex characteristics; exert an important protein-anabolic, growth-promoting effect; and, along with FSH, maintain spermatogenesis.

Secondary Sex Characteristics

The widespread changes in hair distribution, body configuration, and genital size that develop in boys at puberty—the male secondary sex characteristics—are summarized in Table 23–3.

TABLE 23–3 Changes at puberty in boys (male secondary sex characteristics).

External genitalia: Penis increases in length and width. Scrotum becomes pigmented and rugose.
Internal genitalia: Seminal vesicles enlarge and secrete and begin to form fructose. Prostate and bulbourethral glands enlarge and secrete.
Voice: Larynx enlarges, vocal cords increase in length and thickness, and voice becomes deeper.
Hair growth: Beard appears. Hairline on scalp recedes anterolaterally. Pubic hair grows with male (triangle with apex up) pattern. Hair appears in axillas, on chest, and around anus; general body hair increases.
Mental: More aggressive, active attitude. Interest in opposite sex develops.
Body conformation: Shoulders broaden; muscles enlarge.
Skin: Sebaceous gland secretion thickens and increases (predisposing to acne).

The prostate and seminal vesicles enlarge, and the seminal vesicles begin to secrete fructose. This sugar appears to function as the main nutritional supply for the spermatozoa. Although body hair is increased by androgens, scalp hair is decreased. Hereditary baldness often fails to develop unless dihydrotestosterone (DHT) is present.

Anabolic Effects

Androgens increase the synthesis and decrease the breakdown of protein, leading to an increase in the rate of growth. It used to be argued that they cause the epiphyses to fuse to the long bones, thus eventually stopping growth, but it now appears that epiphysial closure is due to estrogens. Secondary to their anabolic effects, androgens cause moderate Na^+, K^+, H_2O, Ca^{2+}, SO_4^{2-}, and PO_4^{-} retention; and they also

increase the size of the kidneys. Doses of exogenous testosterone that exert significant anabolic effects are also masculinizing and increase libido, which limits the usefulness of the hormone as an anabolic agent in patients with wasting diseases.

Mechanism of Action

Like other steroids, testosterone binds to an intracellular receptor, and the receptor/steroid complex then binds to DNA in the nucleus, facilitating transcription of various genes. In addition, testosterone is converted to **DHT** by 5α-reductase in some target cells (Figure 23–5 and **Figure 23–8**), and DHT binds to the same intracellular receptor as testosterone. DHT also circulates, with a plasma level that is about 10% of the testosterone level. Testosterone–receptor complexes are less stable than DHT–receptor complexes in target cells, and they conform less well to the DNA-binding state. Thus, DHT formation is a way of amplifying the action of testosterone in target tissues. Humans have two 5α-reductases that are encoded by different genes. Type 1 5α-reductase is present in skin throughout the body and is the dominant enzyme in the scalp. Type 2 5α-reductase is present in genital skin, the prostate, and other genital tissues. Testosterone–receptor complexes are responsible for the maturation of Wolffian duct structures and consequently for the formation of male internal genitalia during development, but DHT–receptor complexes are needed to form male external genitalia (Figure 23–8).

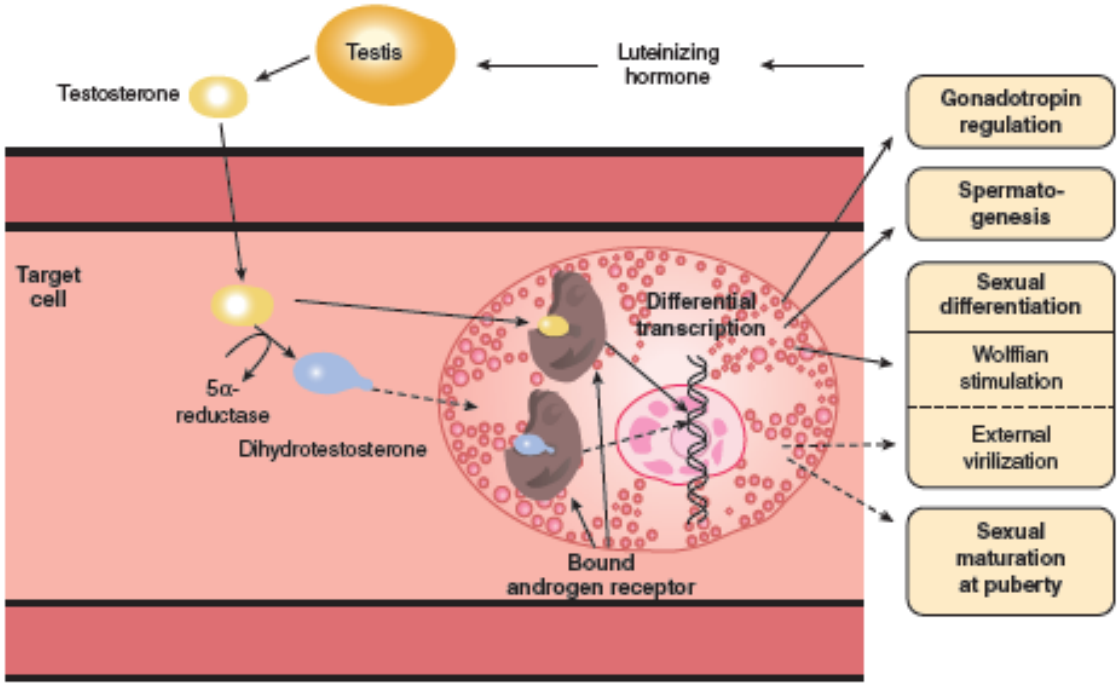


FIGURE 23–8 Schematic diagram of the actions of testosterone (solid arrows) and dihydrotestosterone (dashed arrows).

DHT–receptor complexes are also primarily responsible for enlargement of the prostate and probably of the penis at the time of puberty, as well as for the facial hair, the acne, and the temporal recession of the hairline. On the other hand, the increase in muscle mass and the development of male sex drive and libido depend primarily on testosterone rather than DHT .

CONTROL OF TESTICULAR FUNCTION

FSH is tropic for Sertoli cells, and FSH and androgens maintain the gametogenic function of the testes. FSH also stimulates the secretion of ABP and inhibin. Inhibin feeds back to inhibit FSH secretion. LH is tropic for Leydig cells and stimulates the secretion of testosterone, which in turn feeds back to inhibit LH secretion. Hypothalamic lesions in animals and hypothalamic disease in humans lead to atrophy of the testes and loss of their function.

Inhibins

Testosterone reduces plasma LH but, except in large doses, it has no effect on plasma FSH. Plasma FSH is elevated in patients who have atrophy of the seminiferous tubules but normal levels of testosterone and LH secretion. These observations led to the search for **inhibin,** a factor of testicular origin that inhibits FSH secretion. There are two inhibins in extracts of testes in men and in antral fluid from ovarian follicles in women.

They are formed from three polypeptide subunits: a glycosylated α subunit with a molecular weight of 18,000; and two nonglycosylated β subunits, βA and βB, each with a molecular weight of 14,000. The subunits are formed from precursor proteins (**Figure 23–9**).

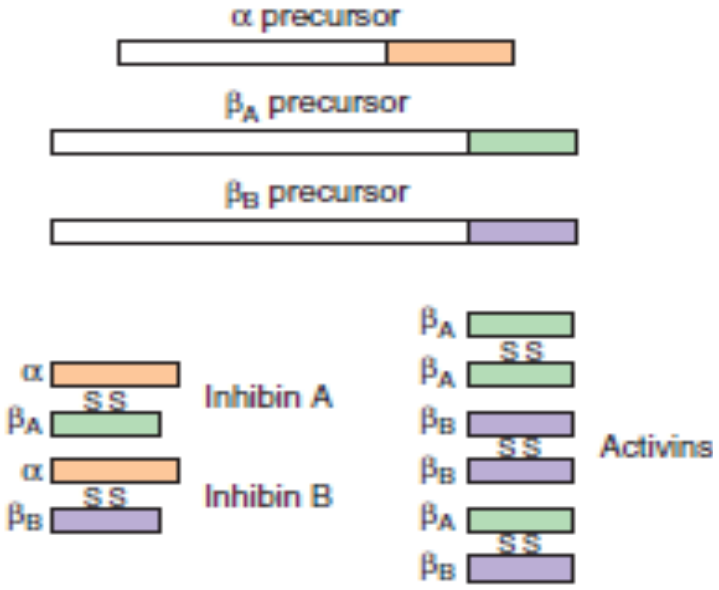


FIGURE 23–9 Inhibin and activin production.

The α subunit combines with βA to form a heterodimer and with βB to form another heterodimer, with the subunits linked by disulfide bonds. Both αβA (inhibin A) and αβB (inhibin B) inhibit FSH secretion by a direct action on the pituitary, although it appears that it is inhibin B that is the FSH-regulating inhibin in adult men and women. Inhibins are produced by Sertoli cells in males and granulosa cells in

females. The heterodimer βAβB and the homodimers βAβA and βBβB are also formed. They stimulate rather than inhibit FSH secretion and consequently are called **activins.** Inhibins and activins are found not only in the gonads but also in the brain and many other tissues. In the bone marrow, activins are involved in the development of white blood cells.

Steroid Feedback

A current "working hypothesis" of the way the functions of the testes are regulated by steroids is shown in **Figure 23–10**.

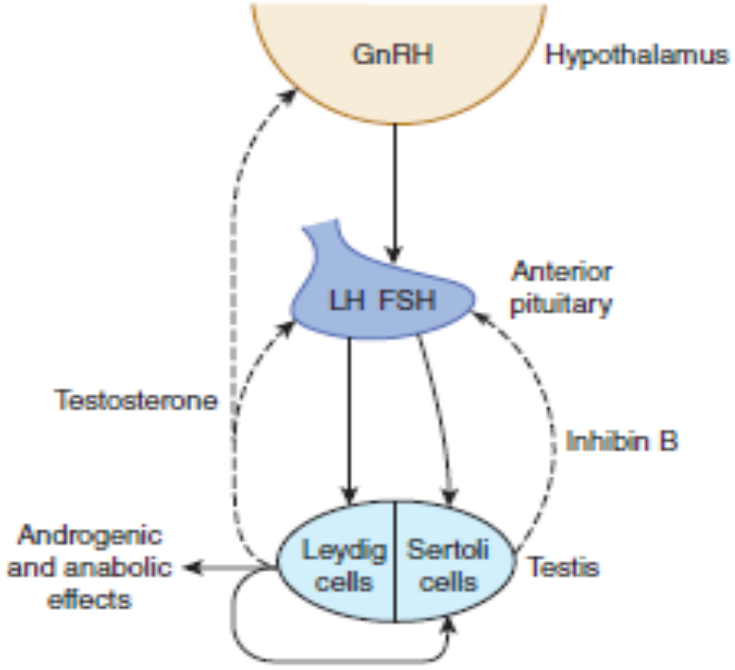


FIGURE 23–10 The hypothalamus, pituitary and testes interact via signaling molecules

Castration is followed by a rise in the pituitary content and secretion of FSH and LH, and hypothalamic lesions prevent on the anterior pituitary and by inhibiting the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Inhibin acts directly on the anterior pituitary to inhibit FSH secretion. In response to LH, some of the testosterone secreted from the Leydig cells bathes the seminiferous

epithelium and provides the high local concentration of androgen to the Sertoli cells that is necessary for normal spermatogenesis. Systemically administered testosterone does not raise the androgen level in the testes to as great a degree, and it inhibits LH secretion. Consequently, the net effect of systemically administered testosterone is generally a decrease in sperm count. Testosterone therapy has been suggested as a means of male contraception. However, the dose of testosterone needed to suppress spermatogenesis causes sodium and water retention. The possible use of inhibins as male contraceptives is being explored.

Chapter 24

Endocrine Functions of the Pancreas & Regulation of Carbohydrate Metabolism

There are four polypeptides with regulatory activity are secreted by the islets of Langerhans in the pancreas. Two of these, insulin and glucagon, are hormones and have important functions in the regulation of the intermediary metabolism of carbohydrates, proteins, and fats. The third polypeptide, somatostatin, plays a role in the regulation of islet cell secretion, and the fourth, pancreatic polypeptide, is probably concerned primarily with the regulation of ion transport in the intestine.

The islets of Langerhans are collections of cells. The cells in the islets can be divided into types on the basis of their staining properties and morphology. Humans have at least four distinct cell types: **A, B, D, and F cells.** A, B, and D cells are also called α, β, and δ cells. β-Islets make up about 2% of the volume of the gland, whereas the exocrine portion of the pancreas makes up 80%, and ducts and blood vessels make up the remainder. Humans have 1 to 2 million islets.

The A cells secrete glucagon, the B cells secrete insulin, the D cells secrete somatostatin, and the F cells secrete pancreatic polypeptide. The B cells, which are the most common and account for 60–75% of the cells in the islets, are generally located in the center of each islet. They tend to be surrounded by the A cells, which make up 20% of the total, and the less common D and F cells.

STRUCTURE, BIOSYNTHESIS, & SECRETION OF INSULIN:

Insulin is a polypeptide containing two chains of amino acids linked by disulfide bridges. Insulin is synthesized in the rough endoplasmic reticulum of the B cells . It

is then transported to the Golgi apparatus, where it is packaged into membrane-bound granules. These granules move to the plasma membrane by a process involving microtubules, and their contents are expelled by exocytosis .

FATE OF SECRETED INSULIN:

- **METABOLISM**

The half-life of insulin in the circulation in humans is about 5 min. Insulin binds to insulin receptors, and some is internalized. It is destroyed by proteases in the endosomes formed by the endocytotic process.

- **EFFECTS OF INSULIN**:

The physiologic effects of insulin are far-reaching and complex. They are conveniently divided into rapid, intermediate, and delayed actions.

TABLE 24–1 Principal actions of insulin.

Rapid (seconds)
Increased transport of glucose, amino acids, and K^+ into insulin-sensitive cells
Intermediate (minutes)
Stimulation of protein synthesis
Inhibition of protein degradation
Activation of glycolytic enzymes and glycogen synthase
Inhibition of phosphorylase and gluconeogenic enzymes
Delayed (hours)
Increase in mRNAs for lipogenic and other enzymes

The insulin has many actions on adipose tissue; skeletal, cardiac, and smooth muscle; and the liver.

In general insulin increase cell growth, but also has specific action on : -adipose tissue: it ↑ glucose entry, ↑ fatty acid synthesis, ↑ glycerol phosphate synthesis, ↑ triglyceride deposition, activation of lipoprotein lipase, inhibition of hormone-sensitive lipase and ↑ K^+ uptake.

- Muscle: ↑ glucose entry, ↑ glycogen synthesis, ↑ amino acid uptake, ↑protein synthesis in ribosomes, ↑ ketone & K^+ uptake and finally ↓ protein catabolism & release of gluconeogenic amino acids.

- Liver : ↑ protein & lipid synthesis, ↓ ketogenesis, ↓glucose output due to decreased gluconeogenesis, increased glycogen synthesis, and increased glycolysis.

TABLE 24–2 Effects of insulin on various tissues.

Adipose tissue
Increased glucose entry
Increased fatty acid synthesis
Increased glycerol phosphate synthesis
Increased triglyceride deposition
Activation of lipoprotein lipase
Inhibition of hormone-sensitive lipase
Increased K^+ uptake
Muscle
Increased glucose entry
Increased glycogen synthesis
Increased amino acid uptake
Increased protein synthesis in ribosomes
Decreased protein catabolism
Decreased release of gluconeogenic amino acids
Increased ketone uptake
Increased K^+ uptake
Liver
Decreased ketogenesis
Increased protein synthesis
Increased lipid synthesis
Decreased glucose output due to decreased gluconeogenesis, increased glycogen synthesis, and increased glycolysis
General
Increased cell growth

Glucose Transporters:

Glucose enters cells by **facilitated diffusion** or, in the intestine and kidneys, by secondary active transport with Na+. In muscle, adipose, and some other tissues, insulin stimulates glucose entry into cells by increasing the number of glucose transporters (GLUTs) in the cell membranes. The GLUTs that are responsible for facilitated diffusion of glucose across cell membranes are a family of closely related proteins that span the cell membrane 12 times and have their amino and carboxyl terminals inside the cell.

Insulin also increases the entry of glucose into liver cells, but it does not exert this effect by increasing the number of GLUT-4 transporters in the cell membranes.

Instead, it induces glucokinase, and this increases the phosphorylation of glucose, so that the intracellular free glucose concentration stays low, facilitating the entry of glucose into the cell.

Mechanism of Action

-Insulin Receptors

Insulin receptors are found on many different cells in the body. The insulin receptor, is a tetramer made up of two α and two β glycoprotein subunits. The α subunits bind insulin and are extracellular, whereas the β subunits span the membrane.

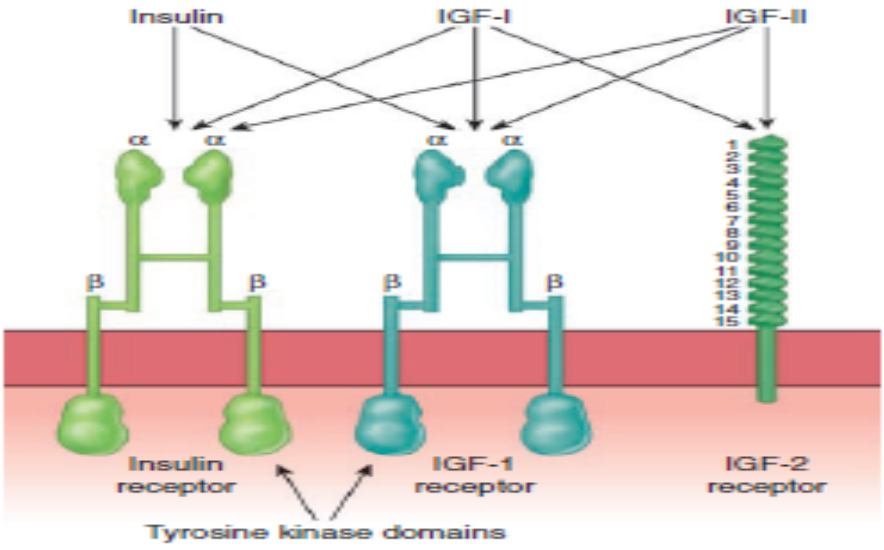


FIGURE 24–5 **Insulin, IGF-I, and IGF-II receptors.** Each

Consequences of Insulin Deficiency:

In humans, insulin deficiency is a common pathologic condition. In animals, it can be produced by pancreatectomy; by administration many of toxins that in appropriate doses cause selective destruction of the B cells of the pancreatic islets; by administration of drugs that inhibit insulin secretion; and by administration of anti-insulin antibodies..

Effects of Hyperglycemia

Hyperglycemia by itself can cause symptoms resulting from the hyperosmolality of the blood. In addition, there is glycosuria because the renal capacity for glucose reabsorption is exceeded. Excretion of the osmotically active glucose molecules entails the loss of large amounts of water (osmotic diuresis). The resultant dehydration activates the mechanisms regulating water intake, leading to polydipsia. When plasma glucose is episodically elevated over time, small amounts of hemoglobin A are non-enzymatically glycated to form $\mathbf{Hb_{AIc}}$. Careful control of the diabetes with insulin reduces the amount formed and consequently HbA>Ic concentration is measured clinically as an integrated index of diabetic control for the 4- to 6-weeks period before the measurement.

Effect of hyperglycemia on protein metabolism

In diabetes, the rate at which amino acids are catabolized to CO2 and H2O is increased. In addition, more amino acids are converted to glucose in the liver. The increased gluconeogenesis has many causes. Adrenal glucocorticoids also contribute to increased gluconeogenesis when they are elevated in severely ill diabetics. The supply of amino acids is increased for gluconeogenesis because, in the absence of insulin, less protein synthesis occurs in muscle and hence blood amino acid levels rise.

Fat Metabolism in Diabetes

The principal abnormalities of fat metabolism in diabetes are accelerated lipid catabolism, with increased formation of ketone bodies, and decreased synthesis of fatty acids and triglycerides. In diabetes, conversion of glucose to fatty acids in the depots is decreased because of the intracellular glucose deficiency. Insulin inhibits

the hormone-sensitive lipase in adipose tissue, and, in the absence of this hormone, the plasma level of **free fatty acids** is more than doubled. Thus, the FFA level parallels the plasma glucose level in diabetes and in some ways is a better indicator of the severity of the diabetic state.

In uncontrolled diabetes, the plasma concentration of triglycerides and chylomicrons as well as FFA is increased, and the plasma is often lipemic. The rise in these constituents is mainly due to decreased removal of triglycerides into the fat depots. The decreased activity of lipoprotein lipase contributes to this decreased removal. In diabetes, the plasma cholesterol level is usually elevated and this plays a role in the accelerated development of the atherosclerotic vascular disease that is a major long-term complication of diabetes in humans. The rise in plasma cholesterol level is due to an increase in the plasma concentration of very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL). These in turn may be due to increased hepatic production of VLDL or decreased removal of VLDL and LDL from the circulation.

