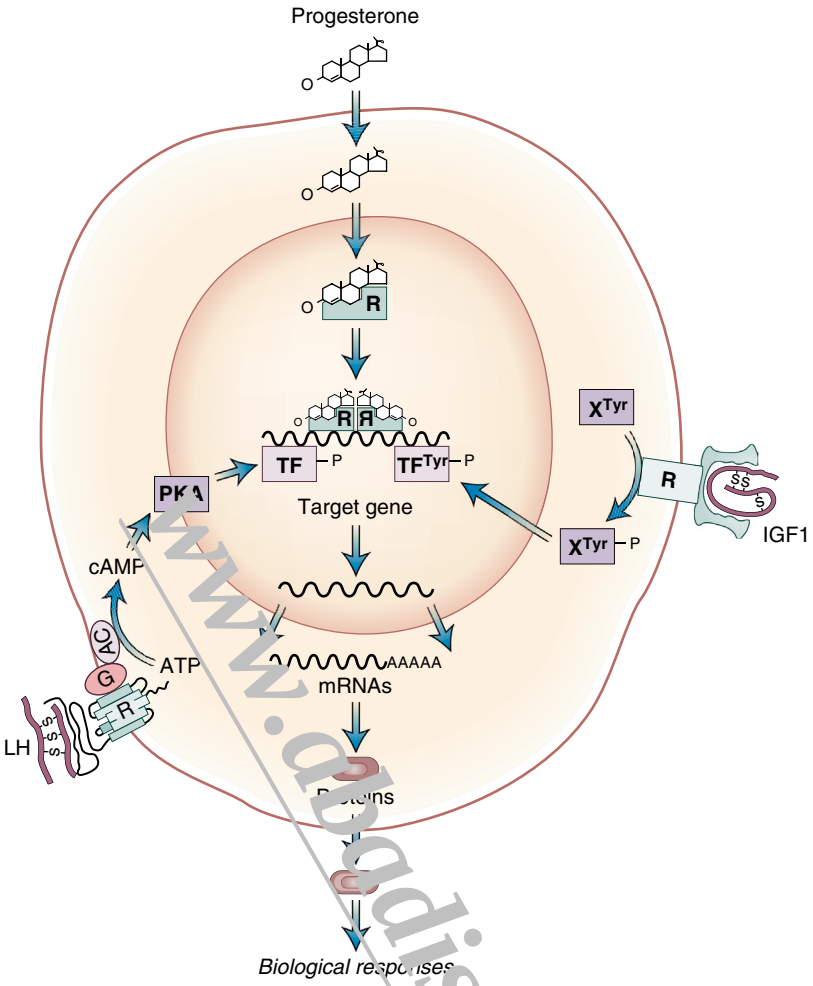


• **Fig. 1.2** Hormonal signaling by cell surface and intracellular receptors. The receptors for the water-soluble polypeptide hormones, luteinizing hormone (LH), and insulin-like growth factor 1 (IGF1) are integral membrane proteins located at the cell surface. They bind the hormone-utilizing extracellular sequences and transduce a signal by the generation of second messengers: cyclic adenosine monophosphate (cAMP) for the LH receptor and tyrosine-phosphorylated substrates for the IGF1 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. *AC,* Adenylyl cyclase; *ATP,* adenosine triphosphate; *G,* heterotrimeric G protein; *mRNAs,* messenger RNAs; *PKA,* protein kinase A; *R,* receptor molecule; *TF,* transcription factor; *Tyr,* tyrosine found in protein X; *X,* unknown protein substrate. (From Mayo K. Receptors: molecular mediators of hormone action. In: Conn PM, Melmed S, eds. *Endocrinology: Basic and Clinical Principles.* Totowa, NJ: Humana Press; 1997:11.)

www.dbadistrib.pub

genetic programs or receptor-receptor interactions at the cell surface (e.g., hetero-oligomerization of dopamine D2 with somatostatin receptor, or insulin with IGF1 receptor) may also confer a specific cellular response to a hormone and provide an additive cellular effect.[10] In addition, effector protein expression may differ in select cells to modulate hormonal response. For example, the glucose transporter-4 protein, which leads to insulin-mediated glucose uptake, is most abundantly expressed in muscle, hepatic, and adipose tissues, causing these tissues to be the most sensitive tissues for insulin-mediated glucose disposal.

A final mechanism of nuclear receptor modulation is prereceptor regulation by intracellular enzymes that convert circulating molecules to more or less potent hormones. In addition to the activation of T_4 and testosterone described earlier, selective hormone inactivation occurs in some cells. In the distal nephron, 11β-hydroxysteroid dehydrogenase type 2 converts the mineralocorticoid-receptor ligand cortisol to inactive cortisone, thus preventing receptor activation. This mechanism allows aldosterone, which is not a substrate for the enzyme, to regulate renal mineralocorticoid activity despite circulating aldosterone concentrations 1000 times lower than those of cortisol.

