

TABLE 25-1 Frequently Measured Hormones and Hormone Precursors

Endocrine Organ and Hormone	Chemical Nature of Hormone	Major Sites of Action	Principal Actions
HYPOTHALAMUS			
Thyrotropin-releasing hormone (TRH)	Peptide (3 aa, Glu-His-Pro)*	Anterior pituitary	Release of TSH and prolactin (PRL)
Gonadotropin-releasing hormone (Gn-RH) or luteinizing hormone-releasing hormone (LH-RH)	Peptide (10 aa)	Anterior pituitary	Release of LH and FSH
Corticotropin-releasing hormone (CRH)	Peptide (41 aa)	Anterior pituitary	Release of ACTH and β -lipotropic hormone (LPH)
Growth hormone-releasing hormone (GH-RH)	Peptides (40, 44 aa)	Anterior pituitary	Release of growth hormone (GH)
Somatostatin [†] (SS) or growth hormone-inhibiting hormone (GH-IH)	Peptides (14 and 28 aa)	Anterior pituitary	Suppression of secretion of many hormones (e.g., GH, TSH, gastrin, vasoactive intestinal polypeptide [VIP], gastric inhibitory polypeptide [GIP], secretin, motilin, glucagon, and insulin)
ANTERIOR PITUITARY LOBE			
Thyrotropin or thyroid-stimulating hormone (TSH)	Glycoprotein heterodimer [‡] (α , 92 aa; β , 112 aa)	Thyroid gland	Stimulation of thyroid hormone formation and secretion
Follicle-stimulating hormone (FSH)	Glycoprotein, heterodimer [‡] (α , 92 aa; β , 117 aa)	Ovary Testis	Growth of follicles with LH, secretion of estrogens, and ovulation Development of seminiferous tubules; spermatogenesis
Luteinizing hormone (LH)	Glycoprotein, heterodimer [‡] (α , 92 aa; β , 121 aa)	Ovary Testis	Ovulation; formation of corpora lutea; secretion of progesterone Stimulation of interstitial tissue; secretion of androgens
Prolactin (PRL)	Peptide (199 aa)	Mammary gland	Proliferation of mammary gland; initiation of milk secretion; antagonist of insulin action
Growth hormone (GH) or somatotropin	Peptide (191 aa)	Liver Liver and peripheral tissues	Production of IGF-I (promoting growth) Antiinsulin and anabolic effects
Corticotropin or adrenocorticotropin (ACTH)	Peptide (39 aa)	Adrenal cortex	Stimulation of adrenocortical steroid formation and secretion
POSTERIOR PITUITARY LOBE (Neurohypophysis)			
Vasopressin or antidiuretic hormone (ADH)	Peptide (9 aa)	Arterioles Renal tubules	Elevation of blood pressure; water reabsorption
Oxytocin	Peptide (9 aa)	Smooth muscles (uterus, mammary gland)	Contraction; action in parturition and in sperm transport; ejection of milk
PINEAL GLAND			
Serotonin or 5-hydroxytryptamine (5-HT)	Indoleamine	Cardiovascular, respiratory, and gastrointestinal systems; brain	Neurotransmitter; stimulation or inhibition of various smooth muscles and nerves
Melatonin	Indoleamine	Hypothalamus	Suppression of gonadotropin and GH secretion; induction of sleep
THYROID GLAND			
Thyroxine (T ₄) and triiodothyronine (T ₃)	Iodoamino acids	General body tissue	Stimulation of oxygen consumption and metabolic rate of tissue
Calcitonin or thyrocalcitonin	Peptide (32 aa)	Skeleton	Uncertain in humans
PARATHYROID GLAND			
Parathyroid hormone (PTH) or parathyrin	Peptide (84 aa)	Kidney Skeleton	Increased calcium reabsorption, inhibited phosphate reabsorption; increased production of 1,25-dihydroxycholecalciferol Increased bone resorption