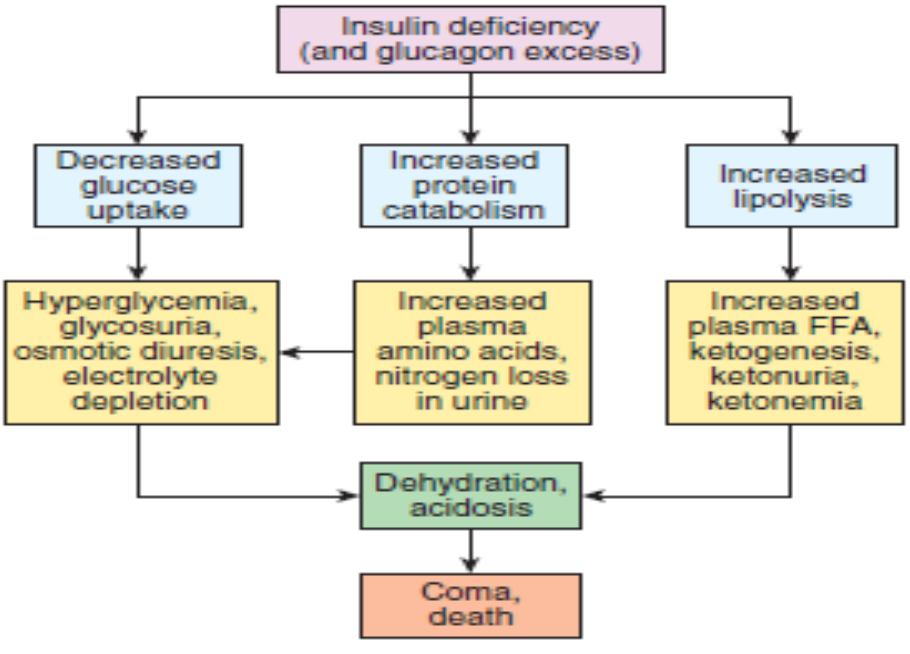


Figure1: Effect of insulin deficiency

Regulation of Insulin Secretion

The glucose acts directly on pancreatic B cells to increase insulin secretion. The response to glucose is biphasic; there is a rapid but short-lived increase in secretion followed by a more slowly developing prolonged increase. Glucose enters the B cells via GLUT-2 transporters and is phosphorylated by glucokinase then metabolized to pyruvate in the cytoplasm . The pyruvate enters the mitochondria and is metabolized to CO2 and H2O via the citric acid cycle with the formation of ATP by oxidative phosphorylation. The ATP enters the cytoplasm, where it inhibits ATP-sensitive K+ channels, reducing K+ efflux. This depolarizes the B cell, and Ca2+ enters the cell via voltage-gated Ca2+ channels. The Ca2+ influx causes exocytosis of a readily releasable pool of insulin-containing secretory granules, producing the initial spike of insulin secretion.

Metabolism of pyruvate via the citric acid cycle also causes an increase in intracellular glutamate. The glutamate appears to act on a second pool of secretory granules, committing them to the releasable form. The release of these granules then produces the prolonged second phase of the insulin response to glucose. The feedback control of plasma glucose on insulin secretion normally operates with great precision so that plasma glucose and insulin levels parallel each other with remarkable consistency.

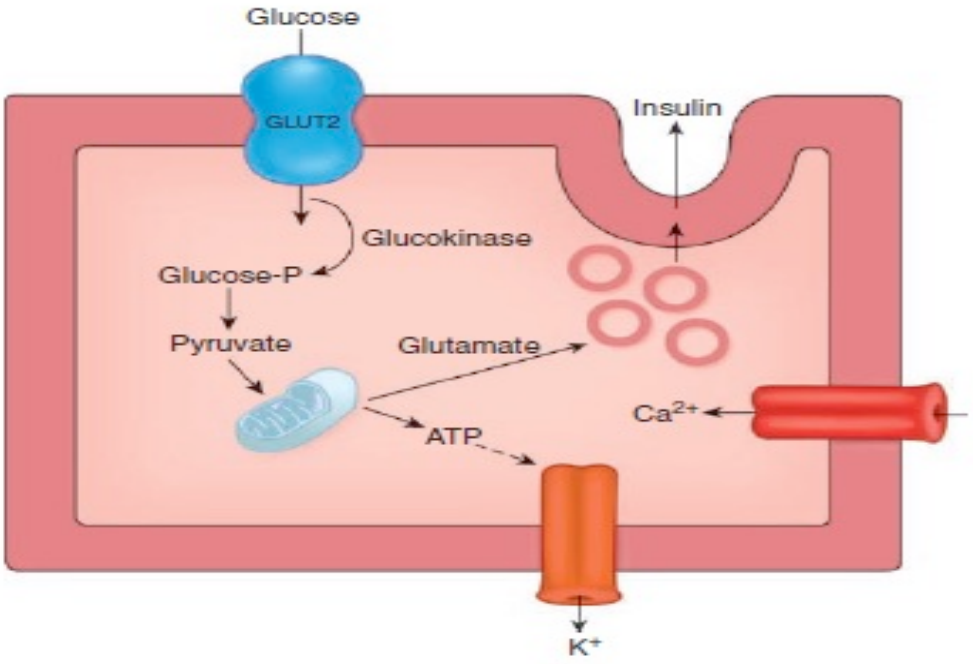


Figure 2: Insulin secretion

Glucagon

is produced by the A cells of the pancreatic islets and the upper gastrointestinal tract. Glucagon is glycogenolytic, gluconeogenic, lipolytic, and ketogenic. In the liver, it acts via Gs to activate adenylyl cyclase and increase intracellular cAMP. This leads via protein kinase A to activation of phosphorylase and therefore to increased breakdown of glycogen and an increase in plasma glucose. However, glucagon acts on different glucagon receptors located on the same hepatic cells to activate phospholipase C, and the resulting increase in cytoplasmic Ca2+ also stimulates glycogenolysis. It increases gluconeogenesis from available amino acids in the liver and elevates the metabolic rate. It increases ketone body formation by decreasing malonyl-CoA levels in the liver. Its lipolytic activity, which leads in turn to increased ketogenesis.

Regulation of Secretion:

The Secretion of glucagon is increased by hypoglycemia and decreased by a rise in plasma glucose. Also, secretion is also increased by stimulation of the sympathetic nerves to the pancreas, and this sympathetic effect is mediated via β-adrenergic receptors and cAMP. A protein meal and infusion of various amino acids increase glucagon secretion. Cholecystokinin and gastrin increase glucagon secretion, whereas secretin inhibits it. Because CCK and gastrin secretion are both increased by a protein meal, either hormone could be the gastrointestinal mediator of the glucagon response.

TABLE 24–5 Factors affecting glucagon secretion.

Stimulators	Inhibitors
Amino acids (particularly the glucogenic amino acids: alanine, serine, glycine, cysteine, and threonine)	Glucose
CCK, gastrin	Somatostatin
Cortisol	Secretin
Exercise	FFA
Infections	Ketones
Other stresses	Insulin
β-Adrenergic stimulators	Phenytoin
Theophylline	α-Adrenergic stimulators
Acetylcholine	GABA

Other Islet Cell Hormones

- **SOMATOSTATIN**

Somatostatin 14 (SS 14) and its amino terminal-extended form somatostatin 28 (SS 28) are found in the D cells of pancreatic islets. Both forms inhibit the secretion of

insulin, glucagon, and pancreatic polypeptide and act locally within the pancreatic islets in a paracrine fashion. SS 28 is more active than SS 14 in inhibiting insulin secretion. The secretion of pancreatic somatostatin is increased by several of the same stimuli that increase insulin secretion, that is, glucose and amino acids. It is also increased by CCK.

Pancreatic Polypeptide

It is produced by F cells in the islets. It is closely related to two other amino acid polypeptides, **polypeptide YY,** a gastrointestinal peptide and **neuropeptide Y,** which is found in the brain and the autonomic nervous system. Its secretion is increased by a meal containing protein and by fasting, exercise, and acute hypoglycemia. Secretion is decreased by somatostatin and intravenous glucose. Pancreatic polypeptide slows the absorption of food in humans.

HYPOGLYCEMIA & DIABETES MELLITUS IN HUMANS

Hypoglycemia "Insulin reactions" are common in type 1 diabetics and occasional hypoglycemic episodes are the price of good diabetic control in most diabetics. Chronic mild hypoglycemia can cause incoordination and slurred speech, and the condition can be mistaken for drunkenness. In **functional hypoglycemia,** the plasma glucose rise is normal after a test dose of glucose, but the subsequent fall overshoots to hypoglycemic levels, producing symptoms 3–4 h after meals. This pattern is sometimes seen in individuals in whom diabetes develops later.

Diabetes Mellitus

The constellation of abnormalities caused by insulin deficiency is called **diabetes mellitus.** Diabetes is characterized by polyuria (passage of large volumes of urine), polydipsia (excessive drinking), weight loss in spite of polyphagia (increased appetite), hyperglycemia, glycosuria, ketosis, acidosis, and coma. The fundamental

defects to which most of the abnormalities can be traced are (1) reduced entry of glucose into various “peripheral” tissues and (2) increased liberation of glucose into the circulation from the liver. Therefore, there is an extracellular glucose excess and, in many cells, an intracellular glucose deficiency—a situation that has been called “**starvation in the midst of plenty**.”.

Diabetes is sometimes complicated by acidosis and coma, and in long-standing diabetes, additional complications occur. These include microvascular, macrovascular, and neuropathic disease. The micro vascular abnormalities are proliferative scarring of the retina **(diabetic retinopathy)** leading to blindness and renal disease **(diabetic nephropathy)** leading to chronic kidney disease. The macrovascular abnormalities are due to accelerated atherosclerosis, which is secondary to increased plasma LDL. The result is an increased incidence of stroke and myocardial infarction. The neuropathic abnormalities **(diabetic neuropathy)** involve the autonomic nervous system and peripheral nerves.

CLINICAL BOX 24–1

Diabetes Mellitus

The constellation of abnormalities caused by insulin deficiency is called **diabetes mellitus.** Greek and Roman physicians used the term "diabetes" to refer to conditions in which the cardinal finding was a large urine volume, and two types were distinguished: "diabetes mellitus," in which the urine tasted sweet; and "diabetes insipidus," in which the urine had little taste. Today, the term "diabetes insipidus" is reserved for conditions in which there is a deficiency of the production or action of vasopressin (see Chapter 38), and the unmodified word "diabetes" is generally used as a synonym for diabetes mellitus.

The cause of clinical diabetes is always a deficiency of the effects of insulin at the tissue level. **Type 1 diabetes,** or **insulin-dependent diabetes mellitus (IDDM),** is due to insulin deficiency caused by autoimmune destruction of the B cells in the pancreatic islets, and it accounts for 3–5% of cases and usually presents in children. **Type 2 diabetes, or non–insulin-dependent diabetes mellitus (NIDDM),** is characterized by the dysregulation of insulin release from the B cells, along with insulin resistance in peripheral tissues such as skeletal muscle, brain, and liver. Type 2 diabetes historically presented in overweight or obese adults, although it is increasingly being diagnosed in children as childhood obesity increases.

Diabetes is characterized by polyuria (passage of large volumes of urine), polydipsia (excessive drinking), weight loss in spite of polyphagia (increased appetite), hyperglycemia, glycosuria, ketosis, acidosis, and coma. Widespread biochemical abnormalities are present, but the fundamental defects to which most of the abnormalities can be traced are (1) reduced entry of glucose into various "peripheral" tissues and (2) increased liberation of glucose into the circulation from the liver. Therefore, there is an extracellular glucose excess and, in many cells, an intracellular glucose deficiency—a situation that has been called "starvation in the midst of plenty." Also, the entry of amino acids into muscle is decreased and lipolysis is increased.

THERAPEUTIC HIGHLIGHTS

In type 1 diabetes, the mainstay of therapy is provision of exogenous insulin, carefully titrated to dietary intake of glucose. In type 2 diabetes, lifestyle changes such as alterations in the diet or increased exercise can often delay symptoms in early disease, but these are difficult to secure. Insulin-sensitizing drugs represent second-line agents (see Chapter 16).

Obesity, the Metabolic Syndrome, & Type 2 Diabetes

Obesity is increasing in incidence, and relates to the regulation of food intake and energy balance and overall nutrition. As body weight increases, insulin resistance increases, that is, there is a decreased ability of insulin to move glucose into fat and muscle and to shut off glucose release from the liver. Weight reduction decreases insulin resistance. Associated with obesity there is hyperinsulinemia, dyslipidemia (characterized by high circulating triglycerides and low high-density lipoprotein [HDL]), and accelerated development of atherosclerosis. This combination of findings is commonly called the **metabolic syndrome.**

Chapter 25

Overview of Gastrointestinal Function & Regulation

The primary function of the gastrointestinal tract is to serve as a portal whereby nutrients and water can be absorbed into the body. The meal is mixed with a variety of secretions that arise from both the gastrointestinal tract itself and organs that drain into it, such as the pancreas, gallbladder, and salivary glands. The parts of the gastrointestinal tract that are encountered by the meal or its residues include, in order, the mouth, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, and anus. Throughout the length of the intestine, glandular structures deliver secretions into the lumen, particularly in the stomach and mouth. Also important in the process of digestion are secretions from the pancreas and the biliary system of the liver. The intestine itself also has a very substantial surface area, which is important for its absorptive function.

GASTROINTESTINAL SECRETIONS

1- **SALIVARY SECRETION** :The first secretion encountered when food is ingested is saliva. Saliva is produced by three pairs of salivary glands (the **parotid, submandibular,** and **sublingual glands**) that drain into the oral cavity. It has a number of organic constituents that serve to initiate digestion (particularly of starch, mediated by amylase) and which also protect the oral cavity from bacteria (such as immunoglobulin A and lysozyme). Secretions of the three glands differ in their relative proportion of proteinaceous and mucinous components, which results from the relative number of serous and mucous salivary acinar cells, respectively. Saliva is also hypotonic compared with plasma and alkaline; the latter feature is important to neutralize any gastric secretions that reflux into

the esophagus. Salivary secretion is almost entirely controlled by neural influences, with the parasympathetic branch of the autonomic nervous system playing the most prominent role. Sympathetic input slightly modifies the composition of saliva (particularly by increasing proteinaceous content), but has little influence on volume. Saliva performs a number of important functions: it facilitates swallowing, keeps the mouth moist, serves as a solvent for the molecules that stimulate the taste buds, aids speech by facilitating movements of the lips and tongue, and keeps the mouth and teeth clean.

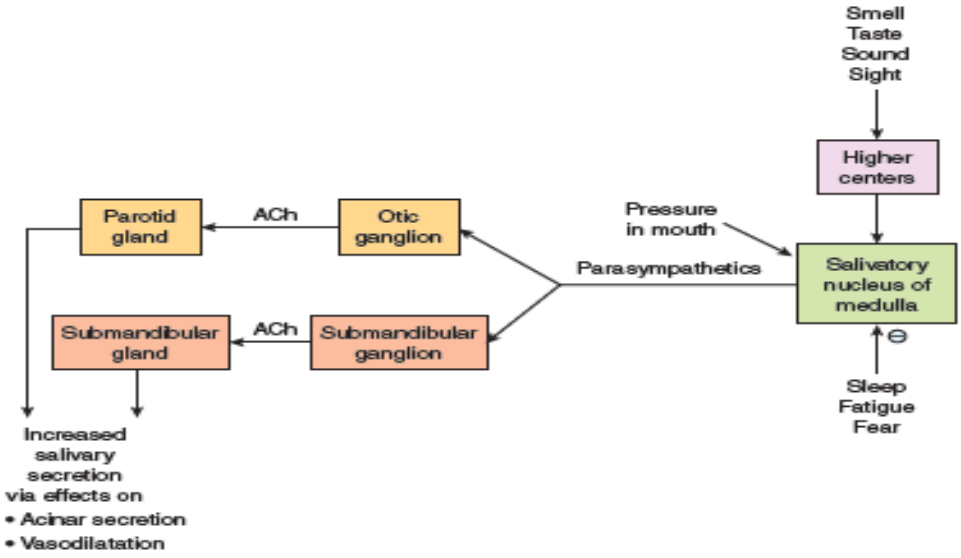


Figure1: Regulation of salivary secreation by parasymothatic nervous system

2- **GASTRIC SECRETION**: Food is stored in the stomach; mixed with acid, mucus, and pepsin; and released at a controlled, steady rate into the duodenum. The stomach also adds a significant volume of digestive juices to the meal. Like salivary secretion, the stomach readies itself to receive the meal before it is actually taken in, during the so-called cephalic phase that can be influenced by food preferences. Subsequently, there is a gastric phase of secretion that is quantitatively the most significant, and finally an intestinal phase once the meal

has left the stomach. Each phase is closely regulated by both local and distant triggers.

The gastric secretions arise from glands in the wall of the stomach that drain into its lumen, and also from the surface cells that secrete primarily mucus and bicarbonate to protect the stomach from digesting itself. Gastric secretion adds about 2.5 L/day to the intestinal contents. The most characteristic secretions derive from the glands in the fundus or body of the stomach. These contain the distinctive parietal cells, which secrete hydrochloric acid and intrinsic factor; and chief cells, which produce pepsinogens and gastric lipase .

TABLE 25–1 Contents of normal gastric juice (fasting state).

Cations: Na^+, K^+, Mg^{2+}, H^+ (pH approximately 3.0)
Anions: Cl^-, HPO_4^{2-}, SO_4^{2-}
Pepsins
Lipase
Mucus
Intrinsic factor

The acid secreted by parietal cells serves to sterilize the meal and also to begin the hydrolysis of dietary macromolecules. Intrinsic factor is important for the later absorption of vitamin B12, or cobalamin. Pepsinogen is the precursor of pepsin, which initiates protein digestion. Lipase similarly begins the digestion of dietary fats.

There are three primary stimuli of gastric secretion, each with a specific role to play in matching the rate of secretion to functional requirements:

1- Gastrin is a hormone that is released by G cells in the antrum of the stomach both in response to a specific neurotransmitter released from enteric nerve endings, known as gastrin-releasing peptide (GRP).
2- Histamine is also a trigger of parietal cell secretion, via binding to H2-receptors.
3- Finally, parietal and chief cells can also be stimulated by acetylcholine, released from enteric nerve endings in the fundus.

Gastric secretion that occurs during the cephalic phase is defined as being activated predominantly by vagal input. Once the meal is swallowed, on the other hand, meal constituents trigger substantial release of gastrin and the physical presence of the meal also distends the stomach and activates stretch receptors, which provoke a "vago-vagal" as well as local reflexes that further amplify secretion during the gastric phase. The presence of the meal also buffers gastric acidity that would otherwise serve as a feedback inhibitory signal to shut off secretion secondary to the release of somatostatin, which inhibits both G and ECL cells as well as secretion by parietal cells themselves. This probably represents a key mechanism whereby gastric secretion is terminated after the meal moves from the stomach into the small intestine.

The Gastric parietal cells are packed with mitochondria that supply energy to drive the apical H+,K+-ATPase, or proton pump, that moves H+ ions out of the parietal cell against a concentration gradient of more than a million-fold. The secretion of protons is also accompanied by the release of equivalent numbers of bicarbonate ions into the bloodstream, which are later used to neutralize gastric acidity once its function is complete.

CLINICAL BOX 25–1

Peptic Ulcer Disease

Gastric and duodenal ulceration in humans is related primarily to a breakdown of the barrier that normally prevents irritation and autodigestion of the mucosa by the gastric secretions. Infection with the bacterium *Helicobacter pylori* disrupts this barrier, as do aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the production of prostaglandins and consequently decrease mucus and HCO_3^- secretion. The NSAIDs are widely used to combat pain and treat arthritis. An additional cause of ulceration is prolonged excess secretion of acid. An example of this is the ulcers that occur in the **Zollinger–Ellison syndrome.** This syndrome is seen in patients with gastrinomas. These tumors can occur in the stomach and duodenum, but most of them are found in the pancreas. The gastrin causes prolonged hypersecretion of acid, and severe ulcers are produced.

THERAPEUTIC HIGHLIGHTS

Gastric and duodenal ulcers can be given a chance to heal by inhibition of acid secretion with drugs such as omeprazole and related drugs that inhibit H^+–K^+ ATPase ("proton pump inhibitors"). If present, *H. pylori* can be eradicated with antibiotics, and NSAID-induced ulcers can be treated by stopping the NSAID or, when this is not advisable, by treatment with the prostaglandin agonist misoprostol. Gastrinomas can sometimes be removed surgically.

3- **PANCREATIC SECRETION**: The pancreatic juice contains enzymes that are of major importance in digestion . Its secretion is controlled in part by a reflex mechanism and in part by the gastrointestinal hormones secretin and cholecystokinin (CCK). Granules containing the digestive enzymes **(zymogen granules)** are formed in the cell and discharged by exocytosis from the apexes of the cells into the lumens of the pancreatic ducts**.** About 1500 mL of pancreatic juice is secreted per day. Bile and intestinal juices are also neutral or alkaline, and these three secretions neutralize the gastric acid, raising the pH of the duodenal contents to 6.0–7.0. The pancreatic juice also contains a range of digestive enzymes, but most of these are released in inactive forms and only activated when they reach the intestinal lumen. The enzymes are activated following proteolytic cleavage by trypsin, itself a pancreatic protease that is released as an inactive precursor (trypsinogen). The potential danger of the release into the pancreas of a small amount of trypsin is apparent; the resulting chain reaction would produce active enzyme that could digest the pancreas. It is

therefore not surprising that the pancreas also normally secretes a trypsin inhibitor. Secretion of pancreatic juice is primarily under hormonal control.

4- BILIARY SECRETION:

An additional secretion important for gastrointestinal function, bile, arises from the liver. The bile acids contained therein are important in the digestion and absorption of fats. Bile is also the only route by which the body can dispose of cholesterol—either in its native form, or following conversion to bile acids. Bile is made up of the bile acids, bile pigments, and other substances dissolved in an alkaline electrolyte solution that resembles pancreatic juice. About 500 mL is secreted per day. Some of the components of the bile are reabsorbed in the intestine and then excreted again by the liver **(enterohepatic circulation)**. The glucuronides of the bile pigments, bilirubin and biliverdin, are responsible for the golden yellow color of bile.

When considering bile as a digestive secretion, it is the bile acids that represent the most important components. They are synthesized from cholesterol and secreted into the bile.

GASTROINTESTINAL REGULATION:

The various functions of the gastrointestinal tract, including secretion, digestion, and absorption , and motility must be regulated in an integrated way to ensure efficient assimilation of nutrients after a meal. There are three main modalities for gastrointestinal regulation that operate in a complementary fashion to ensure that function is appropriate.

