13.1 Principles of hormone action 2245 Rob Fowkes,

13.1 Principles of hormone action 2245 Rob Fowkes, V. Krishna Chatterjee, and Mark Gurnell

ESSENTIALS Hormones, produced by glands or cells, are messengers which act locally or at a distance to coordinate the function of cells and organs. Types of hormone include (1) peptides (e.g. hypothalamic releasing factors) and proteins (e.g. insulin, growth hormone)—these generally interact with membrane receptors located on the cell surface, causing activation of downstream signalling pathways leading to alteration in gene transcription or modulation of biochemical pathways to effect a physiological response; (2) steroids (e.g. cortisol, progesterone, tes- tosterone, oestradiol) and other lipophilic substances (e.g. vitamin D, retinoic acid, thyroid hormone)—these act by crossing the plasma membrane to interact with intracellular receptors, with hormone ac- tion via nuclear receptors altering cellular gene expression directly. Hormone synthesis, processing, and secretion—production of hor- mones can be regulated at many levels, including (1) gene transcrip- tion; (2) mRNA processing; (3) post-translational modification. Some hormones are not significantly concentrated within cells and are re- leased via Golgi-derived transport vesicles that fuse with the plasma membrane (a ‘constitutive’ pathway of secretion). By contrast, many endocrine cells contain an additional ‘regulated’ secretory pathway, which allows the export of high concentrations of hormone stored in cytoplasmic vesicles. Many hormones are released in a rhythmic or pulsatile manner. Control of hormone production—the classical mechanism by which hormone-producing glands are controlled is by negative feedback, e.g. triiodothyronine (T3) inhibits production of thyrotropin-releasing hormone and thyroid-stimulating hormone. Physiological roles of hormones—these are enormously varied and include (1) control of growth and differentiation; (2) maintenance of homeostasis—energy balance, metabolic pathways; fluid, electrolyte, and calcium balance; control of blood pressure; and (3) regulation of

reproduction. Clinical features of endocrine disorders—these comprise conditions of either hormone excess or hormone deficiency or hormone resist- ance, caused by acquired endocrine cellular dysfunction or germline or somatic defects in genes mediating hormone synthesis or action causing inherited syndromes. Definition Endocrinology is the study of hormones secreted by glands or cells which, acting locally or at a distance, facilitate communica- tion between cells and different organs, thus coordinating their activities. Classically, the production of hormones has been associated with specialized glands or tissues including the hypothalamus, pituitary, thyroid, parathyroids, gonads, pancreatic islet cells, ad- renal glands, and placenta. It is now recognized that hormones are also produced by a range of other organs and tissues which are not considered to be classical endocrine glands. The heart is the primary source of atrial natriuretic peptide factor which has effects blood pressure and intravascular volume; endothelin and nitric oxide are derived from vascular endothelium and regulate vascular tone. Endocrine cells are distributed throughout the gastrointestinal tract and are a rich source of hormones such as cholecystokinin, gastrin, secretin, and vasoactive intestinal pep- tide; many of these gastrointestinal hormones are also produced in the brain and central nervous system, where their role is less well understood. Erythropoietin, a circulating factor that stimu- lates erythropoiesis, is derived from the kidney. Adipose tissue produces leptin, a circulating hormone which acts centrally to control appetite. However, as understanding of intercellular communication has advanced, the lines of division that separate different physio- logical systems have become blurred. For example, neuroendo- crinology represents intimate connections between the nervous and endocrine systems: peptide hormones produced in the brain exert effects via the hypothalamus to control hormone secre- tion from the pituitary gland; in the periphery, the sympathetic nervous system modulates hormone production by the adrenal medulla and pancreatic islets. Similarly, there are complex interrelationships between the immune and endocrine systems (e.g. glucocorticoid hormones exert powerful immunosuppres- sive effects); conversely, cytokines (e.g. tumour necrosis factor α and interleukin (IL)-6), produced by cells of the immune system, markedly influence hormone secretion by glands such as the pi- tuitary and adrenal. 13.1 Principles of hormone action Rob Fowkes, V. Krishna Chatterjee, and Mark Gurnell

SECTION 13 Endocrine disorders 2246 Nature of hormones In general, hormones can be classified into those that are based on proteins or peptides and those that are chemically derived. Small peptides include hypothalamic releasing factors produced by neuro- endocrine cells, which act locally on the pituitary; larger polypep- tides such as insulin or growth hormone (GH) are characteristically circulating hormones which act on more distant targets. Biogenic amines including catecholamines, dopamine, and serotonin are de- rived from amino acids. Most protein and peptide hormones interact with membrane receptors located on the cell surface. Binding to membrane receptors activates downstream signalling pathways leading to changes in cellular function which mediate responses to hormones. A second class of hormones includes steroids and other lipophilic substances which act by crossing the plasma membrane to interact with intracellular receptors. Steroid hormones are derived from cholesterol and include cortisol, progesterone, testosterone, and oestradiol. Vitamin D and retinoic acid, which are synthesized from dietary sources, and thyroid hormone produced by modification of tyrosines in thyroglobulin, are structurally dissimilar to steroids but also act via nuclear receptors. Development of endocrine glands The hypothalamus develops from forebrain tissue adjacent to the third ventricle. Neurons secreting releasing factors send cel- lular processes which terminate in portal capillaries that perfuse the pituitary gland. The latter develops from ectoderm to form the