TABLE 25-1 Frequently Measured Hormones and Hormone Precursors—Cont'd

Endocrine Organ and Hormone	Chemical Nature of Hormone	Major Sites of Action	Principal Actions
ADRENAL CORTEX			
Aldosterone	Steroid	Kidney	Salt and water balance
Androstenedione [§]	Steroid	Hormone precursor	Converted to estrogens and testosterone
Cortisol	Steroid	Many	Metabolism of carbohydrates, proteins, and fats; antiinflammatory effects; others
Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS)	Steroids	Hormone precursors	Converted to estrogens and testosterone
17-Hydroxyprogesterone	Steroid	Hormone precursor	Converted to cortisol
ADRENAL MEDULLA			
Norepinephrine and epinephrine	Aromatic amines	Sympathetic receptors	Stimulation of sympathetic nervous system
Epinephrine		Liver and muscle, adipose tissue	Glycogenolysis Lipolysis
OVARY			
DHEA and DHEAS	Steroids	Hormone precursors	Converted to androstenedione
Estrogens	Phenolic steroids	Female accessory sex organs	Development of secondary sex characteristics
Inhibin A	Peptide (α subunit and β_A subunit)	Bone	Control of skeletal maturation
Inhibin B	Peptide (α subunit and β_B subunit)	Hypothalamus, ovarian follicle	Inhibits FSH secretion; stimulates theca cell androgen production
Progesterone	Steroid	See inhibin A above	See inhibin A above
		Female accessory reproductive structure	Preparation of the uterus for ovum implantation, maintenance of pregnancy
TESTIS			
Inhibin B	See above	Anterior pituitary, hypothalamus	Control of LH and FSH secretion
Testosterone	Steroid	Male accessory sex organs	Development of secondary sex characteristics, maturation, and normal function
PLACENTA			
Estrogens	See above	See above	See above
Progesterone	See above	See above	See above
Chorionic gonadotropin (CG) or choriogonadotropin	Glycoprotein, heterodimer [†] (α , 92 aa; β , 145 aa)	Same as LH	Same as LH; prolongation of corpus luteal function
PANCREAS			
Glucagon	Peptide (29 aa)	Liver	Glycogenolysis
Insulin	Peptide [¶]	Liver, fat, muscle	Regulation of carbohydrate metabolism; lipogenesis
GASTROINTESTINAL TRACT			
Gastrin	Peptide (17 aa)	Stomach	Secretion of gastric acid, gastric mucosal growth
Ghrelin (GHRP)	Peptide (28 aa)	Anterior pituitary	Secretion of GH
KIDNEY			
1,25-(OH) ₂ cholecalciferol	Sterol	Intestine Bone	Facilitation of calcium and phosphorus absorption; increase in bone resorption in conjunction with PTH
Erythropoietin	Peptide (165 aa)	Kidney	Increase in reabsorption of filtered calcium
Renin-angiotensin-aldosterone system	Peptides (renin, 297 aa; Ang I, 10 aa; Ang II, 8 aa, produced from Ang I by angiotensin converting enzyme)	Bone marrow Renin (from kidney) catalyzes hydrolysis of angiotensinogen (from liver, 485aa) to Ang I in the intravascular space	Stimulation of red cell formation Ang II increases blood pressure and stimulates secretion of aldosterone (see adrenal)