Control of Hormone Secretion

Anatomically distinct endocrine glands are composed of highly differentiated cells that synthesize, store, and secrete hormones. Circulating hormone concentrations are a function of glandular secretory patterns and hormone clearance rates. Hormone secretion is tightly regulated to attain circulating levels most conducive to eliciting the appropriate target tissue response. For example, longitudinal bone growth is initiated and maintained by exquisitely regulated levels of circulating GH, yet mild GH hypersecretion

TABLE 1.1 Selected Diseases Caused by Mutations in G Protein–Coupled Receptors

Condition[a]	Receptor	Inheritance	Δ Function[b]
Retinitis pigmentosa	Rhodopsin	AD/AR	Loss
Nephrogenic AVP deficiency	Vasopressin V2	X-linked	Loss
Familial glucocorticoid deficiency	ACTH	AR	Loss
Color blindness	Red/green opsins	X-linked	Loss
Familial precocious puberty	LH	AD (male)	Gain
Familial hypercalcemia	Ca^{2+} sensing	AD	Loss
Neonatal severe hyperparathyroidism	Ca^{2+} sensing	AR	Loss
Autosomal-dominant hypocalcemia	Ca^{2+} sensing	AD	Gain
Congenital hyperthyroidism	TSH	AD	Gain
Hyperfunctioning thyroid adenoma	TSH	Somatic	Gain
Metaphyseal chondrodysplasia	PTH-PTHrP	Somatic	Gain
Hirschsprung disease	Endothelin-B	Multigenic	Loss
Coat color alteration (*E* locus, mice)	MSH	AD/AR	Loss and gain
Dwarfism (*little* locus, mice)	GHRH	AR	Loss

[a]All are human conditions with the exception of the final two entries, which refer to the mouse.

[b]*Loss of function* refers to inactivating mutations of the receptor, and *gain of function* refers to activating mutations.

ACTH, Adrenocorticotropic hormone; *AD,* autosomal-dominant inheritance; *AR,* autosomal-recessive inheritance; *AVP,* arginine vasopressin; *GHRH,* growth hormone–releasing hormone; *LH,* luteinizing hormone; *MSH,* melanocyte-stimulating hormone; *PTH-PTHrP,* parathyroid hormone and parathyroid hormone–related peptide; *TSH,* thyroid-stimulating hormone.

From Mayo K. Receptors: molecular mediators of hormone action. In: Conn PM, Melmed S, eds. *Endocrinology: Basic and Clinical Principles.* Totowa, NJ: Humana Press; 1997:27.

TABLE 1.2 Selected Diseases Caused by Mutations in Nuclear Receptors

Condition[a]	Receptor	NR #	Inheritance	Δ Function[b]
Androgen insensitivity (complete/partial)	Androgen	NR3C4	X-limited	Loss
Resistance to thyroid hormone (generalized/pituitary)	Thyroid-beta	NR1A2	AD or AR	Dominant-negative or loss
Resistance to thyroid hormone (generalized)	Thyroid-alpha	NR1A1	AD or AR	Dominant-negative or loss
Estrogen insensitivity	Estrogen-alpha	NR3A1	AR	Loss
Glucocorticoid resistance	Glucocorticoid	NR3C1	AD or AR	Dominant-negative or loss (incomplete)
Pregnancy-induced severe hypertension	Mineralocorticoid	NR3C2	AD	Gain (progesterone responsive)
Vitamin D–dependent (resistant) rickets type 2A	Vitamin D	NR1I1	AR or rarely AD	Loss or rarely dominant-negative
Gonadal failure with/without adrenal insufficiency	Steroidogenic factor 1 (SF1)	NR5A1	AR or rarely AD	Loss or rarely dominant-negative
Adrenal hypoplasia congenita/ hypogonadotrophic hypogonadism (AHC/HH)	Dosage-sensitive sex reversal AHC X-chromosome (DAX1)	NR0B1	X-limited	Loss

[a]All are human conditions with the exception of the final two entries, which refer to the mouse.

[b]*Loss of function* refers to inactivating mutations of the receptor, and *gain of function* refers to activating mutations.

AD, Autosomal-dominant inheritance; *AR,* autosomal-recessive inheritance; *NR,* nuclear receptor

www.abadieb.pub

results in gigantism, and GH deficiency causes growth retardation. Ambient circulating hormone concentrations are not uniform, and secretion patterns determine appropriate physiologic function. Thus, insulin secretion occurs in short pulses elicited by nutrient and other signals; gonadotrophin secretion is episodic, determined by a hypothalamic pulse generator; and PRL secretion appears to be relatively continuous, with secretory peaks elicited during suckling.