adenohypophysis or anterior pituitary; the posterior pituitary or neurohypophysis is formed directly from axonal terminals of hypothalamic neurons which grow downward. The thyroid gland develops from endoderm in the floor of the oropharynx with mi- gration of cells caudally to its final position in the neck. During its descent, parafollicular C cells derived from neural crest tissue within the ultimobranchial body and parathyroid glands from the third and fourth pharyngeal pouches, become incorporated into the thyroid gland. The adrenal glands comprise a steroid-secreting cortex developing from mesoderm, together with a catecholamine- producing medulla composed of chromaffin cells derived from neural crest. Germ cells within indifferent gonadal prim- ordia differentiate to form the ovary or, in the presence of the Y chromosome-encoded sex-determining gene (SRY), develop into testes. Endocrine cells of the pancreas are derived from endoderm and differentiate to form the islets of Langerhans. Various tran- scription factors which control the development of cells within endocrine glands and their differentiation to hormone biosynthesis are listed in Table 13.1.1. Hormone synthesis, processing, and secretion The organization of endocrine genes is homologous to those encoding many other proteins, although there are some character- istic features. Gene transcription is usually regulated by the pro- moter, which is located in the upstream 5′ flanking region of the gene (Fig. 13.1.1). Typically, the promoter may contain three types of regulatory DNA sequence which are recognized by specific tran- scription factors; a hormone response element is recognized by nuclear receptors; a tissue-specific element binds cell-specific Table 13.1.1 Some transcription factors involved in endocrine gland development Gland Transcription factor(s) Pituitary HESX-1, POU1F1, PROP-1, TBX19 Thyroid TTF-1, TTF-2, PAX-8 Adrenal cortex SF-1, DAX-1 Pancreatic islet cells IPF-1 Testis SRY, SF-1 Ovary SF-1, DAX-1 DAX-1, dosage-sensitive sex reversal adrenal hypoplasia critical region on the X-chromosome 1; HESX-1, homeobox gene expressed in embryonic stem cells 1; IPF-1, insulin promoter factor 1; PAX-8, paired box gene 8; POU1F1, POU homeodomain containing pituitary transcription factor 1 (previously known as Pit-1); PROP-1, prophet of Pit-1; SF-1, steroidogenic factor 1; SRY, sex-determining region of the Y chromosome; TBX-19 (also known as TPIT), a T-box containing transcription factor; TTF-1, thyroid transcription factor 1; TTF-2, thyroid transcription factor 2. Signal sequence Prepro- hormone Prohormone cleavage Mature hormone Post-translational modification Secretory granule Ca2+− dependent exocytosis Rough endoplasmic reticulum Golgi network Intracellular Extracellular Nucleus Cytoplasm mRNA Mature polypeptide Basal transcription factors

- ○

Transcription initiation site HRE TSE CRE AP-1 Cell specific transcription factor CREB Fos Nuclear receptor Jun Fig. 13.1.1 Pathway of hormone synthesis, processing, and secretion. See text for explanation.

 transcription factors (see Table 13.1.1), which enhance the tran- scription of the hormone gene in a tissue-specific manner; a third class of response element mediates transcriptional activation in re- sponse to second-messenger signalling pathways. A rise in intra- cellular cAMP leads to the activation of protein kinase A and subsequent phosphorylation of cAMP response element binding proteins (CREBs) which interact with CREs; cell signalling path- ways which activate protein kinase C induce phosphorylation of the Fos-Jun (AP-1) transcription factor complex which binds its cog- nate DNA regulatory sequence. Binding of transcription factors to regulatory DNA response elements, activates and stabilizes basal transcription factors, promoting gene transcription and mRNA synthesis (Fig. 13.1.1). Transcription of the gene