First, **endocrine** regulation is mediated by the release of hormones by triggers associated with the meal. These hormones travel through the bloodstream to change the activity of a distant segment of the gastrointestinal tract, an organ draining into it (eg, the pancreas), or both.

Second, some similar mediators are not sufficiently stable to persist in the bloodstream, but instead alter the function of cells in the local area where they are released, in a **paracrine** fashion.

Finally, the intestinal system is endowed with extensive neural connections. These include connections to the central nervous system **(extrinsic innervation),** but also the activity of a largely autonomous **enteric nervous system** that comprises both sensory and secretomotor neurons.

HORMONES/PARACRINES:

Biologically active polypeptides that are secreted by nerve cells and gland cells in the mucosa act in a paracrine fashion, but they also enter the circulation. Measurement of their concentrations in blood after a meal has shed light on the roles these **gastrointestinal hormones** play in the regulation of gastrointestinal secretion and motility.

GASTRIN:

Gastrin is produced by cells called G cells in the antral portion of the gastric mucosa. Gastrin has a variety of actions, but its principal physiologic actions are stimulation of gastric acid and pepsin secretion and stimulation of the growth of the mucosa of the stomach and small and large intestines **(trophic action)**. Gastrin secretion is affected by the contents of the stomach, the rate of discharge of the vagus nerves, and blood borne factors. Gastrin secretion is also increased by the presence of the products of protein digestion in the stomach, particularly amino acids, which act directly on the G cells. Acid in the antrum inhibits gastrin secretion, partly by a direct action on G cells and partly by release of somatostatin, a relatively potent inhibitor of gastrin secretion. The effect of acid is the basis of a negative feedback loop regulating gastrin secretion. Increased secretion of the hormone increases acid secretion, but the acid then feeds back to inhibit further gastrin secretion.

TABLE 25–6 Stimuli that affect gastrin secretion.

Stimuli that increase gastrin secretion
Luminal
Peptides and amino acids Distention
Neural
Increased vagal discharge via GRP
Bloodborne
Calcium Epinephrine
Stimuli that inhibit gastrin secretion
Luminal
Acid Somatostatin
Bloodborne
Secretin, GIP, VIP, glucagon, calcitonin

Cholecystokinin(CCK):

CCK is secreted by endocrine cells known as I cell in the mucosa of the upper small intestine. The most important action is to be the stimulation of pancreatic enzyme secretion; the contraction of the gallbladder (the action for which it was named); and relaxation of the sphincter of Oddi, which allows both bile and pancreatic juice to flow into the intestinal lumen. In addition to its secretion by I cells, CCK is found in nerves in the distal ileum and colon. It is also found in neurons in the brain, especially the cerebral cortex, and in nerves in many parts of the body.

In the brain, it may be involved in the regulation of food intake, and it appears to be related to the production of anxiety and analgesia. In addition to its primary actions, CCK augments the action of secretin in producing secretion of an alkaline pancreatic juice. It also inhibits gastric emptying, exerts a trophic effect on the pancreas, and may enhance the motility of the small intestine and colon. The secretion of CCK is

increased by contact of the intestinal mucosa with the products of digestion, particularly peptides and amino acids. Because the bile and pancreatic juice that enter the duodenum in response to CCK enhance the digestion of protein and fat, and the products of this digestion stimulate further CCK secretion, a sort of positive feedback operates in the control of CCK secretion.

SECRETIN:

Secretin is secreted by S cells that are located deep in the glands of the mucosa of the upper portion of the small intestine. Only one form of secretin has been isolated, and any fragments of the molecule that have been tested to date are inactive. Its half-life is about 5 min, but little is known about its metabolism.

Secretin increases the secretion of bicarbonate by the duct cells of the pancreas and biliary tract. It thus causes the secretion of a watery, alkaline pancreatic juice. It also augments the action of CCK in producing pancreatic secretion of digestive enzymes. It decreases gastric acid secretion and may cause contraction of the pyloric sphincter. The secretion of secretin is increased by the products of protein digestion and by acid bathing the mucosa of the upper small intestine. The release of secretin by acid is another example of feedback control: Secretin causes alkaline pancreatic juice to flood into the duodenum, neutralizing the acid from the stomach and thus inhibiting further secretion of the hormone.

Gastric Inhibitory Peptide(GIP):

is produced by K cells in the mucosa of the duodenum and jejunum. Its secretion is stimulated by glucose and fat in the duodenum, and because in large doses it inhibits gastric secretion and motility, it was named gastric inhibitory peptide.

In the meantime, it was found that GIP stimulates insulin secretion. Gastrin, CCK, secretin, and glucagon also have this effect, but GIP is the only one of these that stimulates insulin secretion when administered at blood levels comparable to those

produced by oral glucose. For this reason, it is often called glucose-dependent insulinotropic peptide.

MOTILIN:

Motilin is a polypeptide containing 22 amino acid residues that is secreted by enterochromaffin cells and Mo cells in the stomach, small intestine, and colon. It acts on G-protein–coupled receptors on enteric neurons in the duodenum and colon and produces contraction of smooth muscle in the stomach and intestines in the period between meals.

SOMATOSTATIN:

Somatostatin, the growth hormone–inhibiting hormone originally isolated from the hypothalamus, is secreted as a paracrine by D cells in the pancreatic islets and by similar D cells in the gastrointestinal mucosa. It exists in tissues in two forms, somatostatin 14 and somatostatin 28, and both are secreted. Somatostatin inhibits the secretion of gastrin, VIP, GIP, secretin, and motilin. Its secretion is stimulated by acid in the lumen, and it probably acts in a paracrine fashion to mediate the inhibition of gastrin secretion produced by acid. It also inhibits pancreatic exocrine secretion; gastric acid secretion and motility; gallbladder contraction; and the absorption of glucose, amino acids, and triglycerides.

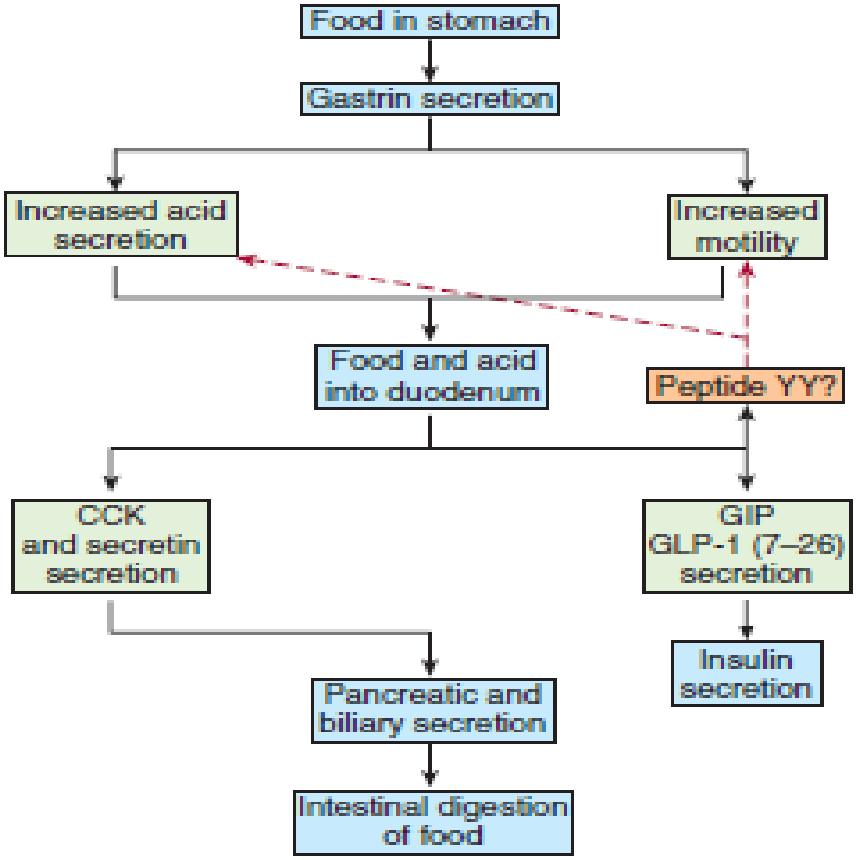


Figure 2: Action of GIT hormones in regulating digestion and utilization of ingested nutrients.

OTHER GASTROINTESTINAL PEPTIDES:

Ghrelin is secreted primarily by the stomach and appears to play an important role in the central control of food intake . It also stimulates growth hormone secretion by acting directly on receptors in the pituitary.

Substance P is found in endocrine and nerve cells in the gastrointestinal tract and may enter the circulation. It increases the motility of the small intestine.

THE ENTERIC NERVOUS SYSTEM

Two major networks of nerve fibers are intrinsic to the gastrointestinal tract: the **myenteric plexus** (Auerbach plexus), between the outer longitudinal and middle circular muscle layers, and the **submucous plexus** (Meissner plexus), between the

middle circular layer and the mucosa . Collectively, these neurons constitute the **enteric nervous system**. The system contains about 100 million sensory neurons, interneurons, and motor neurons in humans as many as are found in the whole spinal cord that is concerned with the regulation of gastrointestinal function. It is sometimes referred to as the “little brain” for this reason. It is connected to the CNS by parasympathetic and sympathetic fibers but can function autonomously without these connections . The myenteric plexus innervates the longitudinal and circular smooth muscle layers and is concerned primarily with motor control, whereas the submucous plexus innervates the glandular epithelium, intestinal endocrine cells, and submucosal blood vessels and is primarily involved in the control of intestinal secretion. The neurotransmitters in the system include acetylcholine, the amines nor-epinephrine and serotonin, the amino acid γ-aminobutyrate (GABA), the purine adenosine triphosphate (ATP), the gases NO and CO, and many different peptides and polypeptides. Some of these peptides also act in a paracrine fashion, and some enter the bloodstream, becoming hormones.

Chapter 26

Digestion, Absorption& Nutritional Principles

Introduction

The gastrointestinal system is the portal through which nutritive substances, vitamins, minerals, and fluids enter the body. Proteins, fats, and complex carbohydrates are broken down into absorbable units (digested), principally, although not exclusively, in the small intestine. The products of digestion and the vitamins, minerals, and water cross the mucosa and enter the lymph or the blood (absorption).

Enzymes from the salivary glands attack carbohydrates (and fats in some species); enzymes from the stomach attack proteins and fats; and enzymes from the exocrine portion of the pancreas attack carbohydrates, proteins, lipids, DNA, and RNA. Other enzymes that complete the digestive process are found in the luminal membranes and the cytoplasm of the cells that line the small intestine. The action of the enzymes is aided by the hydrochloric acid secreted by the stomach and the bile secreted by the liver.

Most substances pass from the intestinal lumen into the enterocytes and then out of the enterocytes to the interstitial fluid. The processes responsible for movement across the luminal cell membrane are often quite different from those responsible for movement across the basal and lateral cell membranes to the interstitial fluid.

DIGESTION & ABSORPTION:

CARBOHYDRATES

- **DIGESTION**

The principal dietary carbohydrates are polysaccharides, disaccharides, and monosaccharides. Starches (glucose polymers) and their derivatives are the only polysaccharides that are digested to any degree in the human gastrointestinal tract by human enzymes. Amylopectin, which typically constitutes around 75% of dietary starch, is a branched molecule, whereas amylose is a straight chain with only 1:4α linkages. The disaccharides lactose (milk sugar) and sucrose (table sugar) are also ingested, along with the mono- saccharides fructose and glucose.

In the mouth, starch is attacked by salivary α-amylase. The optimal pH for this enzyme is 6.7. However, it remains partially active even once it moves into the stomach, despite the acidic gastric juice, because the active site is protected in the presence of substrate to some degree. In the small intestine, both the salivary and the pancreatic α-amylase also act on the ingested polysaccharides. The end products of α-amylase digestion are oligosaccharides: the disaccharide maltose; the trisaccharide maltotriose; and α-limit dextrins, polymers of glucose containing an average of about eight glucose molecules .

The oligosaccharidases responsible for the further digestion of the starch derivatives are located in the brush border of small intestinal epithelial cells. Some of these enzymes have more than one substrate. Isomaltase is mainly responsible for hydrolysis of 1:6α linkages. Along with maltase and sucrase, it also breaks down maltotriose and maltose. Sucrase and isomaltase are initially synthesized as a single glycoprotein chain that is inserted into the brush border membrane. It is then hydrolyzed by pancreatic proteases into sucrase and isomaltase subunits.

Sucrase hydrolyzes sucrose into a molecule of glucose and a molecule of fructose. In addition, lactase hydrolyzes lactose to glucose and galactose.

Deficiency of one or more of the brush border oligosaccharidases may cause diarrhea, bloating, and flatulence after ingestion of sugar (Clinical Box 26–1).

CLINICAL BOX 26–1

Lactose Intolerance

In most mammals and in many races of humans, intestinal lactase activity is high at birth, then declines to low levels during childhood and adulthood. The low lactase levels are associated with intolerance to milk **(lactose intolerance).** Most Europeans and their American descendants retain sufficient intestinal lactase activity in adulthood; the incidence of lactase deficiency in northern and western Europeans is only about 15%. However, the incidence in blacks, American Indians, Asians, and Mediterranean populations is 70–100%. When such individuals ingest dairy products, they are unable to digest lactose sufficiently, and so symptoms such as bloating, pain, gas, and diarrhea are produced by the unabsorbed osmoles that are subsequently digested by colonic bacteria.

THERAPEUTIC HIGHLIGHTS

The simplest treatment for lactose intolerance is to avoid dairy products in the diet, but this can sometimes be challenging (or undesirable for the individual who loves ice cream). Symptoms can be ameliorated by administration of commercial lactase preparations, but this is expensive. Yogurt is better tolerated than milk in intolerant individuals because it contains its own bacterial lactase.

The diarrhea is due to the increased number of osmotically active oligosaccharide molecules that remain in the intestinal lumen, causing the volume of the intestinal contents to increase. In the colon, bacteria break down some of the oligosaccharides, further increasing the number of osmotically active particles. The bloating and flatulence are due to the production of gas (CO_2 and H_2) from disaccharide residues in the lower small intestine and colon.

ABSORPTION

Hexoses are rapidly absorbed across the wall of the small intestine. Essentially all the hexoses are removed before the remains of a meal reach the terminal part of the ileum. The sugar molecules pass from the mucosal cells to the blood in the capillaries draining into the portal vein. The transport of glucose and galactose depends on Na+ in the intestinal lumen; a high concentration of Na+ on the mucosal surface of the

cells facilitates sugar influx into the epithelial cells while a low concentration inhibits sugar influx into the epithelial cells. This is because these sugars and Na+ share the same cotransporter, or symport, the sodium-dependent glucose transporter (SGLT, Na+ glucose cotransporter) (Figure 26–2).

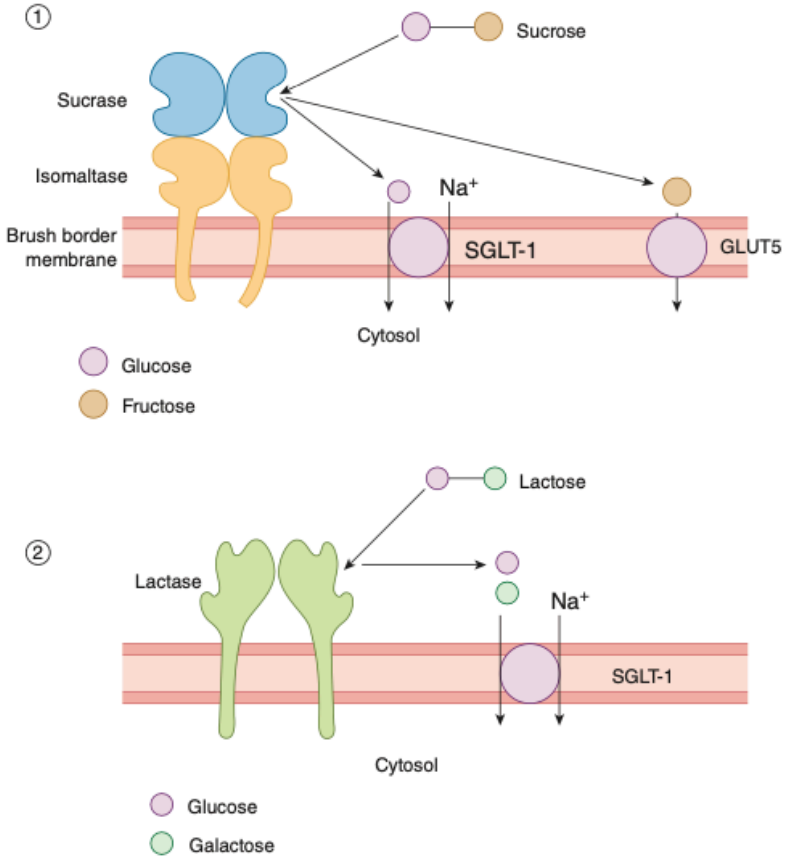


FIGURE 26–2 Brush border digestion and assimilation of the disaccharides sucrose (panel 1) and lactose (panel 2). Uptake of glucose and galactose is driven secondarily by the low intracellular sodium concentration established by the basolateral Na^+, K^+ ATPase (not shown). SGLT-1, sodium-glucose cotransporter-1.

The members of this family of transporters, SGLT-1 and SGLT-2, resemble the glucose transporters (GLUTs) responsible for facilitated diffusion in that they cross the cell membrane 12 times and have their –COOH and –NH2 terminals on the cytoplasmic side of the membrane. However, there is no homology to the GLUT series of transporters. SGLT-1 is responsible for uptake of dietary glucose from the

gut. The related transporter, SGLT-2, is responsible for glucose transport out of the renal tubules.

Because the intracellular Na+ concentration is low in intestinal cells (as it is in other cells), Na+ moves into the cell along its concentration gradient. Glucose moves with the Na+ and is released in the cell (Figure 26–2). The Na+ is transported into the lateral intercellular spaces, and the glucose is transported by GLUT2 into the interstitium and thence to the capillaries. Thus, glucose transport is an example of secondary active transport; the energy for glucose transport is provided indirectly, by the active transport of Na+ out of the cell. This maintains the concentration gradient across the luminal border of the cell, so that more Na+ and consequently more glucose enter. When the Na+/glucose cotransporter is congenitally defective, the resulting glucose/galactose malabsorption causes severe diarrhea that is often fatal if glucose and galactose are not promptly removed from the diet. Glucose and its polymers can also be used to retain Na+ in diarrheal disease.

As indicated, SGLT-1 also transports galactose, but fructose utilizes a different mechanism. Its absorption is independent of Na+ or the transport of glucose and galactose; it is transported instead by facilitated diffusion from the intestinal lumen into the enterocytes by GLUT5 and out of the enterocytes into the interstitium by GLUT2. Some fructose is converted to glucose in the mucosal cells.

Insulin has little effect on intestinal transport of sugars. In this respect, intestinal absorption resembles glucose reabsorption in the proximal convoluted tubules of the kidneys ; neither process requires phosphorylation, and both are essentially normal in diabetes but are depressed by the drug phlorizin. The maximal rate of glucose absorption from the intestine is about 120 g/h.

PROTEINS & NUCLEIC ACIDS

• PROTEIN DIGESTION

Protein digestion begins in the stomach, where pepsins cleave some of the peptide linkages. Like many of the other enzymes concerned with protein digestion, pepsins are secreted in the form of inactive precursors (proenzymes) and activated in the gastrointestinal tract. The pepsin precursors are called pepsinogens and are activated by gastric acid. Human gastric mucosa contains a number of related pepsinogens, which can be divided into two immunohistochemically distinct groups, pepsinogen I and pepsinogen II. Pepsinogen I is found only in acid-secreting regions, whereas pepsinogen II is also found in the pyloric region. Maximal acid secretion correlates with pepsinogen I levels.

Pepsins hydrolyze the bonds between aromatic amino acids such as phenylalanine or tyrosine and a second amino acid, so the products of peptic digestion are polypeptides of very diverse sizes. Because pepsins have a pH optimum of 1.6–3.2, their action is terminated when the gastric contents are mixed with the alkaline pancreatic juice in the duodenum and jejunum. The pH of the intestinal contents in the duodenal bulb is 3.0–4.0, but rapidly rises; in the rest of the duodenum it is about 6.5. In the small intestine, the polypeptides formed by digestion in the stomach are further digested by the powerful proteolytic enzymes of the pancreas and intestinal mucosa. Trypsin, the chymotrypsins, and elastase act at interior peptide bonds in the peptide molecules and are called endopeptidases. The formation of the active endopeptidases from their inactive precursors occurs only when they have reached their site of action, secondary to the action of the brush border hydrolase, enterokinase (Figure 26–3).

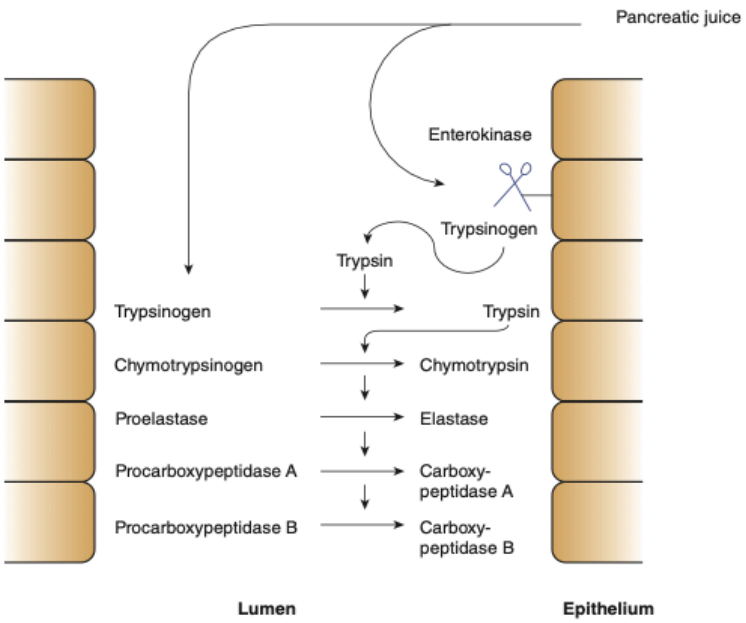


FIGURE 26–3 **Mechanism to avoid activation of pancreatic proteases until they are in the duodenal lumen.** Pancreatic juice contains proteolytic enzymes in their inactive, precursor forms. When the juice enters the duodenal lumen, trypsinogen contacts enterokinase expressed on the apical surface of enterocytes. Trypsinogen is thereby cleaved to trypsin, which in turn can activate additional trypsin molecules as well as the remaining proteolytic enzymes.