Hormone secretion is also characterized by rhythmic patterns. Circadian rhythms serve as adaptive responses to environmental signals and are controlled by a circadian timing mechanism.[11] Light is the major environmental cue adjusting the endogenous clock. The retinohypothalamic tract entrains circadian pulse generators situated within hypothalamic suprachiasmatic nuclei. These signals determine timing mechanisms for the sleep-wake cycle and patterns of hormone secretion and action. Disturbed circadian timing results in hormonal dysfunction and may also be reflective of entrainment or pulse generator lesions. For example, adult GH deficiency due to a damaged hypothalamus or pituitary is associated with elevations in integrated 24-hour leptin concentrations and decreased leptin pulsatility, yet preserved circadian rhythm of leptin. GH replacement restores leptin pulsatility, promoting the loss of body fat mass.[12] Sleep is an important cue regulating hormone pulsatility. About 70% of overall GH secretion occurs during slow-wave sleep, and increasing age is associated with declining slow-wave sleep and a concomitant decline in GH and elevation of cortisol secretion.[13] Most pituitary hormones are secreted in a circadian (day-night) rhythm, best exemplified by ACTH peaks before 9 AM, whereas ovarian steroids follow a 28-day menstrual rhythm. Disrupted episodic rhythms are often a hallmark of endocrine dysfunction. For example, loss of circadian ACTH secretion with high midnight cortisol levels is a feature of Cushing disease.

Hormone secretion is induced by multiple specific biochemical and neural signals. Integration of these stimuli results in the net temporal and quantitative secretion of the hormone (Fig. 1.3). Signals elicited by hypothalamic hormones (growth hormone–releasing hormone [GHRH], somatostatin), peripheral hormones (IGF1, sex steroids, thyroid hormone), nutrients, adrenergic pathways, stress, and other neuropeptides all converge on the somatotroph cell, resulting in the ultimate pattern and quantity of GH secretion. Networks of reciprocal interactions allow for dynamic adaptation and shifts in environmental signals. These regulatory systems involve the hypothalamic, pituitary, and target endocrine glands, as well as the adipocytes and lymphocytes. Peripheral inflammation and stress elicit cytokine signals that interface with the neuroendocrine system, resulting in hypothalamic-pituitary axis activation. Parathyroid and pancreatic secreting cells are less tightly controlled by the hypothalamus, but their functions are tightly regulated by the distal effects they elicit. For example, PTH secretion is induced when serum calcium levels fall, and the signal for sustained PTH secretion is abrogated by rising calcium levels, whereas insulin secretion is induced when blood glucose rises but suppressed when glucose concentrations fall.

Several tiers of control subserve the ultimate net glandular secretion. First, central nervous system signals, including afferent stimuli, neuropeptides, and stress, signal the synthesis and secretion of hypothalamic hormones and neuropeptides (Fig. 1.4). Four hypothalamic-releasing hormones (GHRH, corticotrophin-releasing hormone [CRH], thyrotrophin-releasing hormone [TRH], and gonadotrophin-releasing hormone [GnRH]) traverse the hypothalamic portal vessels and impinge upon their respective transmembrane trophic hormone–secreting cell receptors. These distinct cells express GH, ACTH, TSH, and gonadotrophins, respectively.[14] By contrast, hypothalamic somatostatin and dopamine suppress GH or PRL and TSH secretion, respectively. Trophic hormones maintain the structural and functional integrity of endocrine organs, including the thyroid and adrenal glands and the gonads. Target hormones, in turn, serve as powerful negative feedback regulators of their respective trophic hormones, often also suppressing the secretion of hypothalamic-releasing hormones. In certain circumstances (e.g., during puberty), peripheral sex steroids may positively induce the hypothalamic-pituitary–target gland axis. For example, LH induces ovarian estrogen secretion, which feeds back positively to induce further LH release. Pituitary hormones themselves, in a short feedback loop, also regulate their own respective hypothalamic-controlling hormones. Hypothalamic-releasing hormones are secreted in nanogram amounts and have short half-lives of a few minutes. Anterior pituitary hormones are produced in microgram amounts and have longer half-lives, but peripheral hormones can be produced in up to milligram amounts daily, with much longer half-lives.