generates mRNA which undergoes translation in ribosomes leading to polypeptide synthesis. In some endocrine genes, alternative exon splicing allows substitution or re- moval of particular exons, such that peptides of differing sequence can be produced. For example, alternative splicing of the calcitonin gene in a tissue-specific manner directs the production of calcitonin in the C cells of the thyroid, whereas calcitonin gene-related peptide is produced preferentially in the brain. Secreted polypeptide hormones incorporate a signal sequence at the amino terminus of the protein which directs its translocation across the endoplasmic reticulum where this sequence is cleaved (Fig. 13.1.1). Many hormones are synthesized as larger polypep- tides (prohormones) which undergo proteolytic cleavage to generate smaller functional peptides. Such proteolytic processing is mediated by specific proteases, such as prohormone convertase 1 and 2 (PC1, PC2), which are highly expressed in cells of neuroendocrine lineage. Examples of hormone processing include the cleavage of proinsulin with removal of an internal C peptide to yield insulin, the active hormone. Processing of the polypeptide precursor can also yield multiple functioning products. For example, pro-opiomelanocortin (POMC) is cleaved by endopeptidases to yield adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSHα, β, γ), β-endorphin, and lipocortin. Hormones may also undergo post-translational modification such as amidation of neuropeptides, acylation, or glycosylation. Modification of amino acids by addition of carbohydrate side chains is a particular characteristic of the glycoprotein hormones— luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and human chorionic gonadotropin (hCG)—and such glycosylation affects both their biological activity as well as their half-life in the circulation (see Fig. 13.1.1). Hormones such as growth factors and cytokines are not concen- trated within cells significantly but released via small, clear, Golgi- derived transport vesicles which fuse with the plasma membrane, representing a ‘constitutive’ pathway of secretion. In contrast, many endocrine cells contain an additional ‘regulated’ secretory pathway, which allows the export of high concentrations of hormone stored in cytoplasmic dense-core vesicles. Chromogranin B, an acidic protein, and polypeptide proteases are additional constituents of secretory vesicles. Adrenal cells secreting catecholamine hor- mones contain chromaffin granules which include enzymes (e.g. dopamine β hydroxylase) that catalyse catecholamine biosynthesis. Dense-core vesicle exocytosis is mediated by a rise in intracellular calcium which activates cytoskeletal machinery, promoting vesicle translocation and docking with the plasma membrane (see Fig. 13.1.1). Cells secreting steroid hormones contain abundant mito- chondrial and smooth endoplasmic reticulum which contain en- zymes that mediate steroid biosynthesis. Mitochondrial side-chain cleavage enzyme converts cholesterol to pregnenolone and the latter is converted to glucocorticoid, mineralocorticoid, or sex steroids de- pendent on the cell-specific expression of steroidogenic enzymes. Steroid hormones are not stored to any extent and are secreted constitutively. Control of hormone production The classic mechanism by which hormone-producing glands com- municate is by endocrine pathways, whereby the products from one gland are secreted into the circulation (and exert effects on a dif- ferent, distant target gland). Such endocrine pathways integrate the hypothalamus, pituitary, and various end organs to control the pro- duction of major hormones (Fig. 13.1.2). Thus, peptide-releasing factors (e.g. GnRH, TRH, GHRH, CRH) from the hypothalamus, stimulate production of tropic hormones from specific pituitary cell types; exceptions to this are somatostatin, which inhibits pituitary GH release, and dopamine, which is secreted continuously to in- hibit prolactin secretion. The pituitary hormones act on end organs to generate products which, in turn, exert a negative feedback ef- fect at both hypothalamic and pituitary levels to regulate their own synthesis. Triiodothyronine (T3) inhibits TRH and TSH produc- tion; gonadal steroids and inhibin negatively regulate hypothalamic GnRH and pituitary gonadotropins; cortisol suppresses

CRH and ACTH generation; circulating insulin-like growth factor 1 (IGF-1) inhibits GHRH and GH secretion (Fig. 13.1.2). Osmoreceptors in the hypothalamus sense changes in serum osmolality to control the release of vasopressin from the posterior pituitary. In addition to these endocrine control mechanisms, other types of local regulatory pathways are recognized. Paracrine regulation re- fers to factors that are released by one cell and act upon a nearby cell in the same tissue. For example, somatostatin produced by δ cells in pancreatic islets inhibits the local production of insulin from β cells; in the testis, testosterone produced from Leydig cells exerts an effect on nearby Sertoli cells to enhance spermatogenesis. Autocrine control refers to a factor which acts upon the same cell in which it is produced. Examples include gonadotroph secretion of activin which stimulates production of FSH from the same cell; similarly, T cells produce IL-2 which acts to promote their own proliferation. In addition to discrete hormonal responses, endocrine systems can respond to environmental stimuli by the integrated production of multiple hormones. For example, stress activates an array of path- ways, with sympathetic activation mediating catecholamine release from the adrenals, and stimulation of the hypothalamus inducing multiple axes, resulting in the production of cortisol, GH, prolactin, and vasopressin. The hormonal responses to starvation are also inte- grated by the hypothalamus. Here, diminished production of leptin from adipose tissue inhibits hypothalamic GnRH and TRH secre- tion with a consequent reduction in the production of both gonadal steroids and thyroid hormone to limit reproduction and energy expenditure. In addition to the feedback regulatory mechanisms just outlined, many hormones are released in a rhythmic or pulsatile manner.

 Insulin is secreted in rapid (c. every 10 min) pulses in response to changes in glucose concentration in the pancreatic β cell. GnRH is secreted from the hypothalamus at a lower pulse frequency of every 1.5 to 3 h, stimulating similar pulses of pituitary LH and FSH release; differential release of LH and FSH is controlled by varying GnRH pulse frequency, with low frequency pulses favouring FSH secre- tion and high frequency pulses stimulating LH secretion. Another hypothalamic peptide (kisspeptin) can augment GnRH secretion in a paracrine manner. This hormonal rhythm controls ovarian folliculogenesis and steroid production to establish the female re- productive and menstrual cycle. Pituitary GH secretion is regulated by pulses of stimulatory GHRH and inhibitory somatostatin from the hypothalamus, which are out of phase with each other, corres- ponding to peaks and troughs of circulating GH. Many hormonal pathways are influenced by the light–dark cycle, with circadian variation in their circulating levels. For example, the hypothalamic–pituitary–adrenal axis exhibits most activity in the early morning with peak cortisol production, followed by a nadir in glucocorticoid levels in the evening. Sleep is another environmental regulator: GH secretion is enhanced nocturnally and the release of vasopressin during sleep inhibits diuresis; puberty is associated with nocturnal surges of LH. Hormone-binding proteins Thyroid hormones and many steroids are transported in the circula- tion with serum binding proteins. Thus, thyroxine (T4) and triiodo- thyronine (T3) are bound to thyroxine-binding globulin, albumin, and thyroxine binding prealbumin. Cortisol and progesterone are bound to cortisol binding globulin, while oestrogens and andro- gens are bound to sex hormone-binding globulin. The role of serum binding proteins is to provide a reservoir of circulating hormone. The interaction of hormones with binding proteins is relatively weak compared to their affinity for receptors, enabling them to dis- sociate easily. Only free hormone interacts with receptor to elicit a biological response. Hormone-binding proteins are produced by the liver and their synthesis can be increased (e.g. by oestrogens or in pregnancy) or decreased (e.g. in liver disease), affecting the circulating concentration of total hormones. Accordingly, wher- ever