Continued

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LIVER			
IGF-I, formerly called somatomedin IGF-II	Peptide (70 aa) Peptide (67 aa)	Most cells Most cells	Stimulation of cellular and linear growth Insulin-like activity
HEART			
B-type natriuretic peptide (BNP)	Peptide with an intrachain disulfide bond (32 aa)	Vascular, renal, and adrenal tissues	Regulation of blood volume and blood pressure
ADIPOSE TISSUE			
Adiponectin	Peptide oligomers of 30 kD subunits	Muscle	Increases fatty acid oxidation
Leptin	Peptide (167 aa)	Liver	Suppresses glucose formation
Resistin	Peptide (94 aa)	Hypothalamus	Inhibition of appetite, stimulation of metabolism
Resistin	Peptide (94 aa)	Liver	Insulin resistance
MULTIPLE CELL TYPES			
Parathyroid hormone-related peptide (PTH-RP)	Peptides (139, 141, 173 aa)	Kidney, bone	Physiological function conjectural; PTH-like actions; tumor marker
MONOCYTES/LYMPHOCYTES/MACROPHAGES			
Cytokines (e.g., interleukins 1-18, tumor necrosis factor, interferons)	Peptides	Many	Stimulation or inhibition of cellular growth; other

*aa, Amino acid residues.
†Also produced by gastrointestinal tract and pancreas.
‡Glycoprotein hormones composed of two dissimilar peptides. The α -chains are similar in structure or identical; the β -chains differ among hormones and confer specificity.
§Androstanedione is also produced in the ovary and testis.
||Two chains linked by two disulfide bonds: α , 21aa; β , 30aa.

Regulation of Serum Calcium

A calcium sensing receptor (CaSR) on the parathyroid gland recognizes the ambient concentration of ionized calcium and regulates synthesis and secretion of parathyroid hormone (PTH). When the concentration of ionized calcium falls (so imperceptibly that most analytical methods are not sensitive enough to detect the change), PTH synthesis and secretion are stimulated. This additional PTH will attempt to restore serum (free) calcium by enhancing renal tubular reabsorption of calcium and also calcium efflux from the skeleton. PTH in turn catalyzes the synthesis of the renal hormone calcitriol (1,25-dihydroxyvitamin D), which acts on the intestine to increase absorption of calcium. These very rapid responses of PTH and calcitriol quickly restore the free calcium to a concentration at which the CaSR is no longer activated and both PTH and calcitriol synthesis and secretion return to basal levels.

Regulation of Water and Electrolyte Metabolism

This pathway is regulated by aldosterone from the adrenal gland, renin from the kidney, and vasopressin (antidiuretic hormone [ADH]) from the posterior pituitary gland.

Regulation of Energy Production, Use and Storage

Under normal conditions, these functions of hormones are under tight hormonal control. Under conditions of changing demands, usually for more energy, such as exercise, starvation, infection, trauma, or emotional stress, the circulating concentrations of many hormones are increased to control not only

circulating concentrations of nutrients but also the metabolism of these nutrients into needed energy. This very complex activity, which may involve hormones from different organs, is also under neurological control with a number of neuro-endocrine hormones participating actively in this integrative metabolic process that affects most organs in the body and modulates, for example, heart rate, sweating, fertility, and reproduction.

HORMONE RECEPTORS

The “unique” or specific action of a hormone on its target tissue is a function of the interaction between the hormone and its receptor. As previously discussed, there are several types of hormone-receptor interactions.^{2,4,6,12} The hormone-receptor complex provides the very high specificity of the action of the hormone, allowing the target tissue to recognize the appropriate hormone from among the many molecules to which it is exposed. This is essential since hormones generally circulate in picomolar or nanomolar concentrations (10^{-9} to 10^{-12} mol/L). As noted, hormone receptors may be on the cell surface or intracellular within the cytoplasm or nucleus.