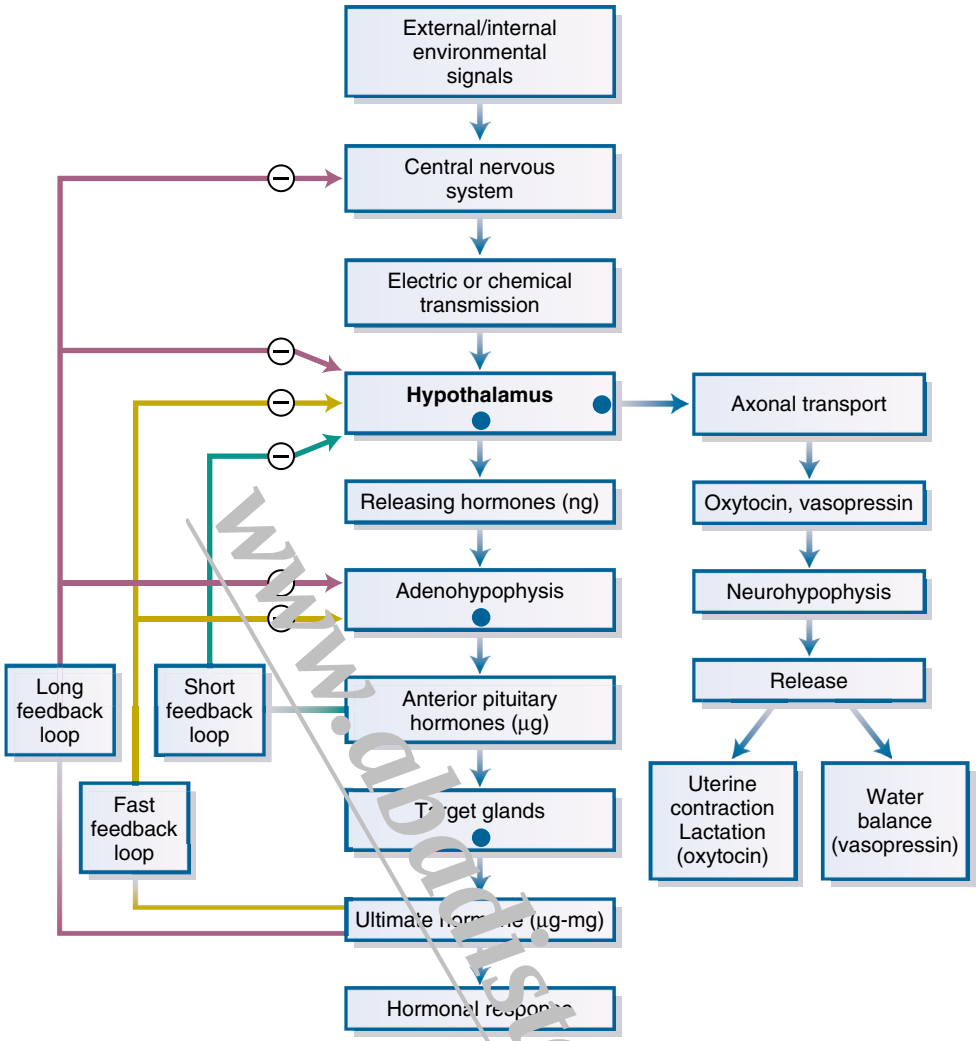
A further level of secretion control occurs within the gland itself. Intraglandular paracrine or autocrine growth peptides serve to autoregulate pituitary hormone secretion, as exemplified by epidermal growth factor (EGF) control of PRL or IGF1 control of GH secretion. Molecules within the endocrine cell may also subserve an intracellular feedback loop. For example, corticotroph SOCS-3 induction by gp130-linked cytokines serves to abrogate the ligand-induced JAK-STAT cascade and block pro-opiomelanocortin (POMC) transcription and ACTH secretion. This rapid on-off regulation of ACTH secretion provides plasticity for the endocrine response to changes in environmental signaling and serves to maintain homeostatic integrity.[15]

In addition to the central nervous system–neuroendocrine interface mediated by hypothalamic chemical signal transduction, the central nervous system may directly control several hormonal secretory processes. For example, posterior pituitary hormone secretion occurs as direct efferent neural extensions; postganglionic sympathetic nerves regulate rapid changes in renin, insulin, and glucagon secretion; and preganglionic sympathetic nerves signal to adrenal medullary cells, eliciting epinephrine release.

Hormone Measurement

Endocrine function can be assessed by measuring basal circulating hormone levels, stimulated or suppressed hormone concentrations, or hormone-binding proteins. Alternatively, hormone function in target tissues can be assessed. When a feedback loop exists between the hypothalamic-pituitary axis and a target gland, the circulating level of the pituitary trophic hormone, such as TSH or ACTH, is typically an exquisitely sensitive index of deficient or excessive function of the thyroid or the adrenal cortex, respectively. Meaningful strategies for timing hormonal measurements vary from system to system. In some cases, circulating hormone concentrations can be measured in randomly collected serum samples. This measurement, when standardized for fasting, environmental stress, age, and sex, is reflective of true hormone concentrations only when levels do not fluctuate appreciably. For example, levels of thyroid hormones, PRL, and IGF1 can be accurately assessed in fasting morning serum samples. On the other hand, when hormone secretion is clearly episodic, timed samples may be required over a defined time course to reflect hormone bioavailability. Thus, early-morning and late-evening cortisol