possible, the concentration of free hormones in the circulation (e.g. T4, T3) or urine (cortisol) is measured. Some protein hor- mones also circulate associated with binding proteins, which may modulate their action. A range of insulin-like growth factor binding proteins bind to IGF-1, with some inhibiting and others facilitating the action of this peptide on target tissue receptors. GH circulates bound to the extracellular domain of its receptor derived by cleavage from the membrane, with the complex prolonging the circulating half-life of the hormone. Functions of hormones The physiological roles of the major hormones can be broadly clas- sified into three areas: control of growth and differentiation; main- tenance of homeostasis; and regulation of reproduction. Some hormones have multiple functions and play a role in more than one area. In addition, some biological effects are mediated by the com- bined action of several different hormonal pathways. The principal actions of major hormones are outlined in Table 13.1.2. Linear growth is dependent on a complex interplay of many hor- mones and growth factors. GH plays a key role and exerts many of its effects by stimulating the hepatic production of IGF-1. Thyroid hormone also stimulates the epiphyseal growth plate in childhood Hormone Effect(s) Effect(s) Target organ Pituitary gland Hypothalamus GnRH −+ Vasopressin Oxytocin TRH CRH Dopamine LH/FSH Gonads TSH Thyroid gland GH Liver ACTH Adrenal cortex PRL Breast Distal nephron Uterus Breast Somatostatin Anterior pituitary Oestrogen Progesterone Testosterone Inhibin ↑Plasma osmolality − − +

- − Cortisol IGF1 T3 Other target organs GHRH Posterior pituitary Fig. 13.1.2 Control of hormone production. Regulatory pathways integrating the hypothalamus, pituitary, and various end organs. Hormones shown in italics exert inhibitory effects. Negative feedback regulation occurs at both hypothalamic and pituitary levels. See text for explanation.

 whereas, at puberty, production of sex steroids leads to epiphyseal closure. Other important actions of thyroid hormone include en- hancement of myocardial contractility and differentiation of the central nervous system. The maintenance of homeostasis includes the control of en- ergy balance, metabolic pathways, fluid, electrolyte and calcium balance, and regulation of blood pressure. Energy homeostasis in- volves regulation of food intake and energy expenditure. Leptin, an adipose tissue-derived hormone, acts via hypothalamic path- ways (e.g. melanocortin 4) to reduce food intake; conversely, rising gastrointestinal production of ghrelin preprandially stimu- lates food intake. Thyroid hormone is an important determinant of resting energy expenditure or basal metabolic rate. Metabolic effects are mediated by several hormones: insulin lowers blood glucose by enhancing its cellular uptake and promotes glycogen synthesis; conversely, GH, cortisol, glucagon, and adrenaline act as counterregulatory hormones to raise blood glucose. Glucagon and adrenaline stimulate glycogenolysis and, together with cortisol, promote gluconeogenesis. Other metabolic pathways are also in- fluenced by these hormones: GH and cortisol are lipolytic whereas insulin mediates lipogenesis; insulin and GH are also anabolic by promoting protein biosynthesis, whereas cortisol increases protein breakdown. Adiponectin, another adipose tissue-derived hormone, enhances tissue insulin sensitivity. Circulating concentrations of ions and water balance are also under hormonal control. Vasopressin promotes water reabsorption via membrane channels (aquaporins) in the distal collecting ducts of the kidney; aldosterone acts at the renal distal convoluted tubule to stimulate sodium reabsorption and potassium excretion, effects which are antagonized by atrial natriuretic peptide (ANP). Both parathyroid hormone and vitamin D increase serum calcium levels; PTH mediates Ca^{2+} resorption from bone and kidney, whereas vitamin D acts on the

gastrointestinal tract as well as these sites. Catecholamines and angiotensin II are potent vasoconstrictors and, together with cortisol, control blood pressure. Hormones involved in reproduction exert effects from early in de- velopment. During embryogenesis, Müllerian inhibiting substance (MIS) from the testis causes regression of female structures (uterus, fallopian tube) and testosterone promotes the development of male structures (vas deferens, epididymis, seminal vesicles) which are Table 13.1.2 Major actions of hormones Hormone Action Homeostasis Energy balance Leptin Reduces food intake Ghrelin Increases hunger Fluid and electrolyte balance Aldosterone Renal Na+/K+ exchange Vasopressin ↓Renal free water clearance Metabolism Insulin ↑Cell glucose uptake; ↑glycogen synthesis; lipogenic; ↑protein synthesis Glucagon Glycogenolysis; gluconeogenic Cortisol Gluconeogenic; lipolysis; ↑protein breakdown Growth hormone Lipolysis; ↑protein synthesis Testosterone ↑Protein synthesis Calcium Parathyroid hormone ↑Ca2+ resorption from bone and kidney; ↑renal 1α hydroxylation of vitamin D Vitamin D ↑Ca2+ absorption from gastrointestinal tract; ↑Ca2+ resorption from bone and kidney Growth and development Growth hormone Growth Thyroid hormone Growth, regulation of basal metabolic rate, central nervous system development Retinoic acid Embryonic development; morphogenesis C-type natriuretic peptide Bone growth, meiosis inhibition, axonal development Reproduction Testosterone Sexual differentiation, virilization, spermatogenesis Dihydrotestosterone Male external genitalia Oestradiol Female external genitalia; mammary gland development Progesterone Uterotrophic Prolactin Lactation Oxytocin Uterine contraction; milk reflex