The powerful protein-splitting enzymes of the pancreatic juice are secreted as inactive proenzymes. Trypsinogen is converted to the active enzyme trypsin by enterokinase when the pancreatic juice enters the duodenum. Enterokinase contains 41% polysaccharide, and this high polysaccharide content apparently prevents it from being digested itself before it can exert its effect. Trypsin converts chymotrypsinogens into chymotrypsins and other proenzymes into active enzymes (Figure 26–3). Trypsin can also activate trypsinogen; therefore, once some trypsin is formed, there is an auto-catalytic chain reaction. Enterokinase deficiency occurs as a congenital abnormality and leads to protein malnutrition. The carboxypeptidases of the pancreas are exopeptidases that hydrolyze the amino acids at the carboxyl ends of the polypeptides (Figure 26–4).

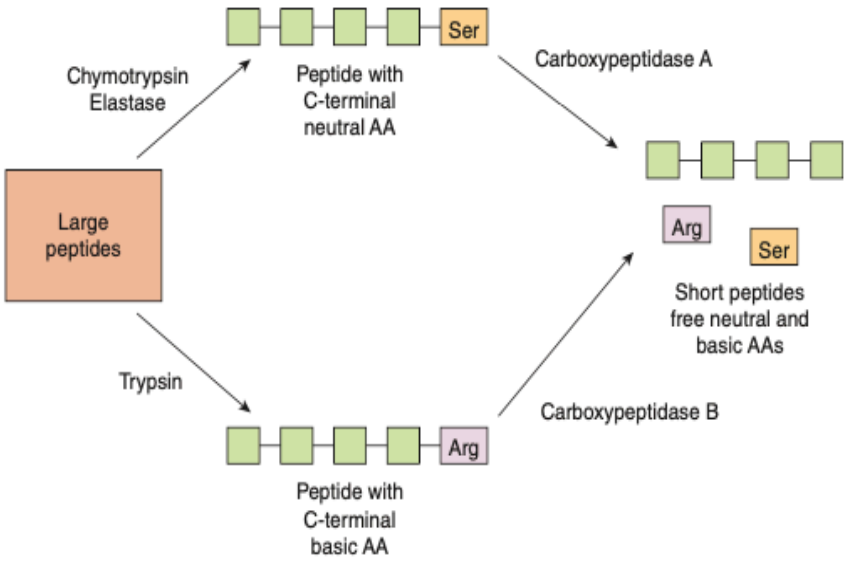


FIGURE 26–4 Luminal digestion of peptides by pancreatic endopeptidases and exopeptidases. Individual amino acids (AAs) are shown as squares.

Some free amino acids are liberated in the intestinal lumen, but others are liberated at the cell surface by the aminopeptidases, carboxypeptidases, endopeptidases, and dipeptidases in the brush border of the mucosal cells. Some dipeptides and tripeptides are actively transported into the intestinal cells and hydrolyzed by intracellular peptidases, with the amino acids entering the bloodstream. Thus, the final digestion to amino acids occurs in three locations: the intestinal lumen, the brush border, and the cytoplasm of the mucosal cells.

ABSORPTION

At least seven different transport systems transport amino acids into enterocytes. Five of these require Na^+ and cotransport amino acids and Na+ in a fashion similar to the cotransport of Na+ and glucose (Figure 26–3). Two of these five also require Cl–. In two systems, transport is independent of Na+.

The dipeptides and tripeptides are transported into enterocytes by a system known as PepT1 (or peptide transporter 1) that requires H+ instead of Na+ (Figure 26–5).

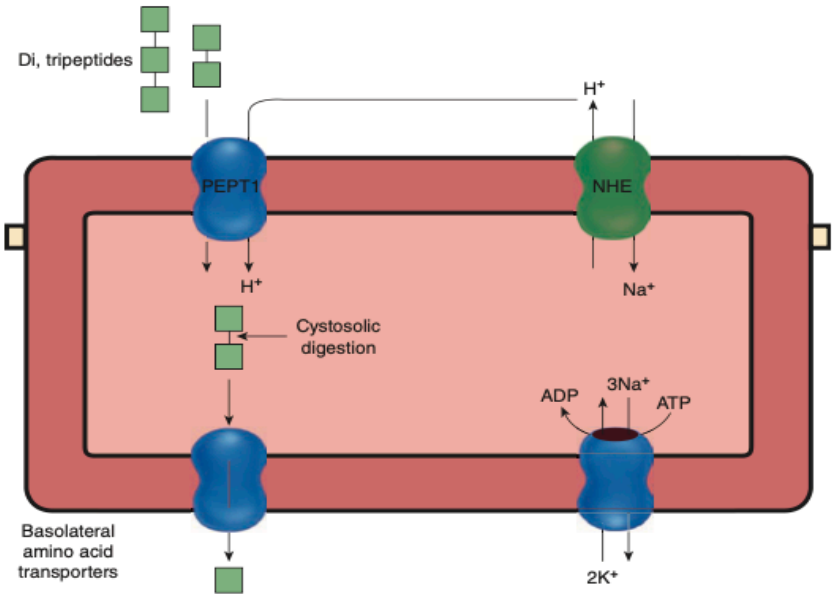


FIGURE 26–5 **Disposition of short peptides in intestinal epithelial cells.** Peptides are absorbed together with a proton supplied by an apical sodium/hydrogen exchanger (NHE) by the peptide transporter 1 (PepT1). Absorbed peptides are digested by cytosolic proteases, and any amino acids that are surplus to the needs of the epithelial cell are transported into the bloodstream by a series of basolateral transport proteins.

There is a very little absorption of larger peptides. In the enterocytes, amino acids released from the peptides by intracellular hydrolysis plus the amino acids absorbed from the intestinal lumen and brush border are transported out of the enterocytes along their basolateral borders by at least five transport systems. From there, they enter the hepatic portal blood. Absorption of amino acids is rapid in the duodenum and jejunum. There is a little absorption in the ileum in health, because the majority of the free amino acids have already been assimilated at that point. Approximately 50% of the digested protein comes from ingested food, 25% from proteins in digestive juices, and 25% from desquamated mucosal cells. Only 2–5% of the protein in the small intestine escapes digestion and absorption.

Some of this is eventually digested by bacterial action in the colon. Almost all of the protein in the stools is not of dietary origin but comes from bacteria and cellular debris. Evidence suggests that the peptidase activities of the brush border and the mucosal cell cytoplasm are increased by resection of part of the ileum and that they

are independently altered in starvation. Thus, these enzymes appear to be subject to homeostatic regulation.

In infants, moderate amounts of undigested proteins are also absorbed. The protein antibodies in maternal colostrum are largely secretory immunoglobulins (IgAs), the production of which is increased in the breast in late pregnancy. They cross the mammary epithelium by transcytosis and enter the circulation of the infant from the intestine, providing passive immunity against infections. Absorption is by endocytosis and subsequent exocytosis.

Absorption of intact proteins declines sharply after weaning, but adults still absorb small quantities. Foreign proteins that enter the circulation provoke the formation of antibodies, and the antigen–antibody reaction occurring on subsequent entry of more of the same protein may cause allergic symptoms. Thus, absorption of proteins from the intestine may explain the occurrence of allergic symptoms after eating certain foods. The incidence of food allergy in children is said to be as high as 8%. Certain foods are more allergenic than others. Crustaceans, mollusks, and fish are common offenders, and allergic responses to legumes, cows' milk, and egg white are also relatively frequent. However, in most individual food allergies do not occur, and there is an evidence for a genetic component in susceptibility.

Absorption of protein antigens, particularly bacterial and viral proteins, takes place in large microfold cells or M cells, specialized intestinal epithelial cells that overlie aggregates of lymphoid tissue (Peyer patches). These cells pass the antigens to the lymphoid cells, and lymphocytes are activated. The activated lymphoblasts enter the circulation, but they later return to the intestinal mucosa and other epithelia, where they secrete IgA in response to subsequent exposures to the same antigen.

NUCLEIC ACIDS

Nucleic acids are split into nucleotides in the intestine by the pancreatic nucleases, and the nucleotides are split into the nucleosides and phosphoric acid by enzymes that appear to be located on the luminal surfaces of the mucosal cells. The nucleosides are then split into their constituent sugars and purine and pyrimidine bases. The bases are absorbed by active transport. Families of equilibrative (ie, passive) and concentrative (ie, secondary active) nucleoside transporters have recently been identified and are expressed on the apical membrane of enterocytes.

LIPIDS

- **FAT DIGESTION**

A lingual lipase is secreted by Ebner glands on the dorsal surface of the tongue in some species, and the stomach also secretes a lipase. They are of little quantitative significance for lipid digestion other than in the setting of pancreatic insufficiency, but they may generate free fatty acids that signal to most distal parts of the gastrointestinal tract (eg, causing the release of CCK).

Most fat digestion therefore begins in the duodenum, pancreatic lipase being one of the most important enzymes involved. This enzyme hydrolyzes the 1- and 3-bonds of the triglycerides (triacylglycerols) with relative ease but acts on the 2-bonds at a very low rate, so the principal products of its action are free fatty acids and 2-monoglycerides (2-monoacylglycerols). It acts on fats that have been emulsified (see below). Its activity is facilitated when an amphipathic helix that covers the active site like a lid is bent back.

Colipase, a protein with a molecular weight of about 11,000, is also secreted in the pancreatic juice, and when this molecule binds to the –COOH-terminal domain of the pancreatic lipase, opening of the lid is facilitated. Colipase is secreted in an

inactive preform and is activated in the intestinal lumen by trypsin. Colipase is also critical for the action of lipase because it allows lipase to remain associated with droplets of dietary lipid even in the presence of bile acids. Another pancreatic lipase that is activated by bile acids has been characterized. This 100,000-kDa cholesterol esteras represents about 4% of the total protein in pancreatic juice. In adults, pancreatic lipase is 10–60 times more active, but unlike pancreatic lipase, cholesterol esterase catalyzes the hydrolysis of cholesterol esters, esters of fat-soluble vitamins, and phospholipids, as well as triglycerides. A very similar enzyme is found in human milk.

Fats are relatively insoluble, which limits their ability to cross the unstirred layer and reach the surface of the mucosal cells. However, they are finely emulsified in the small intestine by the detergent action of bile acids, phosphatidylcholine, and monoglycerides. When the concentration of bile acids in the intestine is high, as it is after contraction of the gallbladder, lipids and bile acids interact spontaneously to form micelles (Figure 26–6).

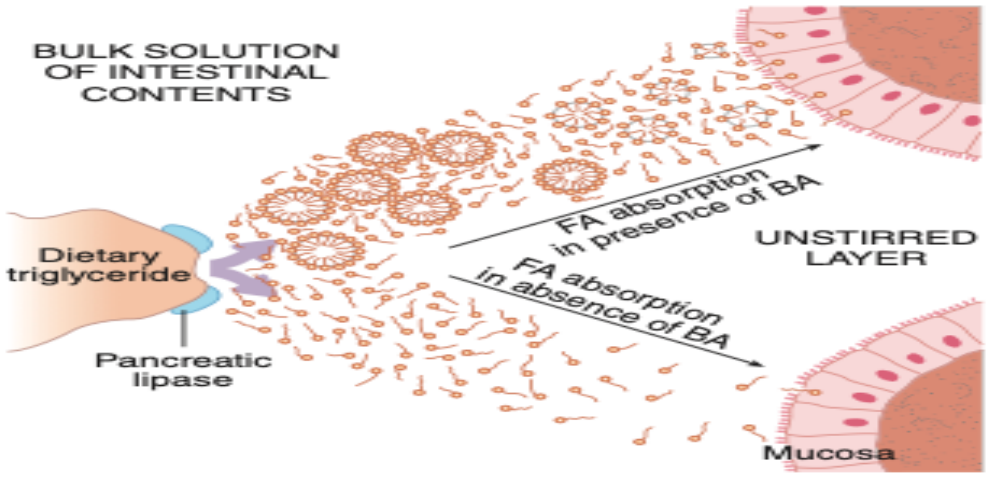


FIGURE 26–6 Lipid digestion and passage to intestinal mucosa. Fatty acids (FA) are liberated by the action of pancreatic lipase on dietary triglycerides and, in the presence of bile acids (BA), form micelles (the circular structures), which diffuse through the unstirred layer to the mucosal surface. Not shown, colipase binds to bile acids on the surface of the triglyceride droplet to anchor lipase to the surface and allow for its lipolytic activity. (Modified with permission from Westergaard H, Dietschy JM: Normal mechanisms of fat absorption and derangements induced by various gastrointestinal diseases. Med Clin North Am Nov; 58(6):1413–1427.)

These cylindrical aggregates take up lipids, and although their lipid concentration varies, they generally contain fatty acids, monoglycerides, and cholesterol in their hydrophobic centers. Micellar formation further solubilizes the lipids and provides a mechanism for their transport to the enterocytes. Thus, the micelles move down their concentration gradient through the unstirred layer to the brush border of the mucosal cells. The lipids diffuse out of the micelles, and a saturated aqueous solution of the lipids is maintained in contact with the brush border of the mucosal cells (Figure 26–6).

Lipids collect in the micelles, with cholesterol in the hydrophobic center and amphipathic phospholipids and monoglycerides lined up with their hydrophilic heads on the outside and their hydrophobic tails in the center. The micelles play an important role in keeping lipids in solution and transporting them to the brush border of the intestinal epithelial cells, where they are absorbed.

FAT ABSORPTION

Traditionally, lipids were thought to enter the enterocytes by passive diffusion, but some evidence now suggests that carriers are involved. Inside the cells, the lipids are rapidly esterified, maintaining a favorable concentration gradient from the lumen into the cells (Figure 26–7).

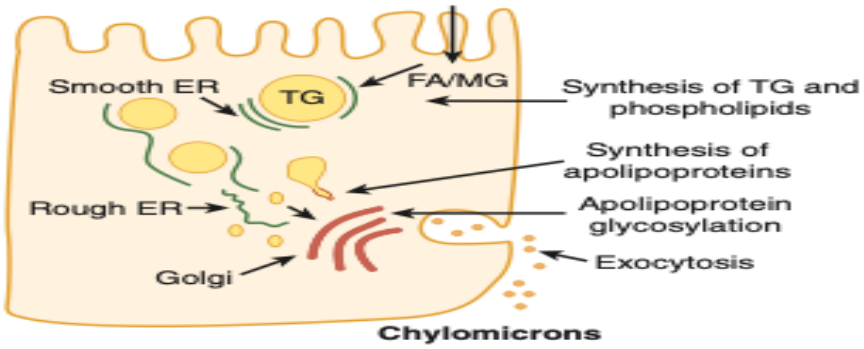


FIGURE 26–7 Intracellular handling of the products of lipid digestion. Absorbed fatty acids (FA) and monoglycerides (MG) are reesterified to form triglyceride (TG) in the smooth endoplasmic reticulum (ER). Apoproteins synthesized in the rough ER are coated around lipid cores, and the resulting chylomicrons are secreted from the basolateral pole of epithelial cells by exocytosis.

There are also carriers that export certain lipids back into the lumen, thereby limiting their oral availability. This is the case for plant sterols as well as cholesterol.

The fate of the fatty acids in enterocytes depends on their size. Fatty acids containing less than 10–12 carbon atoms are water-soluble enough that they pass through the enterocyte unmodified and are actively transported into the portal blood.

They circulate as free (unesterified) fatty acids. The fatty acids containing more than 10–12 carbon atoms are too insoluble for this. They are re-esterified to triglycerides in the enterocytes. In addition, some of the absorbed cholesterol is esterified. The

triglycerides and cholesterol esters are then coated with a layer of protein, cholesterol, and phospholipid to form chylomicrons. These leave the cell and enter the lymphatics, because they are too large to pass through the junctions between capillary endothelial cells (Figure 26–7).

In mucosal cells, most of the triglyceride is formed by the acylation of the absorbed 2-monoglycerides, primarily in the smooth endoplasmic reticulum. However, some of the triglyceride is formed from glycerophosphate, which in turn is a product of glucose catabolism. Glycerophosphate is also converted into glycerophospholipids that participate in chylomicron formation. The acylation of glycerophosphate and the formation of lipoproteins occur in the rough endoplasmic reticulum. Carbohydrate moieties are added to the proteins in the Golgi apparatus, and the finished chylomicrons are extruded by exocytosis from the basolateral aspect

of the cell.

Absorption of long-chain fatty acids is greatest in the upper parts of the small intestine, but appreciable amounts are also absorbed in the ileum. On a moderate fat intake, 95% or more of the ingested fat is absorbed. The processes involved in fat absorption are not fully mature at birth, and infants fail to absorb 10–15% of ingested fat. Thus, they are more susceptible to the ill effects of disease processes that reduce fat absorption.

ABSORPTION of IRON

In adults, the amount of iron lost from the body is relatively small. The losses are generally unregulated, and total body stores of iron are regulated by changes in the rate at which it is absorbed from the intestine. Men lose about 0.6 mg/d, largely in the stools. Premenopausal women have a variable, larger loss averaging about twice this value because of the additional iron lost during menstruation. The average daily

iron intake in the United States and Europe is about 20 mg, but the amount absorbed is equal only to the losses. Thus, the amount of iron absorbed is normally about 3–6% of the amount ingested. Various dietary factors affect the availability of iron for absorption; for example, the phytic acid found in cereals reacts with iron to form insoluble compounds in the intestine, as do phosphates and oxalates.

Most of the iron in the diet is in the ferric (Fe3+) form, whereas it is the ferrous (Fe2+) form that is absorbed. Fe3+ reductase activity is associated with the iron transporter in the brush borders of the enterocytes (Figure 26–8).

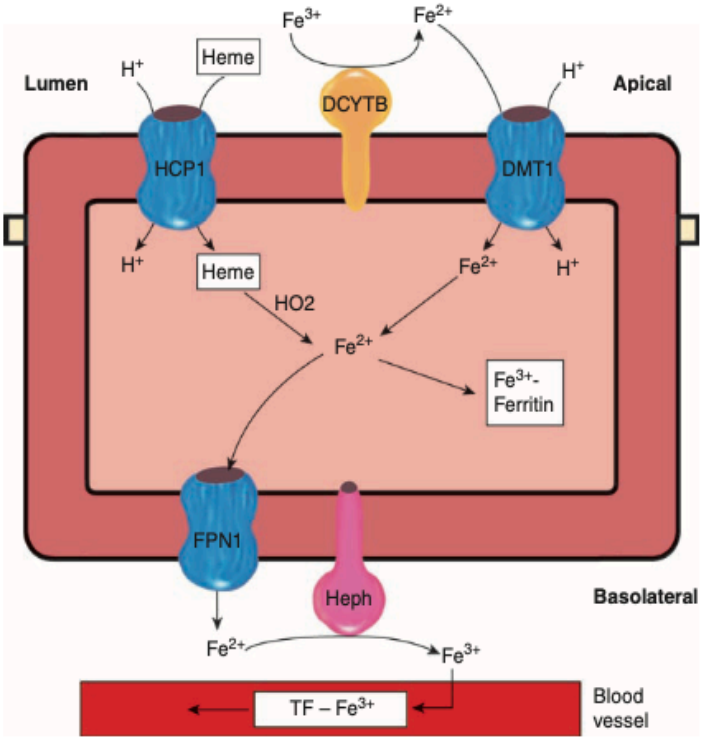


FIGURE 26–8 **Intestinal absorption of iron.** Fe^{3+} is converted to Fe^{2+} by the ferric reductase DCYTB, and Fe^{2+} is transported into the enterocyte by the apical membrane iron transporter DMT1. Heme is transported into the enterocyte by a separate heme transporter (most likely heme carrier protein 1, HCP1), and heme oxygenase-2 (HO2) releases Fe^{2+} from the heme. Some of the intracellular Fe^{2+} is converted to Fe^{3+} and bound to ferritin. The rest binds to the basolateral Fe^{2+} transporter ferroportin-1 (FPN1) and is transported to the interstitial fluid. The transport is aided by hephaestin (Heph) which converts Fe^{2+} to Fe^{3+}. In plasma, Fe^{3+} is transported bound to the iron transport protein transferrin (TF).

Gastric secretions dissolve the iron and permit it to form soluble complexes with ascorbic acid and other substances that aid its reduction to the Fe2+ form. The

importance of this function in humans is indicated by the fact that iron deficiency anemia is a troublesome and relatively frequent complication of partial gastrectomy. Almost all iron absorption occurs in the duodenum.

Transport of Fe^{2+} into the enterocytes occurs via divalent metal transporter 1 (DMT1) (Figure 26–8). Some is stored in ferritin, and the remainder is transported out of the enterocytes by a basolateral transporter named ferroportin 1.

A protein called hephaestin (Hp) is associated with ferroportin 1. It is not a transporter itself, but it facilitates basolateral transport. In the plasma, Fe^{2+} is converted to Fe^{3+} and bound to the iron transport protein transferrin. This protein has two iron-binding sites. Normally, transferrin is about 35% saturated with iron, and the normal plasma iron level is about 130 µg/dL (23 µmol/L) in men and 110 µg/dL (19 µmol/L) in women.