www.ebadistel.pub



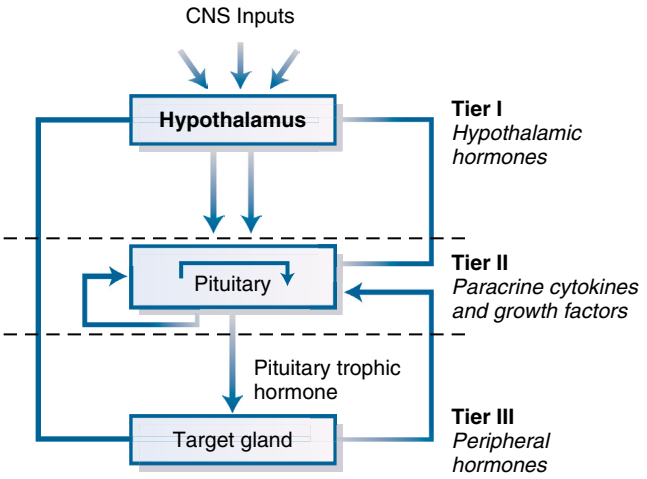
www.abdisteb.pk

• **Fig. 1.3** Peripheral feedback mechanism and a millionfold amplifying cascade of hormonal signals. Environmental signals are transmitted to the central nervous system, which innervates the hypothalamus, which responds by secreting nanogram amounts of a specific releasing hormone. These are transported down a closed portal system, pass the blood-brain barrier at either end through fenestrations, and bind to specific anterior pituitary cell membrane receptors to elicit secretion of micrograms of specific anterior pituitary hormones. These hormones enter the venous circulation through fenestrated local capillaries, bind to specific target gland receptors, trigger release of micrograms to milligrams of daily hormone amounts, and elicit responses by binding to receptors in distal target tissues. Peripheral hormone receptors enable widespread cell signaling by a single initiating environmental signal, thus facilitating intimate homeostatic association with the external environment. Arrows with a large dot at their origin indicate a secretory process. (From Normal AW, Litwack G. *Hormones.* 2nd ed. New York: Academic Press; 1997:14.)

measurements are most appropriate. A 24-hour sampling for GH measurements, with samples collected every 2, 10, or 20 minutes, is expensive and cumbersome, yet it may yield valuable diagnostic information. Random sampling may also reflect secretion peaks or nadirs, thus confounding adequate interpretation of results.

In general, confirmation of failed glandular function is made by attempting to evoke hormone secretion by recognized stimuli. Testing of pituitary hormone reserve may be accomplished by injecting appropriate hypothalamic-releasing hormones. Injection of trophic hormones, including TSH and ACTH, evokes specific target gland hormone secretion. Pharmacologic stimuli (e.g., macimorelin for GH secretion; metoclopramide for induction of PRL secretion) may also be useful tests of hormone reserve. By contrast, hormone hypersecretion can best be diagnosed by suppressing glandular function. Failure to appropriately suppress GH levels after a standardized glucose load implies inappropriate GH hypersecretion. Failure to suppress insulin secretion during hypoglycemia indicates inappropriate hypersecretion of insulin and should prompt a search for the cause, such as an insulin-secreting tumor.

Radioimmunoassays use highly specific antibodies that uniquely recognize the hormone, or a hormone fragment, to quantify hormone levels. Enzyme-linked immunosorbent assays (ELISAs) use enzyme-conjugated antibodies, and enzyme activity is reflective of hormone concentration. Immunometric assays use two antibodies directed to different epitopes of a polypeptide hormone: one "capture" antibody that isolates the hormone to a solid support and one "signal" antibody coupled to a signal-generating molecule such as acridinium ester or an enzyme. These sensitive techniques have allowed ultrasensitive measurements of



• **Fig. 1.4** Model for regulation of anterior pituitary hormone secretion by three tiers of control. Hypothalamic hormones impinge directly on their respective target cells. Intrapituitary cytokines and growth factors regulate trophic cell function by paracrine (and autocrine) control. Peripheral hormones exert negative feedback inhibition of respective pituitary trophic hormone synthesis and secretion. *CNS,* Central nervous system. (From Ray D, Melmed S. Pituitary cytokine and growth factor expression and action. *Endocr Rev.* 1997;18:206–228.)

physiologic hormone concentrations. Hormone-specific receptors may be used in place of the antibody in a radioreceptor assay. However, all antibody-based assays may be subject to artifact, which should be kept in mind, especially when the assay results are discordant with the clinical picture. Many hormones, in particular small molecules such as steroid hormones, can now be measured with high sensitivity using liquid chromatography–mass spectrometry technology.

Endocrine Diseases

Endocrine diseases fall into four broad categories: (1) hormone overproduction, (2) hormone underproduction, (3) altered tissue responses to hormones, and (4) tumors of endocrine glands. An additional, albeit atypical, fifth category is exemplified by consumptive hypothyroidism, in which overexpression of a hormone-inactivating enzyme in a tumor leads to hormone deficiency through inactivation of thyroid hormones. Other disorders of inadequate hormone inactivation include apparent mineralocorticoid excess, vitamin D 24-hydroxylase deficiency, and X-linked hypophosphatemic rickets (PHEX deficiency).