SECTION 13 Endocrine disorders 2250 derived from the Wolffian duct. Dihydrotestosterone promotes de- velopment of the male external genitalia. In both sexes, the gonadal axes are quiescent in childhood and become reactivated at puberty. Testosterone mediates virilization, secondary sexual characteristics, and spermatogenesis in the male; in females, ovarian production of oestrogen and progesterone induces secondary sexual features and controls the menstrual cycle. In both sexes, gonadal steroids are re- quired for the attainment of peak bone density at the end of puberty and its subsequent maintenance. During pregnancy, prolactin acts in concert with oestrogen to promote lactation; oxytocin stimulates uterine contraction at parturition and smooth muscle contraction in the mammary gland during suckling. Hormone action Hormones induce biological responses by interacting with receptors located either on the membrane or intracellularly in the cytoplasm or nucleus. Hormones bind to receptors with high affinity, such that low concentrations of free hormone associate and dissociate from receptors rapidly in a dynamic equilibrium. The interaction of hor- mones with receptors is usually highly specific, with individual receptors being highly selective for a single hormone even within a class of structurally related molecules (e.g. steroid hormones). However, there are exceptions to this: parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP) or LH and hCG share a common receptor, generating similar biological responses; insulin and IGF-1 exhibit some degree of cross-reactivity with their respective receptors; the mineralocorticoid receptor binds cortisol with equal or higher affinity than aldosterone. Hormones that bind to membrane receptors act via effector pro- teins to activate second-messenger signalling pathways. In turn, the second messengers stimulate a cascade of kinases, which then act upon target substrates in the cell membrane, the cytoplasm or nucleus, to alter gene transcription or modulate a biochemical pathway, leading to a physiological response. Hormones that act through nuclear receptors are transported passively, or pumped ac- tively, across the plasma membrane to interact with their targets. The hormone–receptor complex interacts with DNA sequences in target genes to either stimulate or repress their expression. The cellular ac- tions of nuclear receptors are mediated by changes in target gene transcription,

altering mRNA synthesis and, in turn, the levels of protein product. Signalling by membrane receptors Membrane receptors can be divided into several groups (Table 13.1.3) depending on the signalling pathways that they utilize. The largest group consists of receptors with multiple transmembrane domains which are coupled to G proteins; a second class of receptor contains an intracellular domain with tyrosine kinase activity; several hormones signal via membrane proteins that are homologous to cytokine recep- tors; a fourth class of hormone receptor contains an intracellular do- main with serine or threonine kinase activity. G protein-coupled receptors (GPCRs) are characterized by seven separate hydrophobic domains that traverse the membrane phospholipid bilayer (Fig. 13.1.3a). They possess an extracellular domain of variable size, enabling further subclassification of these receptors: glycoprotein hormones or small molecule ligands (e.g. calcium, GABA) interact with large N-terminal extracellular domains; biogenic amines (e.g. catecholamines, serotonin) bind to residues that lie within the transmembrane domain; other polypep- tide hormones interact with residues in both the extracellular and transmembrane domains. The intracellular domains of the receptor enable interaction with G proteins. G proteins typically form a heterotrimeric complex of α, β, and γ subunits which bind the guanine nucleotides GTP and GDP. The complex transduces signals from the receptor to downstream ef- fectors such as adenylate cyclase, phospholipase C, or membrane voltage-dependent calcium channels. A family of different G pro- teins (Gs, Gi, Gq, and others) exists with the ability to couple to dif- ferent receptors and effectors, allowing a large array of potential receptor–G protein–effector complexes, leading to diversity of cel- lular signalling. Several hormones signal via the cAMP pathway (Table 13.1.4) and this mechanism is considered in further detail (Fig. 13.1.4). In the resting state, the G protein complex is inactive and bound to GDP (Fig. 13.1.4a). Following hormone binding to the receptor (Fig. 13.1.4b), the Gα subunit binds GTP, becomes activated and dissociates from the βγ complex, to interact with adenylate cyclase (Fig. 13.1.4c). The latter converts ATP to the second messenger, cAMP. This rise in intracellular cAMP activates protein kinase A (PKA), which can phosphorylate certain cellular targets: phos- phorylation of a transcription factor, CREB, stimulates transcription of genes containing CREs; other targets for PKA include enzymes in biochemical pathways or membrane ion channels. Several mechanisms serve to terminate signalling via a hormone– receptor complex: first, hydrolysis of GTP to GDP by the Gα subunit promotes its reassociation with βγ subunits to reform an inactive complex; second, the hormone–receptor complex is internalized via Table 13.1.3 Membrane receptor families G protein-coupled Glycoprotein hormones FSH, TSH, LH/CG Biogenic amines Adrenaline, noradrenaline, serotonin, histamine, dopamine Peptides Calcitonin, PTH/PTHrP Ghrelin, GHRH, CRH, GnRH, kisspeptin, SRIF, TRH Vasopressin, oxytocin Angiotensin Glucagon, secretin, VIP, gastrin Small molecules Calcium, GABA Tyrosine kinase Insulin, IGF-1 Guanylyl cyclase Atrial natriuretic peptide, CNP, guanylin Cytokine GH, PRL, EPO, leptin Serine/threonine kinase Activin, inhibin, MIS CG, chorionic gonadotrophin; CRH, corticotropin releasing hormone; EPO, erythropoietin; FSH, follicle-stimulating hormone; GABA, γ-aminobutyric acid; GH, growth hormone; GHRH, growth hormone releasing hormone; GnRH, gonadotropin releasing hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; MIS, Müllerian inhibiting substance; PRL, prolactin; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; SRIF, somatostatin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; VIP, vasoactive intestinal polypeptide.