Heme binds to an apical transport protein in enterocytes and is carried into the cytoplasm. In the cytoplasm, HO-2, a subtype of heme oxygenase, removes Fe^{2+} from the porphyrin and adds it to the intracellular Fe^{2+} pool. Seventy percent of the iron in the body is in hemoglobin, 3% in myoglobin, and the rest in ferritin, which is present not only in enterocytes, but also in many other cells. Apoferritin is a globular protein made up of 24 subunits. Ferritin is readily visible under the electron microscope and has been used as a tracer in studies of phagocytosis and related phenomena. Ferritin molecules in lysosomal membranes may aggregate in deposits that contain as much as 50% iron. These deposits are called hemosiderin.

Intestinal absorption of iron is regulated by three factors: recent dietary intake of iron, the state of the iron stores in the body, and the state of erythropoiesis in the bone marrow. The normal operation of the factors that maintain iron balance is essential for health (Clinical Box 26–2).

CLINICAL BOX 26–2

Disorders of Iron Uptake

Iron deficiency causes anemia. Conversely, iron overload causes hemosiderin to accumulate in the tissues, producing **hemosiderosis.** Large amounts of **hemosiderin** can damage tissues, such as is seen in the common genetic disorder of hemochromatosis. This syndrome is characterized by pigmentation of the skin, pancreatic damage with diabetes ("bronze diabetes"), cirrhosis of the liver, a high incidence of hepatic carcinoma, and gonadal atrophy. Hemochromatosis may be hereditary or acquired. The most common cause of the hereditary forms is a mutated *HFE* gene that is common in the white population. It is located on the short arm of chromosome 6 and is closely linked to the HLA-A locus. It is still unknown precisely how mutations in *HFE* cause hemochromatosis, but individuals who are homogenous for *HFE* mutations absorb excess amounts of iron because *HFE* normally inhibits expression of the duodenal transporters that participate in iron uptake. Acquired hemochromatosis occurs when the iron-regulating system is overwhelmed by excess iron loads due to chronic destruction of red blood cells, liver disease, or repeated transfusions in diseases such as intractable anemia.

THERAPEUTIC HIGHLIGHTS

If hereditary hemochromatosis is diagnosed before excessive amounts of iron accumulate in the tissues, life expectancy can be prolonged substantially by repeated withdrawal of blood.

Chapter 27

Gastrointestinal Motility

The digestive and absorptive functions of the gastrointestinal system outlined in the previous chapter depend on a variety of mechanisms that soften the food, propel it through the length of the gastrointestinal tract (Table 27–1), and mix it with bile from the gallbladder and digestive enzymes secreted by the salivary glands and pancreas.

TABLE 27–1 Mean lengths of various segments of the gastrointestinal tract as measured by intubation in living humans.

Segment	Length (cm)
Pharynx, esophagus, and stomach	65
Duodenum	25
Jejunum and ileum	260
Colon	110

Some of these mechanisms depend on intrinsic properties of the intestinal smooth muscle. Others involve the operation of reflexes involving the neurons intrinsic to the gut, reflexes involving the central nervous system (CNS), paracrine effects of chemical messengers, and gastrointestinal hormones.

GENERAL PATTERNS OF MOTILITY

- **PERISTALSIS**

Peristalsis is a reflex response that is initiated when the gut wall is stretched by the contents of the lumen, and it occurs in all parts of the gastrointestinal tract from the

esophagus to the rectum. The stretch initiates a circular contraction behind the stimulus and an area of relaxation in front of it (Figure 27–1).

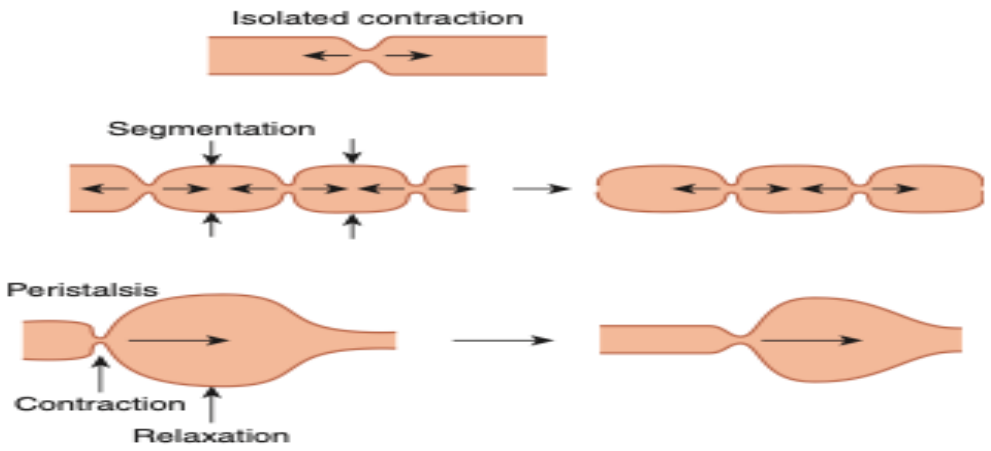


FIGURE 27–1 Patterns of gastrointestinal motility and propulsion. An isolated contraction moves contents orally and aborally. Segmentation mixes contents over a short stretch of intestine, as indicated by the time sequence from left to right. In the diagram on the left, the vertical arrows indicate the sites of subsequent contraction. Peristalsis involves both contraction and relaxation, and moves contents aborally.

The wave of contraction then moves in an oral-to-caudal direction, propelling the contents of the lumen forward at rates that vary from 2 to 25 cm/s. Peristaltic activity can be increased or decreased by the autonomic input to the gut, but its occurrence is independent of extrinsic innervation. Indeed, progression of the contents is not blocked by removal and resuture of a segment of intestine in its original position and is blocked only if the segment is reversed before it is sewn back into place. Peristalsis is an excellent example of the integrated activity of the enteric nervous system. It appears that local stretch releases serotonin, which activates sensory neurons that activate the myenteric plexus. Cholinergic neurons passing in a retrograde direction in this plexus activate neurons that release substance P and acetylcholine, causing smooth muscle contraction behind the bolus. At the same time, cholinergic neurons

passing in an anterograde direction activate neurons that secrete NO and vasoactive intestinal polypeptide (VIP), producing the relaxation ahead of the stimulus.

- **SEGMENTATION & MIXING**

When the meal is present, the enteric nervous system promotes a motility pattern that is related to peristalsis but is designed to retard the movement of the intestinal contents along the length of the intestinal tract to provide time for digestion and absorption (Figure 27–1). This motility pattern is known as segmentation, and it provides for ample mixing of the intestinal contents (known as chyme) with the digestive juices.

A segment of bowel contracts at both ends, and then a second contraction occurs in the center of the segment to force the chyme both backward and forward. Unlike peristalsis, therefore, retrograde movement of the chyme occurs routinely in the setting of segmentation. This mixing pattern persists for as long as nutrients remain in the lumen to be absorbed. It presumably reflects programmed activity of the bowel dictated by the enteric nervous system, and can occur independent of central input, although the latter can modulate it.

- **BASIC ELECTRICAL ACTIVITY & REGULATION OF MOTILITY**

Except in the esophagus and the proximal portion of the stomach, the smooth muscle of the gastrointestinal tract has spontaneous rhythmic fluctuations in membrane potential between about −65 and −45 mV. This basic electrical rhythm (BER) is initiated by the interstitial cells of Cajal, stellate mesenchymal pacemaker cells with smooth muscle-like features that send long multiply branched processes into the intestinal smooth muscle.

In the stomach and the small intestine, these cells are located in the outer circular muscle layer near the myenteric plexus; in the colon, they are at the submucosal border of the circular muscle layer. In the stomach and small intestine, there is a descending gradient in pacemaker frequency, and as in the heart, the pacemaker with the highest frequency usually dominates.

The BER itself rarely causes muscle contraction, but spike potentials superimposed on the most depolarizing portions of the BER waves do increase muscle tension (Figure 27–2).

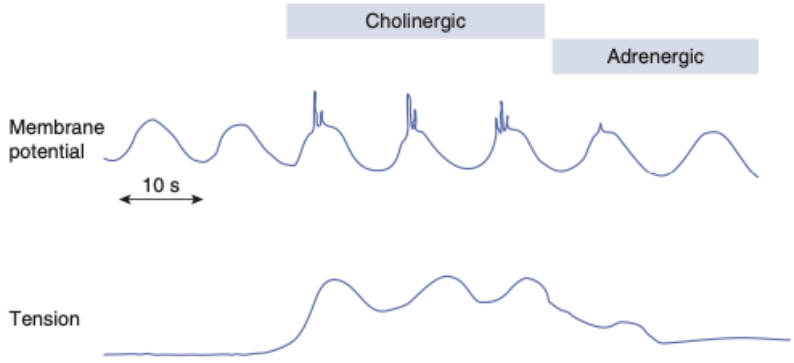


FIGURE 27–2 **Basic electrical rhythm (BER) of gastrointestinal smooth muscle. Top:** Membrane potential showing spike potentials under conditions of maximal cholinergic tone and inhibition under adrenergic tone. **Bottom:** Associated changes in muscle tension.

The depolarizing portion of each spike is due to Ca2+ influx, and the repolarizing portion is due to K+ efflux. Many polypeptides and neurotransmitters affect the BER. For example, acetylcholine increases the number of spikes and the tension of the smooth muscle, whereas epinephrine decreases the number of spikes and the tension. The rate of the BER is about 4/min in the stomach. It is about 12/min in the duodenum and falls to about 8/min in the distal ileum. In the colon, the BER rate rises from about 2/min at the cecum to about 6/min at the sigmoid. The function of the BER is to coordinate peristaltic and other motor activity, such as setting the rhythm of segmentation; contractions can occur only during the depolarizing part of

the waves. After vagotomy or transection of the stomach wall, for example, peristalsis in the stomach becomes irregular and chaotic.

MIGRATING MOTOR COMPLEX

During fasting between periods of digestion, the pattern of electrical and motor activity in gastrointestinal smooth muscle becomes modified so that cycles of motor activity migrate from the stomach to the distal ileum. Each cycle, or migrating motor complex (MMC), starts with a quiescent period (phase I), continues with a period of irregular electrical and mechanical activity (phase II), and ends with a burst of regular activity (phase III) (Figure 27–3).

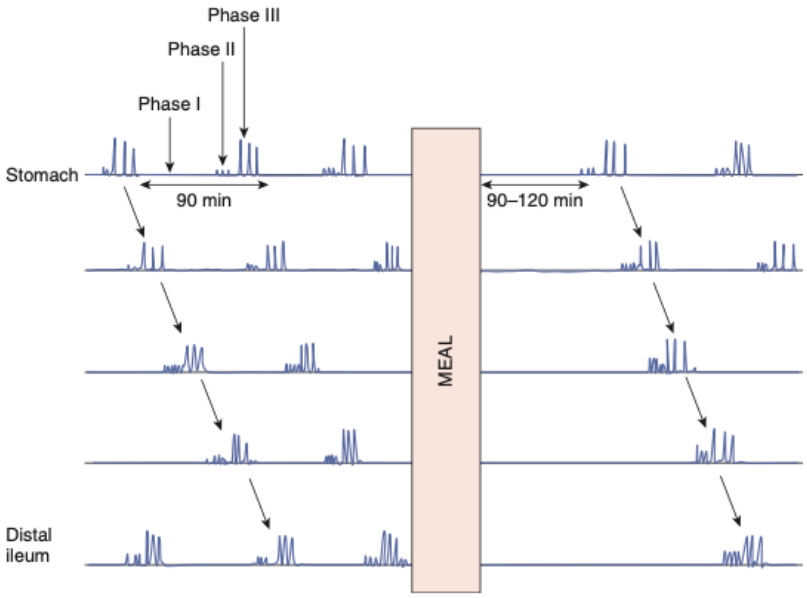


FIGURE 27–3 Migrating motor complexes (MMCs). The three phases include a quiescent phase (phase I); a phase consisting of small, irregular contractions that do not propagate (phase II); and a phase of regular activity lasting about 5 minutes (phase III), which sweeps along the length of the intestine. The entire cycle repeats every 90–100 minutes under fasting conditions. Note that the complexes are completely inhibited by a meal and resume 90–120 min later.

The MMCs are initiated by motilin. The circulating level of this hormone increases at intervals of approximately 100 min in the inter-digestive state, coordinated with the contractile phases of the MMC. The contractions migrate aborally at a rate of about 5 cm/min, and also occur at intervals of approximately 100 min.

Gastric secretion, bile flow, and pancreatic secretion increase during each MMC. They likely serve to clear the stomach and small intestine of luminal contents in preparation for the next meal. Conversely, when a meal is ingested, secretion of motilin is suppressed (ingestion of food suppresses motilin release via mechanisms that have not yet been elucidated), and the MMC is abolished, until digestion and absorption are complete.

Instead, there is a return to peristalsis and the other forms of BER and spike potentials during this time. The antibiotic erythromycin binds to motilin receptors, and derivatives of this compound may be of value in treating patients in whom

gastrointestinal motility is decreased.

STOMACH

Food is stored in the stomach; mixed with acid, mucus, and pepsin; and released at a controlled, steady rate into the duodenum.

- **GASTRIC MOTILITY & EMPTYING**

When food enters the stomach, the fundus and upper portion of the body relax and accommodate the food with little if any increase in pressure (receptive relaxation). Peristalsis then begins in the lower portion of the body, mixing and grinding the food and permitting small, semiliquid portions of it to pass through the pylorus and enter the duodenum. Receptive relaxation is, in part, vagally mediated and triggered by movement of the pharynx and esophagus. Intrinsic reflexes also lead to relaxation as the stomach wall is stretched.

Peristaltic waves controlled by the gastric BER begin soon thereafter and sweep toward the pylorus. The contraction of the distal stomach caused by each wave is sometimes called antral systole and can last up to 10 s. Waves occur 3–4 times per minute. In the regulation of gastric emptying, the antrum, pylorus, and upper duodenum apparently function as a unit. Contraction of the antrum is followed by sequential contraction of the pyloric region and the duodenum. In the antrum, partial contraction ahead of the advancing gastric contents prevents solid masses from entering the duodenum, and they are mixed and crushed instead. The more liquid gastric contents are squirted a bit at a time into the small intestine. Normally, regurgitation from the duodenum does not occur, because the contraction of the pyloric segment tends to persist slightly longer than that of the duodenum. The prevention of regurgitation may also be due to the stimulating action of cholecystokinin (CCK) and secretin on the pyloric sphincter.

- **REGULATION OF GASTRIC MOTILITY & EMPTYING**

The rate at which the stomach empties into the duodenum depends on the type of food ingested. Food rich in carbohydrate leaves the stomach in a few hours. Protein-rich food leaves more slowly, and emptying is slowest after a meal containing fat (Figure 27–6).

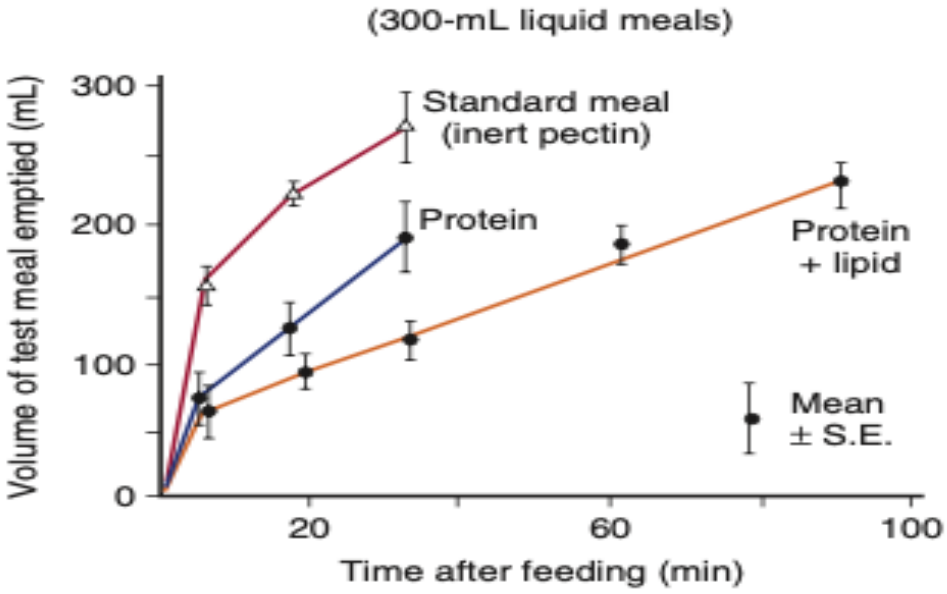


FIGURE 27–6 Effect of protein and fat on the rate of emptying of the human stomach. Persons were fed 300-mL

The rate of emptying also depends on the osmotic pressure of the material entering the duodenum. Hyperosmolality of the duodenal contents is sensed by "duodenal osmoreceptors" that initiate a decrease in gastric emptying, which is probably neural in origin.

Fats, carbohydrates, and acid in the duodenum inhibit gastric acid and pepsin secretion and gastric motility via neural and hormonal mechanisms. The messenger involved is probably peptide YY. CCK has also been implicated as an inhibitor of gastric emptying (Clinical Box 27–2).

CLINICAL BOX 27–2

Consequences of Gastric Bypass Surgery

Patients who are morbidly obese often undergo a surgical procedure in which the stomach is stapled so that most of it is bypassed, and thus the reservoir function of the stomach is lost. As a result, such patients must eat frequent small meals. If larger meals are eaten, because of rapid absorption of glucose from the intestine and the resultant hyperglycemia and abrupt rise in insulin secretion, hypoglycemic symptoms sometimes develop about 2 h after meals in patients who have undergone gastrectomy. Weakness, dizziness, and sweating after meals, due in part to hypoglycemia, are part of the picture of the **"dumping syndrome,"** a distressing syndrome that develops in patients in whom portions of the stomach have been removed or the jejunum has been anastomosed to the stomach. Another cause of the symptoms is rapid entry of hypertonic meals into the intestine; this provokes the movement of so much water into the gut that significant hypovolemia and hypotension are produced.

THERAPEUTIC HIGHLIGHTS

There are no treatments, per se, for the dumping syndrome, other than avoiding large meals, and particularly those with high concentrations of simple sugars. Indeed, its occurrence may account for the overall success of bypass surgery in reducing food intake, and thus obesity, in many patients who undergo this surgery.

VOMITING

Vomiting is an example of central regulation of gut motility functions. Vomiting starts with salivation and the sensation of nausea. Reverse peristalsis empties material from the upper part of the small intestine into the stomach. The glottis closes, preventing aspiration of vomitus into the trachea. The breath is held in mid inspiration. The muscles of the abdominal wall contract, and because the chest is held in a fixed position, the contraction increases intra-abdominal pressure. The lower esophageal sphincter and the esophagus relax, and the gastric contents are ejected. The "vomiting center" in the reticular formation of the medulla (Figure 27–7) consists of various scattered groups of neurons in this region that control the different components of the vomiting act.

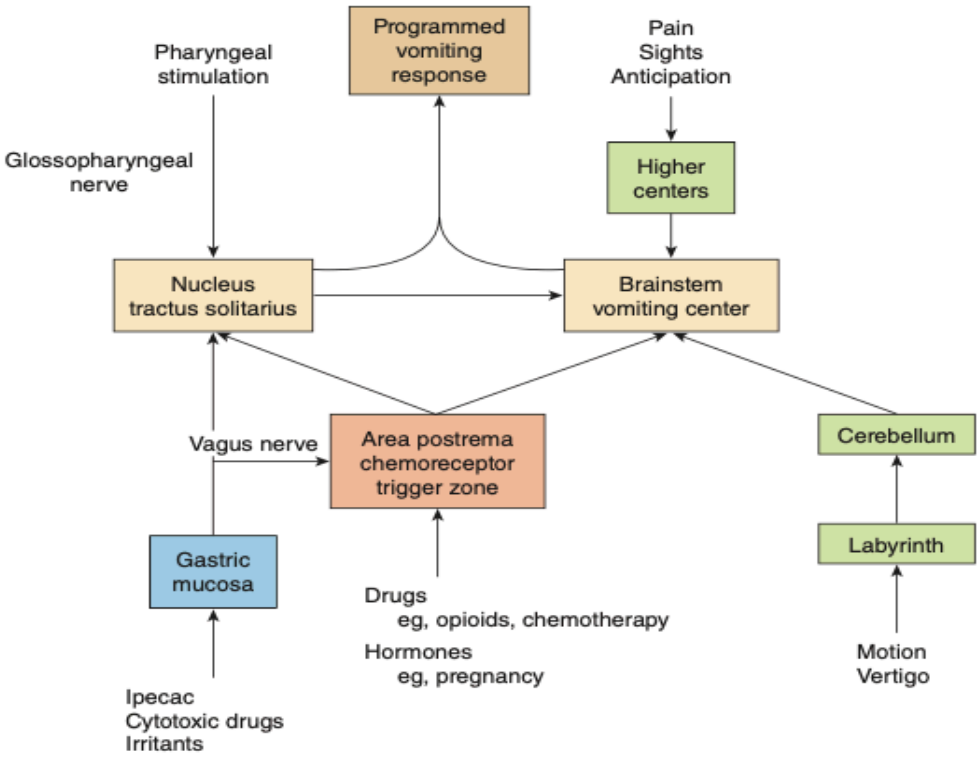


FIGURE 27–7 **Neural pathways leading to the initiation of vomiting in response to various stimuli.**

Irritation of the mucosa of the upper gastrointestinal tract is one trigger for vomiting. Impulses are relayed from the mucosa to the medulla over visceral afferent pathways in the sympathetic nerves and vagi. Other causes of vomiting can arise centrally. For example, afferents from the vestibular nuclei mediate the nausea and vomiting of motion sickness. Other afferents presumably reach the vomiting control areas from the diencephalon and limbic system, because emetic responses to emotionally charged stimuli also occur.