Cell-Surface Receptors

Peptide hormones bind to cell-surface receptors and the conformational change resulting from this binding activates an effector system, which is in turn responsible for the downstream actions of the hormone (Figure 25-2).^{8,9} For most peptide hormones, the intracellular effector that is activated by the hormone-receptor interaction is a specific G-protein (guanyl-nucleotide-binding protein) and the receptors

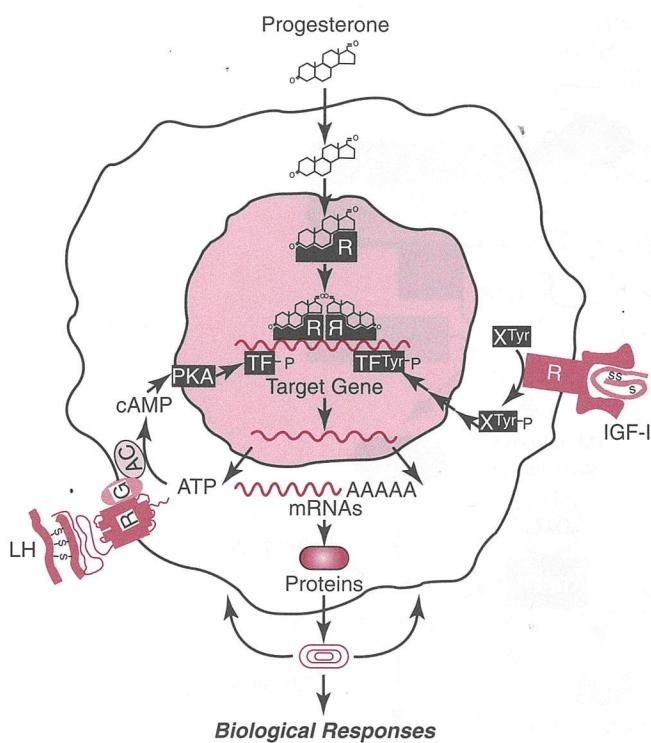


Figure 25-2 Hormonal signaling by cell-surface and intracellular receptors. The receptors for the water-soluble polypeptide hormones, LH, and insulin-like growth factor (IGF)-I, are integral membrane proteins located at the cell surface. They bind the hormone using extracellular sequences and transduce a signal by the generation of second messengers, cAMP for the LH receptor, and tyrosine-phosphorylated substrates for the IGF-I receptor. Although effects on gene expression are indicated, direct effects on cellular proteins (e.g., ion channels) are also observed. In contrast, the receptor for the lipophilic steroid hormone progesterone resides in the cell nucleus. It binds the hormone, and becomes activated and capable of directly modulating target gene transcription. TF, Transcription factor; R, receptor molecule. (From Conn PM, Melmed S. Textbook of endocrinology. Totowa, NJ: Humana Press, 1997.)

are called G-protein-coupled receptors (GPCRs, Figure 25-3).^{3,7,10,13} GPCRs are hepta-helical molecules with seven membrane-spanning domains. The amino terminus is extracellular and the carboxy terminus is intracellular. The major structural classes of GPCRs have been identified, each containing receptors for specific subsets of hormones (Figure 25-4). Group I is the largest group containing receptors for many peptide hormones and catecholamines. Group II contains receptors for the family of gastrointestinal hormones (secretin, glucagon, vasoactive intestinal polypeptide). Group III contains the CaSR and the glutamate receptor. Stimulation of a G-protein initiates the intracellular processes of signal transduction, which characterize the specific action of the hormone. G-proteins are composed of α , β , and γ -subunits and are classified according to the α subunit, of which 20 have been identified to date (Figure 25-4). Among the G-proteins, some stimulate adenylyl cyclase (G_s type of G-proteins) and others

inhibit it (G_i type). Some nonpeptide hormones also use cell-surface receptors.

Intracellular Receptors

Lipid-soluble hormones are transported in plasma bound to carrier proteins with only a small fraction of the hormone being in the free or unbound state. The free hormone enters the cell via passive diffusion and binds to intracellular receptors in the cytoplasm or the nucleus (see Figure 25-2). These receptors are characterized by a hormone-binding domain, a DNA-binding domain, and an amino-terminal variable domain. Just as the interaction of protein or polypeptide hormones with cell-surface receptors changes the conformation of the receptor protein, the binding of a lipid-soluble hormone with its specific hormone-binding domain on the intracellular receptor changes the molecular conformation of the intracellular receptor. This conformational change, called activation of the receptor, enables the hormone-receptor complex to bind to specific regulatory DNA sequences of a target gene permitting control of specific gene expression.⁵ For the receptor with bound hormone to bind to nuclear DNA, it must move to the nucleus if it was not already there.