 cell surface vesicles and targeted for lysosomal degradation; third, following hormone binding, the GPCRs undergo phosphorylation of their intracellular domains by either PKA or other specific kinases (GRKs). Such phosphorylation prevents

further coupling to G pro- teins and promotes receptor internalization desensitizing the cell to hormone action, until further surface receptor is expressed. Activation of their receptors by hormones such as somatostatin or dopamine, is known to decrease intracellular cAMP. Here, the hormone–receptor complex associates with a G protein (Gi), whose α subunit inhibits adenylate cyclase. Although many GPCRs signal via cAMP, some receptors (e.g. TRH, GnRH, Table 13.1.4) are linked to different pathways. These receptors are coupled to Gq, whose α subunit activates membrane phospholipase C (PLC) (Fig. 13.1.5). This enzyme catalyses the hydrolysis of phosphatidylinositol 4,5- bisphosphate (PIP2) to generate the second messengers, inositol 1,4,5-triphosphate (IP3) and 1,2-diacylglycerol (DAG). IP3 inter- acts with a specific receptor located on smooth endoplasmic re- ticulum, inducing opening of intracellular channels leading to a rise in cytoplasmic calcium (Fig. 13.1.5). Interaction of calcium with calmodulin, a cytoplasmic calcium-binding protein, activates a specific kinase (CAM kinase), which regulates several processes including hormone secretion, gene transcription, and metabolic enzymes. The rise in cellular calcium also facilitates DAG activa- tion of protein kinase C (PKC), leading to phosphorylation of the NH2 COOH Transmembrane domain Intracellular domain Extracellular domain (a) (b)

- C N - Ligand-binding domain DNA-binding domain N-terminal domain CoR CoA ‘Zinc fingers’ P box D box n Z n Z A box Dimerization C C C C C C C C Fig. 13.1.3 Schematic representations of (a) G protein-coupled receptor and (b) nuclear receptor, illustrating their functional domains. See text for explanation.

SECTION 13 Endocrine disorders 2252 Fos-Jun transcription factor complex, inducing target gene expres- sion (Fig. 13.1.5). Hormones do not signal exclusively via a single pathway, with glycoprotein hormones and some peptides for ex- ample (Table 13.1.4) activating both cAMP and phosphoinositide signalling. The tyrosine kinase class of receptors is a diverse family that transduces signalling by insulin and IGF-1 but also epidermal, nerve, fibroblast, and platelet-derived growth factors. Growth factor signalling differs from insulin and the latter pathway will be con- sidered (Fig. 13.1.6). Hormone interaction with receptor promotes autophosphorylation of tyrosine residues in their cytoplasmic do- mains. In turn, this promotes phosphorylation of substrates, for example, Shc and insulin receptor substrate 1 (IRS-1), followed by recruitment of adaptor proteins (Grb2/SOS). The Grb2/SOS com- plex recruits Ras, a GTP-binding protein. Ras activation induces signalling via a series of kinases (Raf, Mek, MAP kinase), culmin- ating in the phosphorylation and activation of transcription factors which regulate target genes involved in mitogenesis or cellular dif- ferentiation. On the other hand, IRS-1 recruits phosphatidylinositol- 3′-OH-kinase (PI3-kinase), which in turn activates the AKT cascade. The latter mediates several of the metabolic effects of in- sulin, enhancing translocation of a glucose transporter to the mem- brane to promote cellular glucose uptake, and activating pathways involved in glycogen, lipid, or protein synthesis. Hormones such as prolactin and GH interact uniquely with their receptors; a single polypeptide interacts simultaneously with two receptors promoting their dimerization (Fig. 13.1.7). The hormone– receptor complex recruits Janus kinases (JAKs) which phosphorylate STATs (signal transducers and activators of transcription). STATs translocate to the nucleus, interact with regulatory DNA elements, and promote target gene transcription. Activin and inhibin belong to the transforming growth factor class of peptides which signal via a heterodimeric transmembrane receptor complex with intrinsic protein serine/threonine kinase activity (Fig. 13.1.8). Here, hormone binding promotes the asso- ciation of two surface receptors (type I and type II) with differing properties. Subsequent transphosphorylation of the type I receptor by the intracellular kinase