Thus, we speak of "nauseating smells" and "sickening sights." Chemoreceptor cells in the medulla can also initiate vomiting when they are stimulated by certain circulating chemical agents. The chemoreceptor trigger zone in which these cells are located (Figure 27–7) is in the area postrema, a V-shaped band of tissue on the lateral

walls of the fourth ventricle near the obex. Lesions of the area postrema have little effect on the vomiting response to gastrointestinal irritation or motion sickness, but abolish the vomiting that follows injection of apomorphine and a number of other emetic drugs. Such lesions also decrease vomiting in uremia and radiation sickness, both of which may be associated with endogenous production of circulating emetic substances. Serotonin (5-HT) released from enterochromaffin cells in the small intestine appears to initiate impulses via 5-HT3 receptors that trigger vomiting. In addition, there are dopamine D2 receptors and 5-HT3 receptors in the area postrema and adjacent nucleus of the solitary tract. 5-HT3 antagonists such as ondansetron and D2 antagonists such as chlorpromazine and haloperidol are effective antiemetic agents. Corticosteroids, cannabinoids, and benzodiazepines, alone or in combination with 5-HT3 and D2 antagonists, are also useful in treatment of the vomiting produced by chemotherapy. The mechanisms of action of corticosteroids and cannabinoids are unknown, whereas the benzodiazepines probably reduce the anxiety associated with chemotherapy.

SMALL INTESTINE

In the small intestine, the intestinal contents are mixed with the secretions of the mucosal cells and with pancreatic juice and bile.

INTESTINAL MOTILITY

The MMCs that pass along the intestine at regular intervals in the fasting state and their replacement by peristaltic and other contractions controlled by the BER are described above. In the small intestine, there are an average of 12 BER cycles/min in the proximal jejunum, declining to 8/min in the distal ileum. There are three types of smooth muscle contractions: peristaltic waves, segmentation contractions, and tonic contractions.

Peristalsis is described above. It propels the intestinal contents (chyme) toward the large intestines. Segmentation contractions (Figure 27–1), move the chyme to and from and increase its exposure to the mucosal surface. These contractions are initiated by focal increases in Ca2+ influx with waves of increased Ca2+ concentration spreading from each focus. Tonic contractions are relatively prolonged contractions that in effect isolate one segment of the intestine from another. Note that these last two types of contractions slow transit in the small intestine to the point that the transit time is actually longer in the fed than in the fasted state. This permits longer contact of the chyme with the enterocytes and fosters absorption

COLON

The colon serves as a reservoir for the residues of meals that cannot be digested or absorbed. Motility in this segment is likewise slowed to allow the colon to absorb water, Na+, and other minerals. By removing about 90% of the fluid, it converts the 1000–2000 mL of isotonic chyme that enters it each day from the ileum to about 200–250 mL of semisolid feces.

MOTILITY OF THE COLON

The ileum is linked to the colon by a structure known as the ileocecal valve, which restricts reflux of colonic contents, and particularly the large numbers of commensal bacteria, into the relatively sterile ileum. The portion of the ileum containing the ileocecal valve projects slightly into the cecum, so that increases in colonic pressure squeeze it shut, whereas increases in ileal pressure open it. It is normally closed. Each time a peristaltic wave reaches it, it opens briefly, permitting some of the ileal chyme to squirt into the cecum. When food leaves the stomach, the cecum relaxes and the passage of chyme through the ileocecal valve increases (gastroileal reflex).

This is presumably a vago-vagal reflex. The movements of the colon include segmentation contractions and peristaltic waves like those occurring in the small intestine. Segmentation contractions mix the contents of the colon and, by exposing more of the contents to the mucosa, facilitate absorption. Peristaltic waves propel the contents toward the rectum, although weak antiperistalsis is sometimes seen. A third type of contraction that occurs only in the colon is the mass action contraction, occurring about 10 times per day, in which there is simultaneous contraction of the smooth muscle over large confluent areas. These contractions move material from one portion of the colon to another. They also move material into the rectum, and rectal distension initiates the defecation reflex (see below).

The movements of the colon are coordinated by the BER of the colon. The frequency of this wave, unlike the wave in the small intestine, increases along the colon, from about 2/min at the ileocecal valve to 6/min at the sigmoid.

TRANSIT TIME IN THE SMALL INTESTINE & COLON

The first part of a test meal reaches the cecum in about 4 h in most individuals, and all the undigested portions have entered the colon in 8 or 9 h. On average, the first remnants of the meal traverse the first third of the colon in 6 h, the second third in 9 h, and reach the terminal part of the colon (the sigmoid colon) in 12 h. From the sigmoid colon to the anus, transport is much slower (Clinical Box 27–5).

CLINICAL BOX 27–5

Constipation

Constipation refers to a pathologic decrease in bowel movements. It was previously considered to reflect changes in motility, but the recent success of a drug designed to enhance chloride secretion for the treatment of chronic constipation suggests alterations in the balance between secretion and absorption in the colon could also contribute to symptom generation. Patients with persistent constipation, and particularly those with a recent change in bowel habits, should be examined carefully to rule out underlying organic disease. However, many normal humans defecate only once every 2–3 days, even though others defecate once a day and some as often as three times a day. Furthermore, the only symptoms caused by constipation are slight anorexia and mild abdominal discomfort and distension. These symptoms are not due to absorption of "toxic substances," because they are promptly relieved by evacuating the rectum and can be reproduced by distending the rectum with inert material. In western societies, the amount of misinformation and undue apprehension about constipation probably exceeds that about any other health topic. Symptoms other than those described above that are attributed by the lay public to constipation are due to anxiety or other causes.

THERAPEUTIC HIGHLIGHTS

Most cases of constipation are relieved by a change in the diet to include more fiber, or the use of laxatives that retain fluid in the colon, thereby increasing the bulk of the stool and promoting reflexes that lead to evacuation. As noted above, lubiprostone has recently joined the armamentarium for the treatment of constipation, and is assumed to act by enhancing chloride, and thus water, secretion into the colon thereby increasing the fluidity of the colonic contents.

When small colored beads are fed with a meal, an average of 70% of them are recovered in the stool in 72 h, but total recovery requires more than a week. Transit time, pressure fluctuations, and changes in pH in the gastrointestinal tract can be observed by monitoring the progress of a small pill that contains sensors and a miniature radio transmitter.

Chapter 28

Transport & Metabolic Functions of the Liver

Introduction

The liver is the largest gland in the body. It is essential for life because it conducts a vast array of biochemical and metabolic functions, including ridding the body of substances that would otherwise be injurious if allowed to accumulate, and excreting drug metabolites. It is also the first port of call for most nutrients absorbed across the gut wall, supplies most of the plasma proteins, and synthesizes the bile that optimizes the absorption of fats as well as serving as an excretory fluid. The liver and associated biliary system have therefore evolved an array of structural and physiologic features that underpin this broad range of critical functions.

The Liver

Functional Anatomy

An important function of the liver is to serve as a filter between the blood coming from the gastrointestinal tract and the blood in the rest of the body. Blood from the intestines and other viscera reach the liver via the portal vein. This blood percolates in sinusoids between plates of hepatic cells and eventually drains into the hepatic veins, which enter the inferior vena cava. During its passage through the hepatic plates, it is extensively modified chemically. Bile is formed on the other side at each plate. The bile passes to the intestine via the hepatic duct (Figure 28–1).

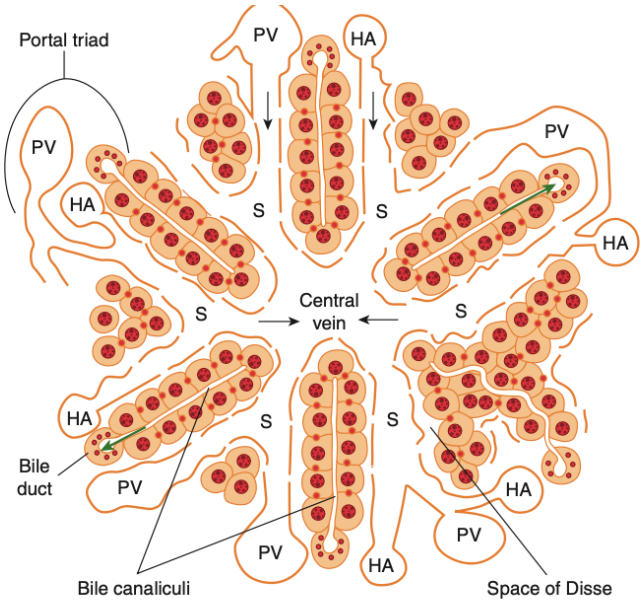


FIGURE 28–1 Schematic anatomy of the liver. Hepatocytes are arranged radially in plates surrounding a central vein. Blood is supplied to the liver by branches of the portal vein (PV) and hepatic artery (HA), which empty into sinusoids (S) surrounding the hepatocytes. The direction of blood flow is indicated with black arrows. The endothelial cells that line the sinusoids are fenestrated and thus provide little hindrance to the transfer of substances from the sinusoids to the space of Disse, which abuts the basolateral membrane of the hepatocytes. The apical membranes of adjacent hepatocytes form bile canaliculi, which transfer bile to the bile ducts lined by cholangiocytes. Bile flows in the opposite direction to blood (green arrows). The bile duct, portal vein, and hepatic artery comprise the "portal triad." (Adapted with permission from Paulsen DF: *Histology and Cell Biology: Examination and Board Review*. 5th edition. New York, NY: McGraw-Hill; 2010.)

Hepatic artery blood also enters the sinusoids. The central veins coalesce to form the hepatic veins, which drain into the inferior vena cava. The average transit time for blood across the liver lobule from the portal venule to the central hepatic vein is about 8.4 s. Additional details of the features of the hepatic microcirculation and macrocirculation, which are critical to organ function, are provided below.

Numerous macrophages (Kupffer cells) are anchored to the endothelium of the sinusoids and project into the lumen. Each liver cell is also opposed to several bile canaliculi. The canaliculi drain into intralobular bile ducts, and these coalesce via interlobular bile ducts to form the right and left hepatic ducts. These ducts join outside the liver to form the common hepatic duct. The cystic duct drains the gallbladder. The hepatic duct unites with the cystic duct to form the common bile duct (Figure 28–1). The common bile duct enters the duodenum at the duodenal

papilla. Its orifice is surrounded by the sphincter of Oddi, and it usually unites with the main pancreatic duct just before entering the duodenum. The sphincter is usually closed, but when the gastric contents enter the duodenum, cholecystokinin (CCK) is released and the gastrointestinal hormone relaxes the sphincter and makes the gallbladder contract.

The walls of the extrahepatic biliary ducts and the gall-bladder contain fibrous tissue and smooth muscle. They are lined by a layer of columnar cells with scattered mucous glands. In the gallbladder, the surface is extensively folded; this increases its surface area and gives the interior of the gall-bladder a honeycombed appearance. The cystic duct is also folded to form the so-called spiral valves. This arrangement is believed to increase the turbulence of bile as it flows out of the gallbladder, thereby reducing the risk that it will precipitate and form gallstones.

Hepatic Circulation

Large gaps occur between endothelial cells in the walls of hepatic sinusoids, and the sinusoids are highly permeable. The way the intrahepatic branches of the hepatic artery and portal vein converge on the sinusoids and drain into the central lobular veins of the liver is shown in Figure 28–1. The functional unit of the liver is the acinus. Each acinus is at the end of a vascular stalk containing terminal branches of portal veins, hepatic arteries, and bile ducts. Blood flows from the center of this functional unit to the terminal branches of the hepatic veins at the periphery .

This is why the central portion of the acinus, sometimes called zone 1, is well oxygenated, the intermediate zone (zone 2) is moderately well oxygenated, and the peripheral zone (zone 3) is least well oxygenated and most susceptible to anoxic injury. The hepatic veins drain into the inferior vena cava. The acini have been

likened to grapes or berries, each on a vascular stem. The human liver contains about 100,000 acini.

Portal venous pressure is normally about 10 mm Hg in humans, and hepatic venous pressure is approximately 5 mm Hg. The mean pressure in the hepatic artery branches that converge on the sinusoids is about 90 mm Hg, but the pressure in the sinusoids is lower than the portal venous pressure, so a marked pressure drop occurs along the hepatic arterioles. This pressure drop is adjusted so that there is an inverse

relationship between hepatic arterial and portal venous blood flow. This inverse relationship may be maintained in part by the rate at which adenosine is removed from the region around the arterioles. According to this hypothesis, adenosine is produced by metabolism at a constant rate. When portal flow is reduced, it is washed away more slowly, and the local accumulation of adenosine dilates the terminal arterioles. In the period between meals, moreover, many of the sinusoids

are collapsed. Following a meal, on the other hand, when portal flow to the liver from the intestine increases considerably, these “reserve” sinusoids are recruited. This arrangement means that portal pressures do not increase linearly with portal flow until all sinusoids have been recruited. This may be important to prevent fluid loss from the highly permeable liver under normal conditions. Indeed, if hepatic pressures are increased in disease states (such as the hardening of the liver that is seen in cirrhosis), many liters of fluid can accumulate in the peritoneal cavity as ascites.

The intrahepatic portal vein radicles have smooth muscle in their walls that is innervated by noradrenergic vasoconstrictor nerve fibers reaching the liver. The vasoconstrictor innervation of the hepatic artery comes from the hepatic sympathetic plexus. No known vasodilator fibers reach the liver.

When systemic venous pressure rises, the portal vein radicles are dilated passively and the amount of blood in the liver increases. In heart failure, this hepatic venous congestion may be extreme. Conversely, when diffuse noradrenergic discharge occurs in response to a drop in systemic blood pressure, the intrahepatic portal radicles constrict, portal pressure rises, and blood flow through the liver is brisk, bypassing most of the organ. Most of the blood in the liver enters the systemic

circulation. Constriction of the hepatic arterioles diverts blood from the liver, and constriction of the mesenteric arterioles reduces portal inflow. In severe shock, hepatic blood flow may be reduced to such a degree that patchy necrosis of the liver takes place.

FUNCTIONS OF THE LIVER

The liver has many complex functions that are summarized in Table 28–1. Several will be touched upon briefly here.

TABLE 28–1 Principal functions of the liver.

Formation and secretion of bile
Nutrient and vitamin metabolism
Glucose and other sugars
Amino acids
Lipids
Fatty acids
Cholesterol
Lipoproteins
Fat-soluble vitamins
Water-soluble vitamins
Inactivation of various substances
Toxins
Steroids
Other hormones
Synthesis of plasma proteins
Acute-phase proteins
Albumin
Clotting factors
Steroid-binding and other hormone-binding proteins
Immunity
Kupffer cells

METABOLISM & DETOXIFICATION

It is beyond the scope of this volume to touch upon all of the metabolic functions of the liver. Instead, this chapter will focus on those aspects most closely aligned to gastrointestinal physiology. First, the liver plays key roles in carbohydrate metabolism, including glycogen storage, conversion of galactose and fructose to glucose, and gluconeogenesis. The substrates for these reactions derive from the products of carbohydrate digestion and absorption that are transported from the intestine to the liver in the portal blood. The liver also plays a major role in maintaining the stability of blood glucose levels in the postprandial period, removing excess glucose from the blood and returning it as needed—the so-called glucose buffer function of the liver. In liver failure, hypoglycemia is commonly seen. Similarly, the liver contributes to fat metabolism. It supports a high rate of fatty acid oxidation for energy supply to the liver itself and other organs. Amino acids and two carbon fragments derived from carbohydrates are also converted in the liver to fats for storage. The liver also synthesizes most of the lipoproteins required by the body and preserves cholesterol homeostasis by synthesizing this molecule and also converting excess cholesterol to bile acids.

Part of this function is physical in nature—bacteria and other particulates are trapped in and broken down by the strategically located Kupffer cells. The remaining reactions are biochemical, and mediated in their first stages by the large number of cytochrome P450 enzymes expressed in hepatocytes. These convert xenobiotics and other toxins to inactive, less lipophilic metabolites. Detoxification reactions are divided into phase I (oxidation, hydroxylation, and other reactions mediated by cytochrome P450s) and phase II (esterification). Ultimately, metabolites are secreted into the bile for elimination via the gastrointestinal tract. In this regard, in addition to disposing of drugs, the liver is responsible for metabolism of essentially all steroid

hormones. Liver disease can therefore result in the apparent overactivity of the relevant hormone systems.

SYNTHESIS OF PLASMA PROTEINS

Albumin is quantitatively the most significant, and accounts for the majority of plasma oncotic pressure. Many of the products are acute-phase proteins, proteins synthesized and secreted into the plasma on exposure to stressful stimuli . Others are proteins that transport steroids and other hormones in the plasma, and still others are clotting factors. Following blood loss, the liver replaces the plasma proteins in days to weeks. The only major class of plasma proteins not synthesized by the liver is the immunoglobulins.

BILE

Bile is made up of the bile acids, bile pigments, and other substances dissolved in an alkaline electrolyte solution that resembles pancreatic juice (Table 28–2).

TABLE 28–2 Composition of human hepatic duct bile.

Water	97.0%
Bile salts	0.7%
Bile pigments	0.2%
Cholesterol	0.06%
Inorganic salts	0.7%
Fatty acids	0.15%
Phosphatidylcholine	0.2%
Fat	0.1%
Alkaline phosphatase	...

About 500 mL is secreted per day. Some of the components of the bile are reabsorbed in the intestine and then excreted again by the liver (enterohepatic circulation). In addition to its role in digestion and absorption of fats, bile (and subsequently the feces) is the major excretory route for lipid-soluble waste products.

The glucuronides of the bile pigments, bilirubin and biliverdin, are responsible for the golden yellow color of bile.

BILIRUBIN METABOLISM & EXCRETION

Most of the bilirubin in the body is formed in the tissues by the breakdown of hemoglobin . The bilirubin is bound to albumin in the circulation. Most of it is tightly bound, but some of it can dissociate in the liver, and free bilirubin enters liver cells via a member of the organic anion transporting polypeptide (OATP) family, and then becomes bound to cytoplasmic proteins (Figure 28–5).

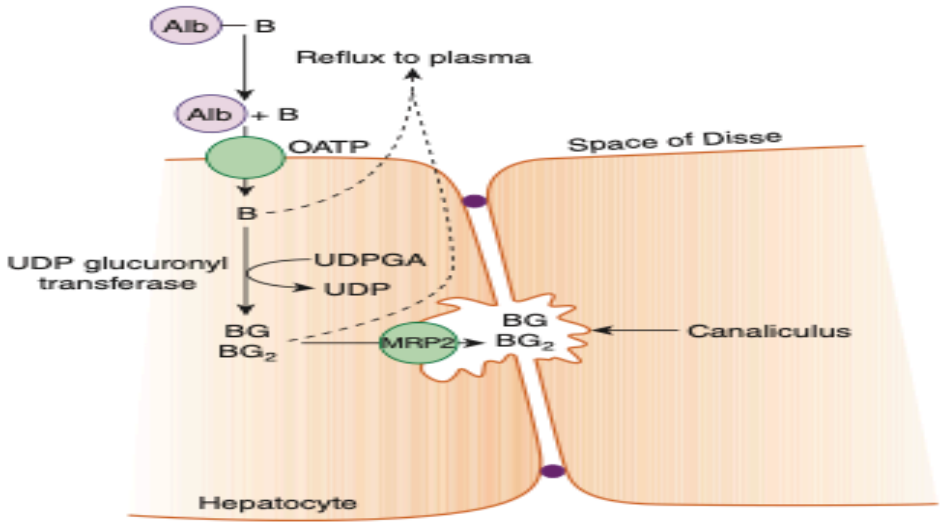


FIGURE 28–5 Handling of bilirubin by hepatocytes. Albumin (Alb)-bound bilirubin (B) enters the space of Disse adjacent to the basolateral membrane of hepatocytes, and bilirubin is selectively transported into the hepatocyte. Here, it is conjugated with glucuronic acid (G). The conjugates are secreted into bile via the multidrug resistance protein 2 (MRP-2). Some unconjugated and conjugated bilirubin also refluxes into the plasma. OATP, organic anion transporting polypeptide. The purple circles linking the two adjacent cells represent the tight junctions. BG, bilirubin monoglucuronide; BG_2, bilirubin diglucuronide.

It is next conjugated to glucuronic acid in a reaction catalyzed by the enzyme glucuronyl transferase (UDP-glucuronosyl-transferase). This enzyme is located primarily in the smooth endoplasmic reticulum. Each bilirubin molecule reacts with two uridine diphosphoglucuronic acid (UDPGA) molecules to form bilirubin diglucuronide. This glucuronide, which is more water-soluble than the free bilirubin, is then transported against a concentration gradient most likely by an active transporter known as multidrug resistance protein-2 (MRP-2) into the bile canaliculi. A small amount of the bilirubin glucuronide escapes into the blood, where it is bound less tightly to albumin than is free bilirubin, and is excreted in the urine. Thus, the total plasma bilirubin normally includes free bilirubin plus a small amount of conjugated bilirubin. Most of the bilirubin glucuronide passes via the bile ducts to the intestine.

The intestinal mucosa is relatively impermeable to conjugated bilirubin but is permeable to unconjugated bilirubin and to urobilinogens, a series of colorless derivatives of bilirubin formed by the action of bacteria in the intestine. Consequently, some of the bile pigments and urobilinogens are reabsorbed in the portal circulation. Some of the reabsorbed substances are again excreted by the liver (enterohepatic circulation), but small amounts of urobilinogens enter the general circulation and are excreted in the urine.

JAUNDICE

When free or conjugated bilirubin accumulates in the blood, the skin, scleras, and mucous membranes turn yellow. This yellowness is known as jaundice (icterus) and is usually detectable when the total plasma bilirubin is greater than 2 mg/dL (34 μmol/L). Hyperbilirubinemia may be due to (1) excess production of bilirubin (hemolytic anemia), (2) decreased uptake of bilirubin into hepatic cells, (3) disturbed intracellular protein binding or conjugation, (4) disturbed secretion of conjugated bilirubin into the bile canaliculi, or (5) intrahepatic or extrahepatic bile duct obstruction. When it is due to one of the first three processes, the free bilirubin rises. When it is due to disturbed secretion of conjugated bilirubin or bile duct obstruction, bilirubin glucuronide regurgitates into the blood, and it is predominantly the conjugated bilirubin in the plasma that is elevated.