Hormone Overproduction

Occasionally, hormones are secreted in increased amounts because of genetic abnormalities that cause abnormal regulation of hormone synthesis or release. For example, in glucocorticoid-remediable hyperaldosteronism, an abnormal chromosomal crossover event creates a fusion gene that encodes a protein with aldosterone synthase activity under the control of the ACTH-regulated 11β-hydroxylase promoter. More often, diseases of hormone overproduction are associated with an increase in the total number of hormone-producing cells. For example, hyperthyroidism associated with Graves disease, in which antibodies mimic TSH and activate the TSH receptors on thyroid cells, is accompanied by an increase in thyroid cell proliferation, synthesis, and release of thyroid hormones. In this example, the increase in thyroid cell number represents a polyclonal expansion of thyroid cells, in which large numbers of thyroid cells proliferate in response to an abnormal stimulus. However, most endocrine tumors are not polyclonal expansions but rather represent monoclonal expansions of a single mutated cell. Pituitary and parathyroid tumors, for example, are usually monoclonal expansions caused by somatic mutations in a spectrum of tumor suppressor genes and proto-oncogenes. These mutations lead to an increase in the proliferation or survival of the mutant cells. Sometimes this proliferation is associated with abnormal secretion of hormones from each tumor cell. For example, mutant $G_s\alpha$ proteins in somatotrophs can lead to both increased cellular proliferation and increased secretion of GH from the monoclonal tumor.

Hormone Underproduction

Hormone underproduction can result from gland destruction or ablation prompted by several processes. For example, these may range from surgical removal of parathyroid glands during neck surgery to tuberculous destruction of adrenal glands to iron deposition in pancreatic β-cells of islets in hemochromatosis. A frequent cause of destruction of hormone-producing cells is autoimmunity. Autoimmune destruction of β-cells in type 1 diabetes mellitus and of thyroid cells in chronic lymphocytic (Hashimoto) thyroiditis are two of the most common disorders treated by endocrinologists. Direct passage of insulin fragments by exocytosis from pancreatic islets to lymphoid tissue may trigger autoimmune diabetes in mice.[16] Multiple genetic abnormalities also lead to decreased hormone production. These disorders can result from abnormal development of hormone-producing cells (e.g., hypogonadotrophic hypogonadism caused by *KAL* gene mutations), from abnormal synthesis of hormones (e.g., deletion of the GH gene), or from abnormal regulation of hormone secretion (e.g., the hypocalcemia associated with decreased PTH secretion due to activating mutations of the parathyroid cell's calcium-sensing receptor). Drugs are important causes of endocrine gland dysfunction, as exemplified by immune checkpoint inhibitors leading to multiple inflammatory or immune-mediated endocrinopathies.

Altered Tissue Responses to Hormones

Resistance to hormones can be caused by a variety of genetic disorders. Examples include mutations in the GH receptor in Laron dwarfism and mutations in the $G_s\alpha$ gene in the hypocalcemia of pseudohypoparathyroidism type 1A. Insulin resistance in muscle and liver central to the cause of type 2 diabetes mellitus is complex in origin, resulting from inherited variations in many genes, as well as from theoretically reversible physiologic stresses. Type 2 diabetes is also an example of a disease in which end-organ insensitivity is worsened by signals from other organs, in this case by signals originating in fat cells. In other cases, the target organ of hormone action is more directly abnormal, as in PTH resistance occurring with renal failure.

Increased end-organ function can be caused by mutations in signal reception and propagation. For example, activating mutations in TSH, LH, and PTH receptors can cause increased activity of thyroid cells, Leydig cells, and osteoblasts, even in the absence of ligand. Similarly, activating mutations in the $G_s\alpha$ protein can cause precocious puberty, hyperthyroidism, and acromegaly in McCune-Albright syndrome.

www.abdistep.pub

Tumors of Endocrine Glands

Tumors of the endocrine glands often result in hormone overproduction. Some endocrine gland tumors produce little if any hormone but cause disease by local, compressive symptoms or by metastatic spread. Examples include so-called nonfunctioning pituitary adenomas, which are usually benign but can cause a variety of symptoms due to compression of adjacent vital structures, and thyroid cancer, which can metastasize without causing hyperthyroidism.

Excessive Hormone Inactivation or Destruction

Although most enzymes important for endocrine systems activate a prohormone or precursor protein, there are also those whose function is to inactivate the hormone in a physiologically regulated fashion. An example is the type 3 iodothyronine deiodinase (D3), which inactivates T_3 and T_4 by removing an inner ring iodine atom from the iodothyronine, thereby generating the hormonally inactive reverse T3 (rT_3). *Consumptive hypothyroidism* is a rare paraneoplastic condition, most commonly associated with infantile hemangiomas, caused by overexpression of D3 and an inactivation rate of thyroid hormones that exceeds its production.[17,18] Furthermore, D3 may also be induced in other tumors by tyrosine kinase inhibitors. In theory, accelerated destruction of other hormones could occur from similar processes as yet to be determined.