domain of the type II receptor leads to phosphorylation and dimerization of cytoplasmic Smad proteins. The Smad complex translocates to the nucleus to activate target gene expression (Fig. 13.1.8). The membrane guanylyl cyclases act as receptors for natriuretic peptides. ANP and CNP bind their selective receptors (guanylyl cyclase A and B, respectively), which exist as phosphorylated homodimers, leading to intrinsic guanylyl cyclase activity. This leads to elevated cGMP generation, and subsequent activation of cGMP-binding proteins such as phosphodiesterases (PDEs), cyclic nucleotide-gated ion channels, and protein kinase G (Fig. 13.1.9). As just described, GPCR signalling is usually coupled to responses (e.g. hormone secretion) by Gα subunit activation of cAMP or phosphoinositide pathways. However, following receptor activation in some cellular contexts, the dissociated Gβ/γ dimer subunit com- plex is also capable of stimulating effectors (e.g. Ras, PI3-kinase), to enhance MAP kinase activity and elicit a mitogenic response. Nuclear receptor signalling The nuclear receptors are a family of transcription factors which mediate the action of steroid and other lipophilic hormones. The human genome encodes approximately 60 to 70 different recep- tors and it is clear that only a minority of these are targets for the action of major hormones (Table 13.1.5). The remainder com- prise a large group classified as ‘orphan receptors’, reflecting the fact that either their ligands and/or physiological roles remain to be elucidated. Based on homologies in their primary amino acid sequence, nu- clear receptors can be divided into distinct domains which mediate specific functions (Fig. 13.1.3b). A central DNA binding domain contains cysteine-rich peptide motifs which chelate zinc to form two ‘zinc fingers’. The latter mediate receptor binding to specific DNA sequences or hormone response elements, usually located in target gene promoters. The C-terminal region of receptors encompasses their hormone-binding function as well as their ability to dimerize. Nuclear receptors can be divided into two major subclasses, the steroid receptors and heterodimeric receptors, which differ in their mode of action. Steroid receptors (e.g. GR, MR, ER, PR, AR) bind to hormone response elements as homodimers (Fig. 13.1.10b). Some recep- tors (e.g. GR, PR, AR) are bound to cytosolic heat shock proteins. Hormone binding to receptors promotes their dissociation from these, enabling translocation to the nucleus, dimerization, and inter- action with DNA. In contrast, the thyroid, retinoid, and vitamin D receptors are constitutively nuclear and form heterodimers with a Table 13.1.4 Signalling pathways of membrane receptors Signalling pathway Hormone/receptor Gsα/cAMP↑ β-Adrenergic receptor CRH GHRH ACTH Giα/cAMP↓ Somatostatin Dopamine α-Adrenergic receptor Gqα/IP3 and DAG TRH GnRH Gsα/cAMP↑ and Gqα/IP3 and DAG LH FSH TSH PTH Calcitonin JAK-STAT GH PRL EPO Leptin cGMP↑ ANP CNP Tyrosine kinase/MAP kinase Insulin IGF-1 Ser/Thr kinase/SMAD Activin, inhibin, MIS Abbreviations as for Table 13.1.3.

 common partner (retinoid X receptor, RXR), to interact with DNA even in the absence of hormone or ligand (Fig. 13.1.10a). In some target gene contexts, RXR can also form homodimers to mediate retinoid signalling. In contrast to other transcription factors whose activity is con- trolled by post-translational modification (e.g. phosphorylation), the hallmark of nuclear receptors is their ability to modulate gene expression in a hormone-dependent manner. Thus, in the absence of ligand, the thyroid and retinoic acid receptors actively silence target gene transcription by recruiting a corepressor complex of cofactors (Fig. 13.1.10a). For all nuclear receptors, hormone binding induces a conformational change with dissociation of corepressors and re- cruitment of coactivator proteins (Fig. 13.1.10b). This latter com- plex acts to relax the interaction between histone proteins and DNA in chromatin, thereby facilitating the access of basal transcription factors and RNA polymerase, which induce gene transcription. A further mechanism which controls signalling via nuclear recep- tors is regulation of the supply of their ligands to cells

and tissues. A specific membrane transporter (MCT8) mediates cellular entry of thyroid hormone in the central nervous system. T3, the ligand Hormone Extracellular Plasma membrane Intracellular Adenylate cyclase Adenylate cyclase Adenylate cyclase Hormone GTP GTP (a) (b) (c) ATP cAMP PKA CRE CREB CREB Nucleus Cytoplasm P Gsα Gsα β γ +

- ○

GDP Hormone Gsα GDP β β P γ γ Fig. 13.1.4 G protein-coupled receptor signalling via the cAMP pathway. See text for explanation.

 Hormone Extracellular Plasma membrane Intracellular P Jun Fos Jun Fos + ++ PKC PLC DAG + Cytoplasm Nucleus Calmodulin Smooth endoplasmic reticulum CAM kinase IP3R IP3 PIP2 Ca2+ P β γ Gqα Fig. 13.1.5 G protein-coupled receptor signalling via the phosphoinositide pathway. See text for explanation. α α β β Insulin P P P P PI3 Kinase Plasma membrane Extracellular Intracellular P P P P P P P P IRS-1 IRS-2 IRS-3 IRS-4 AKT ‘cascade’ Glycogen synthesis Cbl CAP P Glucose GLUT4 vesicle Shc Grb2 P SOS Ras Raf MAPK MEK Mitogenesis Differentiation GTP GDP GSK3 Protein synthesis mTOR Lipid synthesis Fig. 13.1.6 Insulin action via its tyrosine kinase receptor and signalling cascade. See text for explanation.