THE BILIARY SYSTEM

BILE FORMATION

Bile contains substances that are actively secreted into it across the canalicular membrane, such as bile acids, phosphatidylcholine, conjugated bilirubin, cholesterol, and xenobiotics. Each of these enters the bile by means of a specific canalicular transporter. It is the active secretion of bile acids, however, that is

believed to be the primary driving force for the initial formation of canalicular bile. Because they are osmotically active, the canalicular bile is transiently hypertonic. However, the tight junctions that join adjacent hepatocytes are relatively permeable and thus a number of additional substances passively enter the bile from the plasma by diffusion. These substances include water, glucose, calcium, glutathione, amino acids, and urea.

Phosphatidylcholine that enters the bile forms mixed micelles with the bile acids and cholesterol. The ratio of bile acids: phosphatidylcholine: cholesterol in canalicular bile is approximately 10:3:1. Deviations from this ratio may cause cholesterol to precipitate, leading to one type of gallstones.

Functions of the Gallbladder

In normal individuals, bile flows into the gallbladder when the sphincter of Oddi is closed (ie, the period in between meals). In the gallbladder, the bile is concentrated by absorption of water. The degree of this concentration is shown by the increase in the concentration of solids (Table 28–3)

TABLE 28–3 Comparison of human hepatic duct bile and gallbladder bile.

	Hepatic Duct Bile	Gallbladder Bile
Percentage of solids	2–4	10–12
Bile acids (mmol/L)	10–20	50–200
pH	7.8–8.6	7.0–7.4

hepatic bile is 97% water, whereas the average water content of gallbladder bile is 89%. However, because the bile acids are a micellar solution, the micelles simply

become larger, and since osmolarity is a colligative property, bile remains isotonic. However, bile becomes less alkaline as sodium ions are exchanged for protons (although the overall concentration of sodium ions rises with a concomitant loss of chloride and bicarbonate as the bile is concentrated).

When the bile duct and cystic duct are clamped, the intra- biliary pressure rises to about 320 mm of bile in 30 min, and bile secretion stops. However, when the bile duct is clamped and the cystic duct is left open, water is reabsorbed in the gallbladder, and the intra-biliary pressure rises only to about 100 mm of bile in several hours.

REGULATION OF BILIARY SECRETION

When food enters the mouth, the resistance of the sphincter of Oddi decreases under both neural and hormonal influences (Figure 28–8).

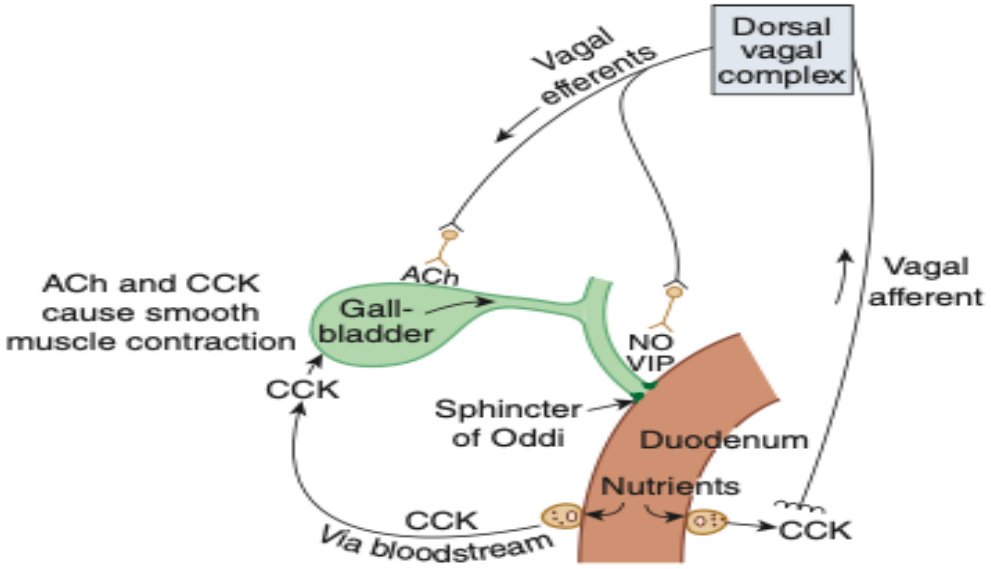


FIGURE 28–8 Neurohumoral control of gallbladder contraction and biliary secretion. Endocrine release of cholecystokinin (CCK) in response to nutrients causes gallbladder contraction. CCK, also activates vagal afferents to trigger a vagovagal reflex that reinforces gallbladder contraction (via acetylcholine [ACh]) and relaxation of the sphincter of Oddi to permit bile outflow (via NO and vasoactive intestinal polypeptide [VIP]).

Fatty acids and amino acids in the duodenum release CCK, which causes gallbladder contraction. The production of bile is increased by stimulation of the vagus nerves and by the hormone secretin, which increases the water and HCO3 − content of bile. Substances that increase the secretion of bile are known as choleretics. Bile acids them- selves are among the most important physiologic choleretics.

Chapter 31

Blood as a Circulatory Fluid & the Dynamics of Blood & Lymph Flow

Introduction

The circulatory system supplies inspired O2 as well as substances absorbed from the gastrointestinal tract to the tissues, returns CO2 to the lungs and other products of metabolism to the kidneys, functions in the regulation of body temperature, and distributes hormones and other agents that regulate cell function. The blood, the carrier of these substances, is pumped through a closed system of blood vessels by the heart. The blood flow to each tissue is regulated by local chemical and general neural and humoral mechanisms that dilate or constrict its vessels. Blood is a specialized type of connective tissue, red in color, syrupy fluid which has specific gravity 1.055 and the viscosity 2.5 times that of water. Blood is alkaline (PH=7.4) and appear scarlet red when taken from arteries and purplish from veins. The difference in color is due to its O_2 content . Blood consists of a protein-rich fluid known as plasma, in which are suspended cellular elements: white blood cells, red blood cells, and platelets. The normal total circulating blood volume is about 8% of the body weight (5600 mL in a 70-kg man). About 55% of this volume is plasma. Blood plays a role in maintaining the cellular environment by serving as a transport medium of the body. The various functions of blood result from specialization within the cellular elements or the plasma or the interaction between the two .

BLOOD AS A CIRCULATORY FLUID

Blood consists of a protein-rich fluid known as plasma, in which are suspended cellular elements: white blood cells, red blood cells, and platelets. The normal total

circulating blood volume is about 8% of the body weight (5600 mL in a 70-kg man). About 55% of this volume is plasma.

BONE MARROW

In the adult, red blood cells, many white blood cells, and platelets are formed in the bone marrow. In the fetus, blood cells are also formed in the liver and spleen, and in adults such extramedullary hematopoiesis may occur in diseases in which the bone marrow becomes destroyed or fibrosed. In children, blood cells are actively produced in the marrow cavities of all the bones. By age 20, the marrow in the cavities of the long bones, except for the upper humerus and femur, has become inactive. Active cellular marrow is called red marrow; inactive marrow that is infiltrated with fat is called yellow marrow. The bone marrow is actually one of the largest organs in the body, approaching the size and weight of the liver. It is also one of the most active. Normally, 75% of the cells in the marrow belong to the white blood cell–producing myeloid series and only 25% are maturing red cells, even though there are over 500 times as many red cells in the circulation as there are white cells. This difference in the marrow reflects the fact that the average life span of white cells is short, whereas that of red cells is long.

Hematopoietic stem cells (HSCs) are bone marrow cells that are capable of producing all types of blood cells. They differentiate into one or another type of committed stem cells (progenitor cells). These in turn form the various differentiated types of blood cells. There are separate pools of progenitor cells for megakaryocytes, lymphocytes, erythrocytes, eosinophils, and basophils; neutrophils and monocytes arise from a common precursor. The bone marrow stem cells are also the source of osteoclasts, Kupffer cells mast cells, dendritic cells, and Langerhans cells. The HSCs are few in number but are capable of completely replacing the bone marrow when injected into a patient whose own bone marrow has been entirely destroyed.

WHITE BLOOD CELLS

Normally, human blood contains 4000–11,000 white blood cells per microliter (Table 31–1).

TABLE 31–1 Normal values for the cellular elements in human blood.

Cell	Cells/μL (average)	Approximate Normal Range	Percentage of Total White Cells
Total white blood cells	9000	4000–11,000	…
Granulocytes			
Neutrophils	5400	3000–6000	50–70
Eosinophils	275	150–300	1–4
Basophils	35	0–100	0.4
Lymphocytes	2750	1500–4000	20–40
Monocytes	540	300–600	2–8
Erythrocytes			
Females	4.8×10^6	…	…
Males	5.4×10^6	…	…
Platelets	300,000	200,000–500,000	…

Of these, the granulocytes (polymorphonuclear leukocytes, PMNs) are the most numerous. Young granulocytes have horseshoe-shaped nuclei that become multilobed as the cells grow older (Figure 31–3). Most of them contain neutrophilic granules (neutrophils), but a few contain granules that stain with acidic dyes (eosinophils), and some have basophilic granules (basophils)

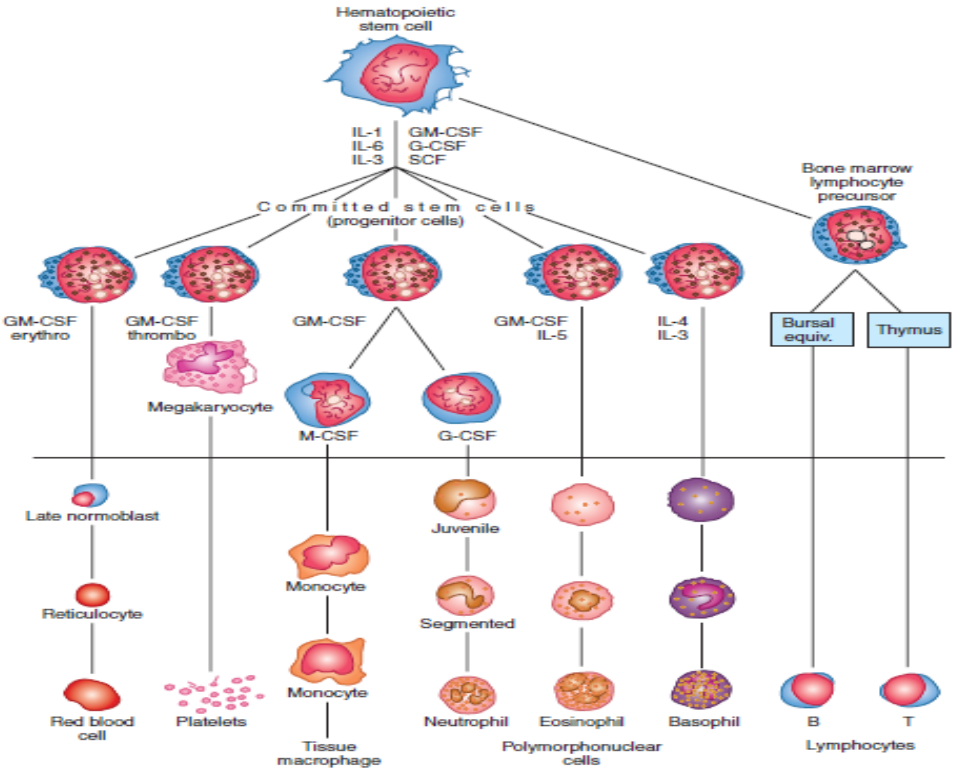


FIGURE 31–3 Development of various formed elements of the blood from bone marrow cells. Cells below the horizontal line are found in normal peripheral blood. The principal sites of action of erythropoietin (erythro) and the various colony-stimulating factors (CSF) that stimulate the differentiation of the components are indicated. G, granulocyte; M, macrophage; IL, interleukin; thrombo, thrombopoietin; erythro, erythropoietin; SCF, stem cell factor.

The other two cell types found normally in peripheral blood are lymphocytes, which have large round nuclei and scanty cytoplasm, and monocytes, which have abundant agranular cytoplasm and kidney-shaped nuclei (Figure 31–3). Acting together, these cells provide the body with the powerful defenses against tumors and viral, bacterial, and parasitic infections .

PLATELETS

Platelets are small, granulated bodies that aggregate at sites of vascular injury. They lack nuclei and are 2–4 μm in diameter). There are about 300,000/μL of circulating blood, and they normally have a half-life of about 4 days. The megakaryocytes, giant cells in the bone marrow, form platelets by pinching off bits of cytoplasm and extruding them into the circulation. Between 60% and 75% of the platelets that have been extruded from the bone marrow are in the circulating blood, and the remainder

are mostly in the spleen. Splenectomy causes an increase in the platelet count (thrombocytosis).

RED BLOOD CELLS

The red blood cells (erythrocytes) carry hemoglobin in the circulation. They are biconcave disks that are manufactured in the bone marrow. In mammals, they lose their nuclei before entering the circulation. In humans, they survive in the circulation for an average of 120 days. The average normal red blood cell count is 5.4 million/μL in men and 4.8 million/μL in women. The number of red cells is also conveniently expressed as the hematocrit, or the percentage of the blood, by volume, that is occupied by erythrocytes. Each human red blood cell is about 7.5 μm in diameter and 2 μm thick, and each contains approximately 29 pg of hemoglobin (Table 31-2).

TABLE 31–2 Characteristics of human red cells.[a]

		Male	Female
Hematocrit (Hct) (%)		47	42
Red blood cells (RBC) (10^6/μL)		5.4	4.8
Hemoglobin (Hb) (g/dL)		16	14
Mean corpuscular volume (MCV) (fL)	$= \frac{\text{Hct} \times 10}{\text{RBC } (10^6/\mu\text{L})}$	87	87
Mean corpuscular hemoglobin (MCH) (pg)	$= \frac{\text{Hb} \times 10}{\text{RBC } (10^6/\mu\text{L})}$	29	29
Mean corpuscular hemoglobin concentration (MCHC) (g/dL)	$= \frac{\text{Hb} \times 100}{\text{Hct}}$	34	34
Mean cell diameter (MCD) (μm)	= Mean diameter of 500 cells in smear	7.5	7.5

[a]Cells with MCVs > 95 fL are called macrocytes; cells with MCVs < 80 fL are called microcytes; cells with MCHCs < 25 g/dL are called hypochromic.

There are thus about 3×10^{13} red blood cells and about 900 g of hemoglobin in the circulating blood of an adult man (Figure 31–5). The feedback control of erythropoiesis by erythropoietin hormone released by renal tissue in presence of low O_2 content in blood .

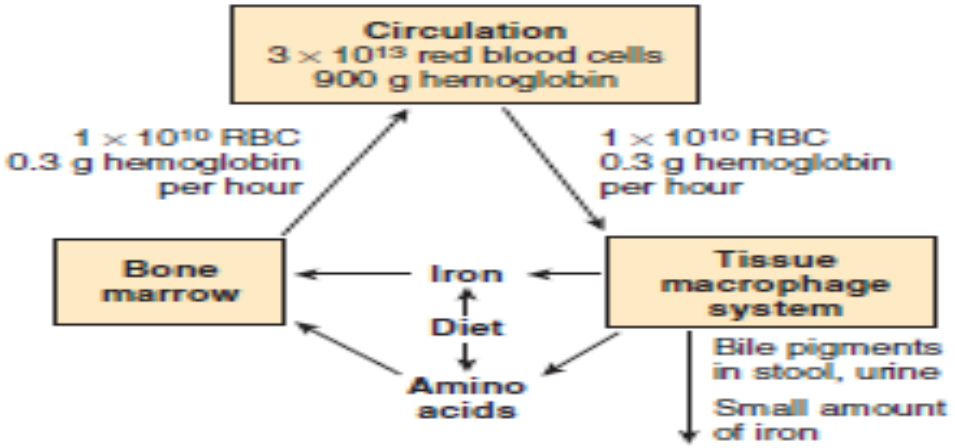


FIGURE 31–5 Red cell formation and destruction. RBC, red blood cells.

HEMOGLOBIN

The red, oxygen-carrying pigment in the red blood cells of vertebrates is hemoglobin, a protein with a molecular weight of 64,450. Hemoglobin is a globular molecule made up of four subunits (Figure 31–6).

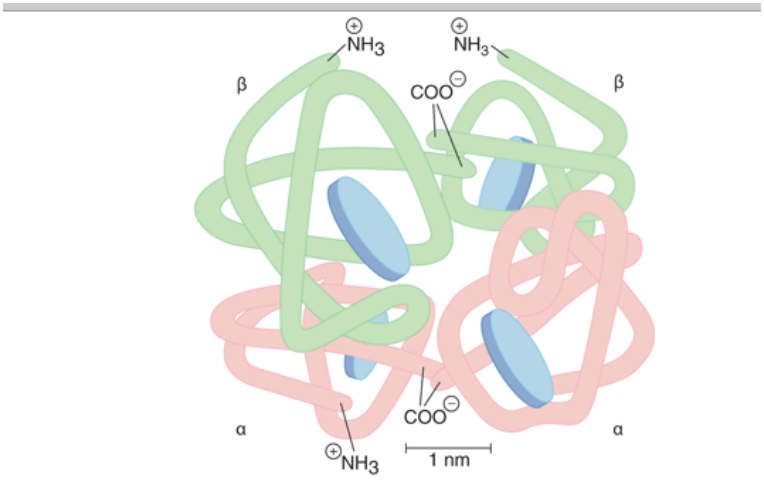


Figure (31-6) Diagrammatic representation of a molecule of hemoglobin A, showing the four subunits.

Each subunit contains a heme moiety conjugated to a polypeptide. Heme is an iron-containing porphyrin derivative. The polypeptides are referred to collectively as the

globin portion of the hemoglobin molecule. There are two pairs of polypeptides in each hemoglobin molecule. In normal adult human hemoglobin (hemoglobin A), the two polypeptides are called α chains and β chains. Thus, hemoglobin A is designated α2β2. Not all the hemoglobin in the blood of normal adults is hemoglobin A. About 2.5% of the hemoglobin is hemoglobin A2, in which β chains are replaced by δ chains (α2δ2). The δ chains contain 10 individual amino acid residues that differ from those in β chains. There are small amounts of hemoglobin A derivatives closely associated with hemoglobin A that represent glycated hemoglobins. HbA_{1a} , HbA_{1b} , HbA_{1c} one of these, hemoglobin A1c (HbA1c), has a glucose attached to the terminal valine in each β chain and is of special interest because it increases in the blood of patients with poorly controlled diabetes mellitus and is measured clinically as a marker of the progression of that disease and/or the effectiveness of treatment.

REACTIONS OF HEMOGLOBIN

O2 binds to the Fe2+ in the heme moiety of hemoglobin to form oxyhemoglobin. The affinity of hemoglobin for O2 is affected by pH, temperature, and the concentration in the red cells of 2,3-bisphosphoglycerate (2,3-BPG). 2,3-BPG λ arise in temperature or fall in PH or an increase in the concentration of 2,3-BPG lower the affinity of hemoglobin for O_2 causing more O_2 to be liberated and H+ compete with O2 for binding to deoxygenated hemoglobin, decreasing the affinity of hemoglobin for O2 by shifting the positions of the four peptide chains (quaternary structure). When blood is exposed to various drugs and other oxidizing agents in vitro or in vivo, the ferrous iron ($Fe^{2+)}$ that is normally present in hemoglobin is converted to ferric iron (Fe^{3+}), forming methemoglobin. Methemoglobin is dark-colored, and when it is present in large quantities in the circulation, it causes a dusky discoloration of the skin resembling cyanosis. Some oxidation of hemoglobin to methemoglobin occurs normally, but an enzyme system in the red cells, the dihydronicotinamide

adenine dinucleotide (NADH)-methemoglobin reductase system, converts methemoglobin back to hemoglobin. Carbon monoxide reacts with hemoglobin to form carbon monoxyhemoglobin (carboxyhemoglobin). The affinity of hemoglobin for O2 is much lower than its affinity for carbon monoxide, which consequently displaces O2 on hemoglobin, reducing the oxygen-carrying capacity of blood .

SYNTHESIS OF HEMOGLOBIN

The average normal hemoglobin content of blood is 16 g/dL in men and 14 g/dL in women, all of it in red cells. In the body of a 70-kg man, there are about 900 g of hemoglobin, and 0.3 g of hemoglobin is destroyed and 0.3 g synthesized every hour (Figure 31–5). The heme portion of the hemoglobin molecule is synthesized from glycine and succinyl-CoA **(Clinical Box 31–2)**

Clinical box 31–2 : Abnormalities of Hemoglobin Production There are two major types of inherited disorders of hemoglobin in humans: the hemoglobinopathies, in which abnormal globin polypeptide chains are produced, and the thalassemias and related disorders, in which the chains are normal in structure but produced in decreased amounts or absent because of defects in the regulatory portion of the globin genes.. In one of the most common examples, hemoglobin S, the α chains are normal but the β chains have a single substitution of a valine residue for one glutamic acid, leading to sickle cell anemia . The cell assume a sickle shape , easily ruptured and the Hb – s loss its ability to carry O_2 he rigid shape of the sickle cell inhibit their movement through the capillaries so they stick forming a pile behind the stuck cells that inhibit O_2 supply to the tissue .

CATABOLISM OF HEMOGLOBIN

When old red blood cells are destroyed by tissue macrophages, the globin portion of the hemoglobin molecule is split off, and the heme is converted to biliverdin. In

humans, most of the biliverdin is converted to bilirubin and excreted in the bile. The iron from the heme is reused for hemoglobin synthesis. Exposure of the skin to white light converts bilirubin to lumirubin, which has a shorter half-life than bilirubin. Phototherapy (exposure to light) is of value in treating infants with jaundice due to hemolysis. Iron is essential for hemoglobin synthesis; if blood is lost from the body and the iron deficiency is not corrected, iron deficiency anemia results .