POSTRECEPTOR ACTIONS OF HORMONES

Cell surface and intracellular receptors have different postreceptor actions.

Cell-Surface Receptors

Once GPCRs are occupied by a hormone, the G-protein subunits begin a cascade of activation of specific enzymes that generate molecules that serve as second messengers to effect the hormone response. The best known of these are (1) adenylyl cyclase, which generates cyclic adenosine monophosphate (cAMP), and (2) phospholipase C, which generates inositol 1, 4, 5-triphosphate (IP₃) and diacylglycerol. The production of second messengers, and the subsequent magnitude of the effect of the hormone, is a function of the amount of hormone bound to the GPCR. The binding of a small number of hormone molecules on the cell surface leads to the production of many molecules of second messenger, thus amplifying the signal sent by the hormone (which is thought of as the first messenger).

cAMP-dependent protein kinases are a family of enzymes that, in the presence of cAMP, phosphorylate a number of intracellular enzymes and other proteins to activate or inactivate the function of these enzymes and proteins thereby regulating their function. As a further means of regulating hormone action, these cAMP-dependent kinases consist of two catalytic and two regulatory subunits. The regulatory subunits exist as a dimer that binds molecules of cAMP, and the binding of cAMP releases the catalytic subunits, which are then active as phosphorylating enzymes.

Phospholipase C acts on inositol phospholipids within the cell membrane to produce IP₃ and diacylglycerol. An effect of IP₃ is to open up ion channels to facilitate entry of calcium into the cytoplasm where it appears to act as a second messenger.

The insulin receptor represents a class of cell-surface receptors that contain intrinsic hormone-activated tyrosine kinase activity and are thought to not need a small molecule that functions as a soluble second messenger.¹¹ The structure of the insulin receptor serves as the prototype of this kind of