Diagnostic and Therapeutic Uses of Hormones

In general, hormones are used pharmacologically for their replacement or suppressive effects. Hormones may also be used for diagnostic stimulatory effects (e.g., hypothalamic hormones) to evoke target-organ responses or to diagnose endocrine hyperfunction by suppressing hormone hypersecretion (e.g., T_3). Ablation of endocrine gland function due to genetic or acquired causes can be restored by hormone replacement therapy. Thyroid hormones and some steroids can be replaced orally, whereas peptide hormones and analogues (e.g., insulin, PTH, GH) are administered parenterally or absorbed through mucous membranes (e.g., inhaled insulin, intranasal desmopressin). Recently, oral small molecules behaving as polypeptide hormone-receptor agonists (e.g., oral somatostatin) and oral formulations of polypeptide hormones have been introduced.[19] Gastrointestinal absorption and first-pass kinetics determine oral hormone dosage and availability. Physiologic replacement can both achieve appropriate hormone levels (e.g., thyroid) and approximate hormone secretory patterns (e.g., GnRH delivered intermittently via a pump). Cellular replacement approaches may ultimately provide normal physiologic hormone levels and are also under development, such as with pancreatic β-cell replacement for type 1 diabetes. Hormones can also be used to treat diseases associated with glandular hyperfunction. Long-acting depot preparations of somatostatin receptor ligands suppress GH hypersecretion in acromegaly and hypersecretion of diarrhea-causing mediators from neuroendocrine tumors of the pancreas and small intestine. Estrogen receptor antagonists (e.g., tamoxifen) are useful for some patients with breast cancer, and GnRH analogues may downregulate the gonadotrophin axis and benefit patients with prostate cancer.

Novel formulations of receptor-specific hormone ligands (e.g., estrogen agonists/antagonists, somatostatin receptor subtype-specific ligands, or peroxisome proliferator-activated receptor alpha [PPARα] ligands) result in more selective therapeutic targeting. Modes of hormone injection (e.g., for PTH) may also determine therapeutic specificity and efficacy. Improved hormone delivery systems, including computerized minipumps, intranasal sprays (e.g., for desmopressin), pulmonary inhalers, depot intramuscular injections, and orally bioavailable peptide formulations, will also enhance patient compliance and improve ease of administration. Cell-based therapies using the reprogramming of human cells to perform differentiated functions, either through differentiation of induced pluripotent stem cells or directed differentiation of one somatic cell type into another, are under active investigation.[20] Novel technologies offer the promise of marked prolongation in the half-life of peptide hormones, thereby requiring infrequent administration. Peptide hormones may be modified to slow degradation, or they can be bound to molecules such as fatty acids or engineered antibodies for improved pharmacokinetics, longer half-life, and reduced dosing frequency. For example, a once-weekly preparation of glucagon-like peptide-1 (GLP1) analogue is used in the treatment of type 2 diabetes.

Insulin has also been modified to provide faster- and slower-acting analogues. Preparations with differing pharmacokinetics allow the normal physiology of insulin secretion to be more closely mimicked. Although the delivery of insulin usually still relies on frequent administration, continuous insulin administration via subcutaneous pump infusion enhances therapeutic effectiveness in carefully selected patients. Novel algorithms have now been developed that can couple continuous glucose-sensing technology with variable rates of insulin delivery via insulin pumps, such that the dose of insulin via the pump is automatically adjusted, depending on the continuously monitored interstitial glucose concentrations, to better match immediate patient needs. Implementation of such closed-loop systems has the potential to substantially reduce the burden of this disease, and together these drug modifications and new technologies enhance patient compliance and quality of life. Future approaches may include cell replacement therapies or designer insulins that "sense" ambient glucose and undergo conformational changes, with biologic activity suppressed when glucose concentrations are low.[21]

Hormones are biologically powerful molecules that exert therapeutic benefit and effectively replace pathologic deficits. However, overreplacement is also associated with disease; thus, hormone therapies should not be prescribed without clear-cut indications and should not be administered without careful evaluation by an appropriately qualified medical practitioner.