BLOOD TYPES

The membranes of human red cells contain a variety of blood group antigens, which are also called agglutinogens. The most important and best known of these are the A and B antigens, but there are many more.

THE ABO SYSTEM The A and B antigens are inherited as mendelian dominants, and individuals are divided into four major blood types on this basis. Type A individuals have the A antigen, type B have the B, type AB have both, and type O have neither. The A and B antigens are complex oligosaccharides that differ in their terminal sugar. An H gene codes for a fucose transferase that adds a terminal fucose, forming the H antigen that is usually present in individuals of all blood types .Individuals who are type A also express a second transferase that catalyzes placement of a terminal N-acetylgalactosamine on the H antigen, whereas individuals who are type B express . a transferase that places a terminal galactose. Individuals who are type AB have both transferases. Individuals who are type O have neither, so the H antigen persists. Antibodies against red cell agglutinogens are called agglutinins. Antigens very similar to A and B are common in intestinal bacteria and possibly in foods to which newborn individuals are exposed. Therefore, infants rapidly develop antibodies against the antigens not present in their own cells. Thus, type A individuals develop anti-B antibodies, type B individuals develop anti-

A antibodies, type O individuals develop both, and type AB individuals develop neither (Table 31–3).

TABLE 31–3 Summary of ABO system.

Blood Type	Agglutinins in Plasma	Frequency in United States %	Plasma Agglutinates Red Cells of Type:
O	Anti-A, anti-B	45	A, B, AB
A	Anti-B	41	B, AB
B	Anti-A	10	A, AB
AB	None	4	None

When the plasma of a type A individual is mixed with type B red cells, the anti-B antibodies cause the type B red cells to clump (agglutinate), as shown in Figure 31–10. The other agglutination reactions produced by mismatched plasma and red cells are summarized in Table 31–3. ABO blood typing is performed by mixing an individual's red blood cells with antisera containing the various agglutinins on a slide and seeing whether agglutination occurs.

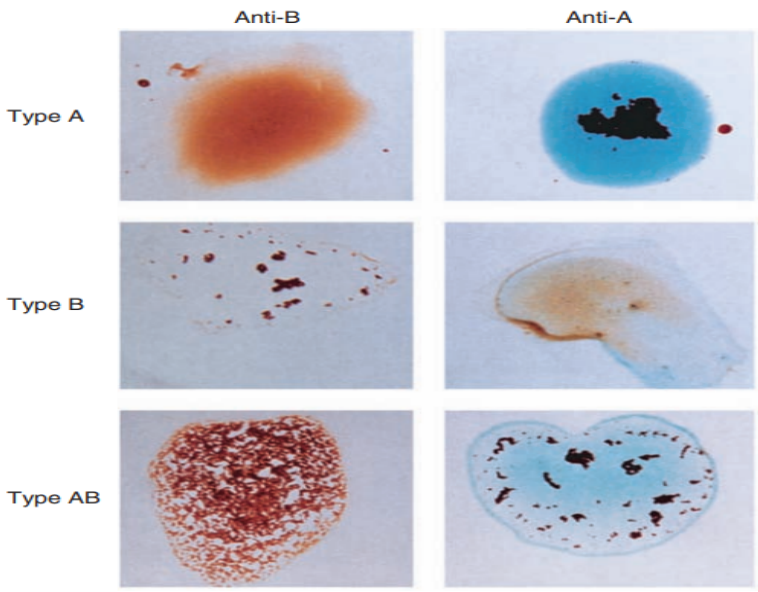
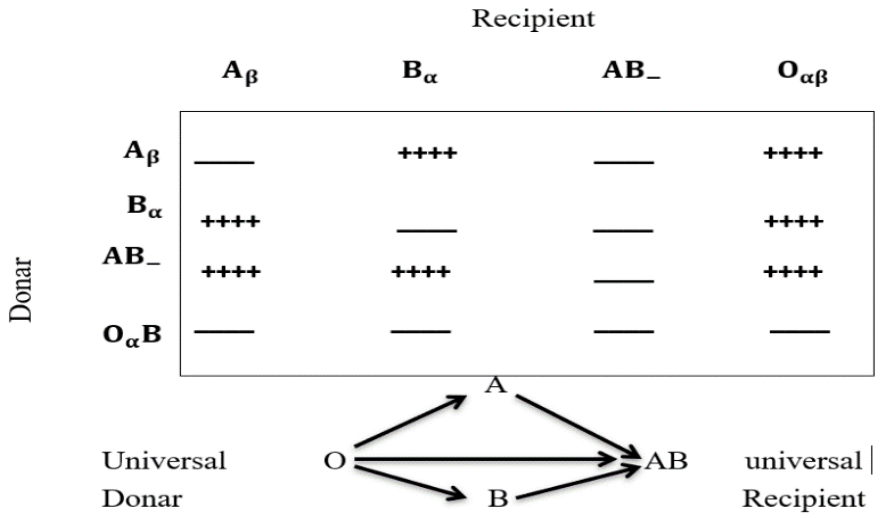


FIGURE 31–10 Red cell agglutination in incompatible plasma.

TRANSFUSION REACTIONS

Dangerous hemolytic transfusion reactions occur when blood is transfused into an individual with an incompatible blood type; that is, an individual who has agglutinins against the red cells in the transfusion. The plasma in the transfusion is usually so diluted in the recipient that it rarely causes agglutination even when the titer of agglutinins against the recipient's cells is high. However, when the recipient's plasma has agglutinins against the donor's red cells, the cells agglutinate and hemolyze. Free hemoglobin is liberated into the plasma. The severity of the resulting transfusion reaction may vary from an asymptomatic minor rise in the plasma bilirubin level to severe jaundice and renal tubular damage leading to anuria and death. Incompatibilities in the ABO blood group system are summarized in Table 31–3. Persons with type AB blood are "universal recipients" because they have no circulating agglutinins and can be given blood of any type without developing a transfusion reaction due to ABO incompatibility. Type O individuals are "universal donors" because they lack A and B antigens, and type O blood can be

given to anyone without producing a transfusion reaction due to ABO incompatibility. This does not mean, however, that blood should ever be transfused without being cross-matched except in the most extreme emergencies, since the possibility of reactions or sensitization due to incompatibilities in systems other than ABO systems always exists. In cross-matching, donor red cells are mixed with recipient plasma on a slide and checked for agglutination. It is advisable to check the action of the donor's plasma on the recipient cells in addition, even though, as noted above, this is rarely a source of trouble.



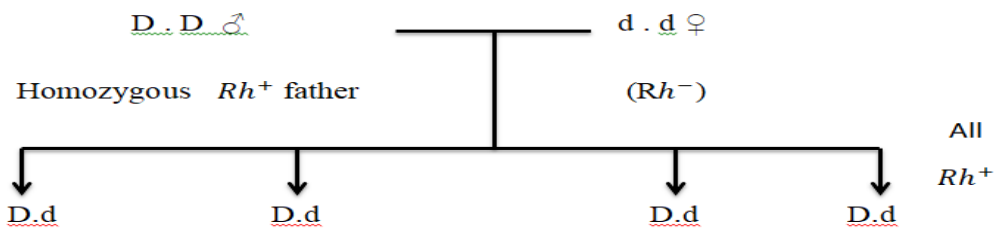
A procedure that has recently become popular is to withdraw the patient's own blood in advance of elective surgery and then infuse this blood back (autologous transfusion) if a transfusion is needed during the surgery. With iron treatment, 1000–1500 mL can be withdrawn over a 3-weeks period. The popularity of banking one's own blood is primarily due to fear of transmission of infectious diseases by heterologous transfusions, but of course another advantage is elimination of the risk of transfusion reactions.

THE RH GROUP

Aside from the antigens of the ABO system, those of the Rh system are of the greatest clinical importance. The Rh factor, named for the rhesus monkey because it was first studied using the blood of this animal, is a system composed primarily of the C, D, and E antigens, although it actually contains many more. Unlike the ABO antigens, the system has not been detected in tissues other than red cells. D is by far the most antigenic component, and the term Rh-positive as it is generally used means that the individual has agglutinogen D. The D protein is not glycosylated, and its function is unknown. The Rh-negative individual has no D antigen and forms the anti-D agglutinin when injected with D-positive cells. The Rh typing serum used in routine blood typing is anti-D serum. Eighty-five percent of whites are D-positive and 15% are D-negative; over 99% of Asians are D-positive. Unlike the antibodies of the ABO system, anti-D antibodies do not develop without exposure of a D-negative individual to D-positive red cells by transfusion or entrance of fetal blood into the maternal circulation. However, D-negative individuals who have received a transfusion of D-positive blood (even years previously) can have appreciable anti-D titers and thus may develop transfusion reactions when transfused again with D-positive blood .

HEMOLYTIC DISEASE OF THE NEWBORN

Another complication due to Rh incompatibility arises when an Rh-negative mother carries an Rh-positive fetus.



Small amounts of fetal blood leak into the maternal circulation at the time of delivery, and some mothers develop significant titers of anti-Rh agglutinins during the postpartum period. During the next pregnancy, the mother's agglutinins cross the placenta to the fetus. In addition, there are some cases of fetal-maternal hemorrhage during pregnancy, and sensitization can occur during pregnancy. In any case, when anti-Rh agglutinins cross the placenta to an Rh-positive fetus, they can cause hemolysis and various forms of hemolytic disease of the newborn (erythroblastosis fetalis). If hemolysis in the fetus is severe, the infant may die in utero or may develop anemia, severe jaundice, and edema (hydrops fetalis). Kernicterus, a neurologic syndrome in which unconjugated bilirubin is deposited in the basal ganglia, may also develop, especially if birth is complicated by a period of hypoxia. Bilirubin rarely penetrates the brain in adults, but it does in infants with erythroblastosis, possibly in part because the blood–brain barrier is more permeable in infancy. However, the main reasons that the concentration of unconjugated bilirubin is very high in this condition are that production is increased and the bilirubin-conjugating system is not yet mature. About 50% of Rh-negative individuals are sensitized (develop an anti-Rh titer) by transfusion of Rh-positive blood. Because sensitization of Rh-negative mothers by carrying an Rh-positive fetus generally occurs at birth, the first child is usually normal. However, hemolytic disease occurs in about 17% of the Rh-positive fetuses born to Rh-negative mothers who have previously been pregnant one or more times with Rh-positive fetuses. Fortunately, it is usually possible to prevent sensitization from occurring the first time by administering a single dose of anti-Rh antibodies in the form of Rh immune globulin during the postpartum period. Such passive immunization does not harm the mother and has been demonstrated to prevent active antibody formation by the mother. In obstetric clinics, the institution of such treatment on a routine basis to unsensitized Rh-negative women who have delivered an Rh-positive baby has

reduced the overall incidence of hemolytic disease by more than 90%. In addition, fetal Rh typing with material obtained by amniocentesis or chorionic villus sampling is now possible, and treatment with a small dose of Rh immune serum will prevent sensitization during pregnancy.

PLASMA

The fluid portion of the blood contains 92% water and 8% solid , the plasma, is a remarkable solution containing an immense number of ions, inorganic molecules, and organic molecules that are in transit to various parts of the body or aid in the transport of other substances. Normal plasma volume is about 5% of body weight, or roughly 3500 mL in a 70-kg man. Plasma clots on standing, remaining fluid only if an anticoagulant is added. If whole blood is allowed to clot and the clot is removed, the remaining fluid is called serum. Serum has essentially the same composition as plasma, except that its fibrinogen and clotting factors II, V, and VIII have been removed and it has a higher serotonin content because of the breakdown of platelets during clotting.

PLASMA PROTEINS

Constitute 7% of the solid in the plasma ,the plasma proteins consist of albumin, globulin, and fibrinogen fractions. Most capillary walls are relatively impermeable to the proteins in plasma, and the proteins therefore exert an osmotic force of about 25 mm Hg across the capillary wall (oncotic pressure; that pulls water into the blood. The plasma proteins are also responsible for 15% of the buffering capacity of proteins in the blood (including hemoglobin) because of the weak ionization of their substituent COOH and NH2 groups. At the normal plasma pH of 7.40, the proteins are mostly in the anionic .Plasma proteins may have specific functions (eg, antibodies and the proteins concerned with blood clotting), whereas others function as nonspecific carriers for various hormones, other solutes, and drugs. Circulating

antibodies are manufactured by lymphocytes. Most of the other plasma proteins are synthesized in the liver.

HEMOSTASIS

Hemostasis is the process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system. A collection of complex interrelated systemic mechanisms operates to maintain a balance between coagulation and anticoagulation

RESPONSE TO INJURY

When a small blood vessel is transected or damaged, the injury initiates a series of events that lead to the formation of a clot(31-11).

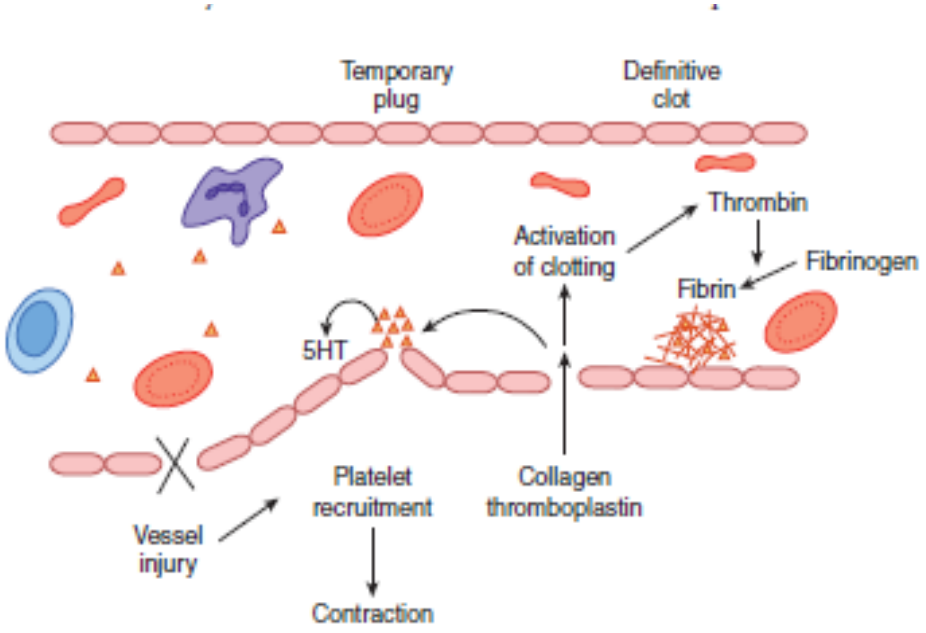


FIGURE 31–11 Summary of reactions involved in hemostasis.

This seals off the damaged region and prevents further blood loss. The initial event is constriction of the vessel and formation of a temporary hemostatic plug of platelets that is triggered when platelets bind to collagen and aggregate. This is followed by conversion of the plug into the definitive clot. The constriction of an injured arteriole

or small artery may be so marked that its lumen is obliterated, at least temporarily. The vasoconstriction is due to serotonin and other vasoconstrictors liberated from platelets that adhere to the walls of the damaged vessels.

THE CLOTTING MECHANISM

The loose aggregation of platelets in the temporary plug is bound together and converted into the definitive clot by fibrin. Fibrin formation involves a cascade of enzymatic reactions and a series of numbered clotting factors .The fundamental reaction is conversion of the soluble plasma protein fibrinogen to insoluble fibrin (Figure 31–12).

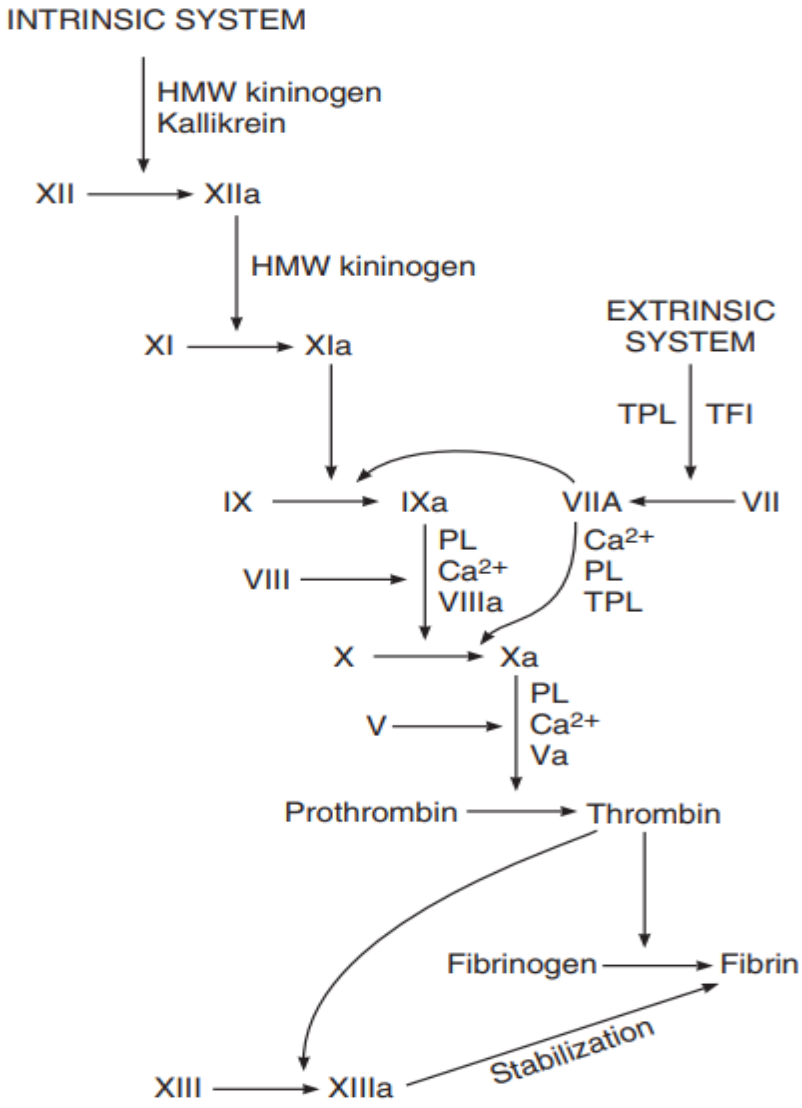


FIGURE 31–12 The clotting mechanism. a, active form of clotting factor. TFI, tissue factor pathway inhibitor; TPL, tissue

The process involves the release of two pairs of polypeptides from each fibrinogen molecule. The remaining portion, fibrin monomer, then polymerizes with other monomer molecules to form fibrin. The fibrin is initially a loose mesh of interlacing strands. It is converted by the formation of covalent cross-linkages to a dense, tight aggregate (stabilization). This latter reaction is catalyzed by activated factor XIII and requires Ca2+. The conversion of fibrinogen to fibrin is catalyzed by thrombin. Thrombin is a serine protease that is formed from its circulating precursor,

prothrombin, by the action of activated factor X. It has additional actions, including activation of platelets, endothelial cells, and leukocytes via so-called proteinase activated receptors, which are G-protein–coupled. Factor X can be activated by either of two systems, known as intrinsic and extrinsic .

ANTICLOTTING MECHANISMS

The tendency of blood to clot is balanced in vivo by reactions that prevent clotting inside the blood vessels, break down any clots that do form, or both. These reactions include the interaction between the platelet-aggregating effect of thromboxane A2 and the antiaggregating effect of prostacyclin, which causes clots to form at the site when a blood vessel is injured but keeps the vessel lumen free of clot . **Antithrombin III** is a circulating protease inhibitor that binds to serine proteases in the coagulation system, blocking their activity as clotting factors. This binding is facilitated by heparin, a naturally occurring anticoagulant that is a mixture of sulfated polysaccharides. The clotting factors that are inhibited are the active forms of factors IX, X, XI, and XII. The endothelium of the blood vessels also plays an active role in preventing the extension of clots. All endothelial cells produce thrombomodulin, a thrombin-binding protein, on their surfaces. In circulating blood, thrombin is a procoagulant that activates factors V and VIII, but when it binds to thrombomodulin, it becomes an anticoagulant. **Plasmin** (fibrinolysin) is the active component of the plasminogen (fibrinolytic) system. This enzyme lyses fibrin and fibrinogen, with the production of fibrinogen degradation products (FDP) that inhibit thrombin.

LYMPH

Lymph is tissue fluid that enters the lymphatic vessels. It drains into the venous blood via the thoracic and right lymphatic ducts. It contains clotting factors and clots on standing in vitro. In most locations, it also contains proteins that have traversed

capillary walls and can then return to the blood via the lymph. Nevertheless, its protein content is generally lower than that of plasma, which contains about 7 g/dL, but lymph protein content varies with the region from which the lymph drains Water-insoluble fats are absorbed from the intestine into the lymphatics, and the lymph in the thoracic duct after a meal is milky because of its high fat content .Lymphocytes also enter the circulation principally through the lymphatics, and there are appreciable numbers of lymphocytes in thoracic duct lymph .

STRUCTURAL FEATURES OF THE CIRCULATION :

Here, the two major cell types that make up the blood vessels and how they are arranged into the various vessel types that subserve the needs of the circulation will be described.

ENDOTHELIUM

Located between the circulating blood and the media and adventitia of the blood vessels, the endothelial cells constitute a large and important organ. They respond to flow changes, stretch, a variety of circulating substances, and inflammatory mediators. They secrete growth regulators and vasoactive substances

VASCULAR SMOOTH MUSCLE

The smooth muscle in blood vessel walls has been one of the most-studied forms of visceral smooth muscle because of its importance in the regulation of blood pressure and hypertension. The membranes of the muscle cells contain various types of K^+, Ca^{2+}, and Cl^- channels. Contraction is produced primarily by the myosin light chain mechanism. However, vascular smooth muscle also undergoes prolonged contractions that determine vascular tone. These may be due in part to the latch-bridge mechanism but other factors also play a role. In these cells, influx of Ca^{2+}

via voltage-gated Ca2+ channels produces a diffuse increase in cytosolic Ca2+ that initiates contraction.