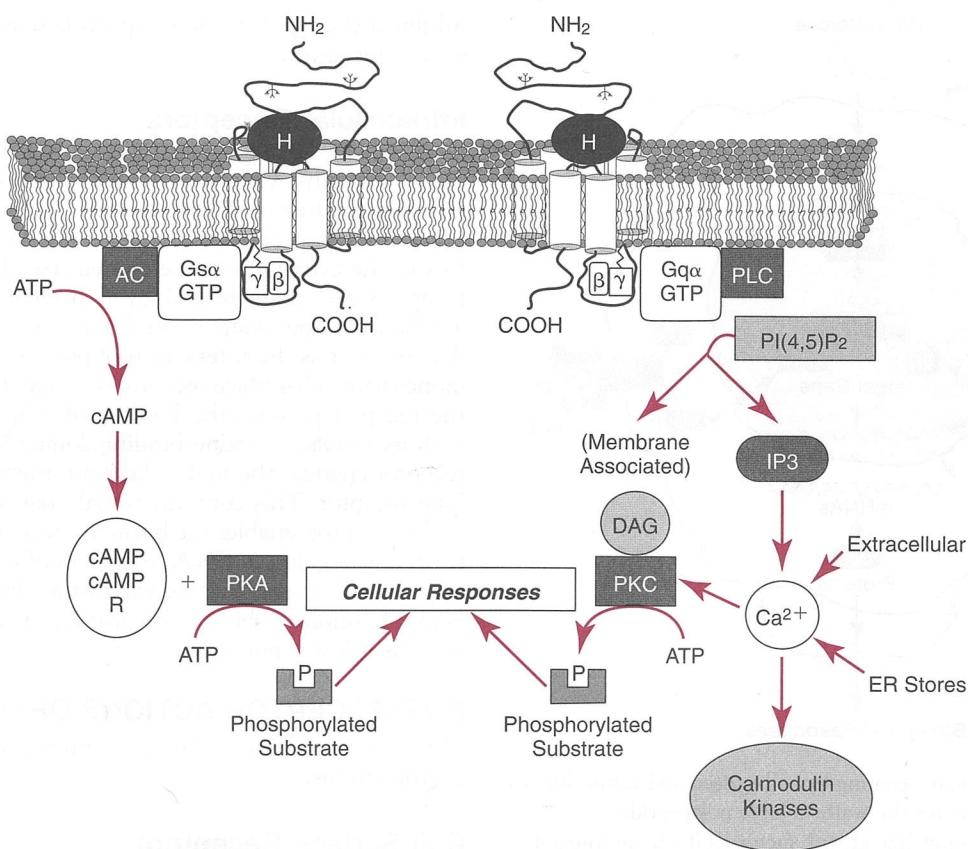


Figure 25-3 Signal transduction by cell-surface receptors that are coupled to G-proteins. Two seven-transmembrane domains, coupled to different G-proteins (G_s and G_q) are shown. Activation of G_s leads to stimulation of the effector enzyme adenylate cyclase and the production of a cAMP second messenger, causing the activation of protein kinase A (PKA) and the initiation of potential phosphorylation cascades. Activation of G_q leads to stimulation of the effector enzyme phospholipase C- β and the production of IP3 and diacylglycerol (DAG) second messengers, one effect of which is to activate protein kinase C (PKC) and initiate a potential phosphorylation cascade. (From Conn PM, Melmed S, eds. Textbook of endocrinology. Totowa, NJ: Humana Press, 1997.)

receptor. It consists of two α - and two β -subunits joined by disulfide bridges. The extracellular, hormone-binding domains are the α -subunits, whereas the β -subunits are intracellular. They contain an adenosine triphosphate (ATP)-binding site and a catalytic kinase domain through which tyrosine kinase is activated immediately upon insulin binding to the receptor. The tyrosine kinase modifies the activities of intracellular proteins by phosphorylating them, thereby transmitting the "message" from insulin to the cell.

Since hormones serve a regulatory function, there are many self-limiting steps in the above processes. For cAMP, this involves the inactivation of G-protein stimulation of adenylate cyclase by guanosinetriphosphatase (GTPase). In the absence of hormone interaction with the GPCR (basal or unstimulated state), G_s is bound to guanosine diphosphate (GDP). Once the hormone is bound to the receptor, GDP is released from G_s and replaced by GTP and the G_s -GTP complex activates adenylate cyclase (Figure 25-5). The G_s -GTP complex is inactivated by GTPase restoring the G_s -GDP state that cannot stimulate formation of cAMP until further hormone binding to the GPCR takes place. Within a few minutes (or less) of the hormone-GPCR interaction and the initiation of hormone

action, the receptor is phosphorylated by protein kinase A and protein kinase C. This phosphorylation of the hormone receptor permits internalization of the complex from the cell surface into the inside of the cell. Then dephosphorylation occurs permitting degradation of the hormone and recycling of the GPCR to its original transmembrane location, awaiting coupling with more hormone.

Intracellular Receptors

Physiologically, lipid-soluble hormones bind to the hormone-binding domain of cytosolic or nuclear receptors.^{8,9} This results in a conformational change that enables the hormone-receptor complex to bind to specific regulatory DNA sequences in the 5' end of the target gene.⁵ The binding specificity of the (hormone-bound) receptor for specific regions of the DNA of the target gene is determined by so-called zinc-finger structures in the receptor's DNA-binding domain. It is the binding of the hormone-receptor complex to DNA regulatory elements that either increases or represses gene transcription. The messenger RNA, which is either increased or decreased by the hormone-receptor binding to the target gene, regulates the synthesis of specific proteins that mediate the hormone's