Future Perspectives

An introduction to the principles underlying endocrinology should emphasize the rapidly changing dynamics of discovery in this field and attempt to foresee what remains to be discovered. New hormones are continually being discovered, from the recent focus on major regulators of metabolism and phosphate homeostasis (FGF19, FGF21, and FGF23) to the continued quest to identify ligands for orphan nuclear and G protein–coupled receptors.[22] Presumably other equally important hormones remain to be discovered. The observation that nuclear receptors, like most transcription factors, bind to thousands of specific sites within the cell's nucleus stresses how little we understand about hormone action. Even the name "nuclear receptors" may be viewed as misleading in the future, as there is an increasing appreciation of the extranuclear, rapid actions of nuclear receptors. Many diagnostic

www.abadistel.pub

tests are severely limited by both technology and our inability to foresee novel diagnostic targets. For example, the "disappearance" of isolated GH deficiency when many children with that diagnosis achieve adulthood means either that we have little understanding of the etiology/pathogenesis of that childhood deficiency or that our diagnostic tools today yield many false-positive results. Although endocrinologists pride themselves on having rational and targeted treatments for many diseases, these treatments seldom address their underlying causes. We have no satisfactory tools for preventing autoimmune endocrine deficiencies or for preventing the benign tumors that underlie many diseases characterized by hormone excess. Treatments for diseases such as type 1 diabetes, although highly effective, are still obtrusive in the lives of our patients.

This new edition communicates major advances that have been made in our field over the past 5 years, yet gaps in our knowledge about endocrinology remain. Importantly, debilitating chronic endocrine illnesses with significant morbidity (e.g., diabetes and Cushing disease), as well as the debilitation associated with aging, still pose significant diagnostic and therapeutic challenges.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for the complete reference list.

www.abadisteb.pub

References

1. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science*. 2006;311:1770–1773.
2. Chawla A, Repa JJ, Evans RM, Mangelsdorf DJ. Nuclear receptors and lipid physiology: opening the X-files. *Science*. 2001;294:1866–1870.
3. Coscia F, Taler-Verčič A, Chang VT, et al. The structure of human thyroglobulin. *Nature*. 2020;578:627–630.
4. Mendel CM, Weisiger RA, Jones AL, Cavalieri RR. Thyroid hormone-binding proteins in plasma facilitate uniform distribution of thyroxine within tissues: a perfused rat liver study. *Endocrinology*. 1987;120:1742–1749.
5. Mendel CM. The free hormone hypothesis: a physiologically based mathematical model. *Endocr Rev*. 1989;10:232–274.
6. Safadi FF, Thornton P, Magiera H, et al. Osteopathy and resistance to vitamin D toxicity in mice null for vitamin D binding protein. *J Clin Invest*. 1999;103:239–251.
7. Mayerl S, Muller J, Bauer R, et al. Transporters MCT8 and OATP1C1 maintain murine brain thyroid hormone homeostasis. *J Clin Invest*. 2014;124:1987–1999.
8. Hammes A, Andreassen TK, Spoelgen R, et al. Role of endocytosis in cellular uptake of sex steroids. *Cell*. 2005;122:751–762.
9. Thomou T, Mori MA, Dreyfuss JM, et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. *Nature*. 2017;542:450–455.
10. Rocheville M, Lange DC, Kumar U. Receptors for dopamine and somatostatin: formation of hetero-oligomers with enhanced functional activity. *Science*. 2000;288:154–157.
11. Moore RY. Circadian rhythms: basic neurobiology and clinical applications. *Annu Rev Med*. 1997;48:253–266.
12. Ahmad AM, Guzder R, Wallace AM. Circadian and ultradian rhythm and leptin pulsatility in adult GH deficiency: effects of GH replacement. *J Clin Endocrinol Metab*. 2001;86:3499–3506.
13. Van Cauter E, Leproult R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *JAMA*. 2000;284:861–868.
14. Melmed S, Kaiser UB, Lopes MB, et al. Clinical biology of the pituitary adenoma. *Endocr Rev*. 2022;43:1003–1037.
15. Melmed S. Series introduction. The immuno-neuroendocrine interface. *J Clin Invest*. 2001;108:1563–1566.
16. Wan X, Zinselmeyer BH, Zakharov PN, et al. Pancreatic islets communicate with lymphoid tissues via exocytosis of insulin peptides. *Nature*. 2018;560:107–111.
17. Huang SA, Tu HM, Harney JW, et al. Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. *N Engl J Med*. 2000;343:185–189.
18. Bianco AC, Salvatore D, Gereben B. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev*. 2002;23:38–89.
19. Samson SL, Nachtigall LB, et al. Maintenance of acromegaly control in patients switching from injectable somatostatin receptor ligands to oral octreotide. *J Clin Endocrinol Metab*. 2020;105:e3785–e3797.
20. Romitti M, Tourneur A, de Faria da Fonseca B, et al. Transplantable human thyroid organoids generated from embryonic stem cells to rescue hypothyroidism. *Nat Commun*. 2022;13:7057.
21. Lin NP, Chou DH. Modifying insulin to improve performance. *Science*. 2022;376:1270–1271.
22. Evans RM, Mangelsdorf DJ. Nuclear receptors, RXR, and the Big Bang. *Cell*. 157:255–266.

www.dbadisteb.pub