 for TR, is generated from circulating thyroxine by the action of type 1 or type 2 deiodinase enzymes expressed in the liver and central nervous system respectively; the enzyme 5α reductase converts tes- tosterone to dihydrotestosterone in tissues of the male external geni- talia. In contrast, the enzyme 11β-hydroxysteroid dehydrogenase type 2 catabolizes cortisol in the renal cells, thereby enabling the mineralocorticoid receptor to respond selectively to aldosterone ra- ther than to glucocorticoid, which it is also capable of binding with high affinity. Finally, in contrast to classical effects of steroid hormones to modulate gene expression, recent evidence indicates that they can also modulate cellular functions such as hormone secretion or neur- onal excitability within seconds or minutes. These rapid effects of steroid hormones occur independent of the genome and can occur either by hormone interaction with a cell surface receptor or by direct interaction of the nuclear receptor with cytoplasmic signalling molecules. Genetic defects and endocrine disease Most endocrine diseases can be divided into conditions of hor- mone excess, hormone deficiency, and hormone resistance. Defects in genes involved in hormone synthesis and action give rise to a spectrum of disorders (Tables 13.1.6 and 13.1.7). Both germline gene defects causing inherited syndromes and somatic mutations leading to acquired endocrine cellular dysfunction have been described. Defects in developmental transcription factors are usually associ- ated with endocrine gland hypoplasia: mutations in HESX-1 cause optic and pituitary hypoplasia with agenesis of the corpus callosum; Plasma membrane Extracellular Intracellular P P P P JAK JAK P P P P S T A T S T A T ++ + Nucleus Cytoplasm Hormone S T T A S T T A Fig. 13.1.7 Hormone signalling via the JAK-STAT pathway. See text for explanation. Plasma membrane Extracellular Intracellular P P Hormone RII RI GS Smad2 P Smad4

- ○

Nucleus Cytoplasm Smad2 P Smad4 P Smad2 Smad4 Fig. 13.1.8 Hormone signalling by the transforming growth factor peptide family. See text for explanation. Plasma Membrane Extracellular Intracellular PDE Hormone PKG GTP cGMP Ion channel Guanylyl cyclase domain Kinase homology domain Fig. 13.1.9 Hormone signalling via membrane guanylyl cyclases, which

act as receptors for peptides. See text for explanation.

SECTION 13 Endocrine disorders 2256 both Pit-1 (POU1F1) and PROP-1 mutations disrupt development of multiple pituitary cell types resulting in a combination of hor- mone deficiencies; defects in TTF-1, TTF-2, and PAX-8 result in thyroid dysgenesis manifesting as neonatal hypothyroidism; muta- tions in the SRY gene lead to failure of testis development and sex reversal in XY males. Mutations in DAX-1 or SF-1, orphan members of the nuclear receptor family, disrupt both adrenal and gonadal development. Defects in other nuclear receptors (e.g. VDR, TR, GR) are char- acterized by tissue resistance to their respective hormone ligands. Vitamin D resistance leads to rickets together with abnormalities of skin differentiation, hair growth, and lymphocyte function, em- phasizing its important extraskeletal actions. Point mutations in the androgen receptor are associated with a spectrum of pheno- types ranging from complete feminization of XY individuals to mildly impaired virilization in men. In addition, expansion of a polyglutamine repeat sequence in the N-terminal domain of AR is associated with adult-onset neuronal degeneration leading to spinal and bulbar muscular atrophy. A homozygous defect in the oestrogen receptor in a male led to failure of epiphyseal closure re- sulting in tall stature together with severe osteoporosis. These mani- festations suggest that testosterone effects on the male skeleton are, in part, mediated by its enzymatic conversion to oestrogens. A growing number of disorders associated with defects in trans- membrane receptors or their signalling intermediates have been described (Table 13.1.7). However, in addition to mutations which disrupt protein function, gain-of-function mutations causing con- stitutive activation of the receptor or signalling protein also occur. With GPCRs, diverse loss-of-function mutations, occurring most frequently in the extracellular domain, block hormone binding or signalling, leading to insensitivity to hormone action. Such hor- mone resistance can lead to both hypofunction (e.g. ACTH, TSH receptors) or hypoplasia (e.g. LH, FSH receptors) of target glands expressing the receptor. Conversely, gain-of-function mutations in GPCRs typically occur in the third intracellular loop, causing constitutive activation of the receptor in the absence of hormonal ligand. Again, the functional consequence is either autonomous hyperfunction (e.g. calcium, LH, FSH receptors) or excessive neoplastic proliferation (e.g. TSH receptor, RET tyrosine kinase receptor) of the target tissues in which the receptor is expressed Table 13.1.5 Hormone signalling via nuclear receptors Nuclear receptor Hormone Homodimeric GR Cortisol MR Aldosterone ERα/β Oestradiol PR Progesterone AR Testosterone, dihydrotestosterone Heterodimeric TRα/β Triiodothyronine RARα/β/γ all-trans-Retinoic acid RXRα/β/γ 9-cis-Retinoic acid VDR 1,25-Dihydroxyvitamin D3 PPARα/β/γ Unsaturated fatty acids, eicosanoids AR, androgen receptor; ER, oestrogen receptor α or β subtypes; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; PPAR, peroxisome proliferator-activated receptor α, β, or γ subtypes; PR, progesterone receptor; RAR, retinoic acid receptor α, β or γ subtypes; RXR, retinoid X receptor α, β, or γ subtypes; TR, thyroid hormone receptor α or β subtypes; VDR, vitamin D receptor. Nucleus Cytoplasm RXR NR Coactivator ‘complex’ HRE Histone Acetylation Activation RXR NR HRE BTFs Corepressor ‘complex’ Histone deacetylation Repression NR NR or Nucleus Cytoplasm (a) (b) L L BTFs Fig. 13.1.10 Transcriptional regulation by nuclear receptors. (a) In the absence of hormone, a subset of heterodimeric nuclear receptors (thyroid, retinoic acid) recruit corepressors to inhibit gene transcription. (b) Hormone occupancy of homodimeric or heterodimeric receptors promotes their association with coactivators, leading to transcriptional activation. Table 13.1.6 Genetic defects in transcription factors or nuclear receptors and endocrine disorders Gene Disorder or phenotype Transcription factors HESX-1 Septo-optic dysplasia POU1F1/PROP-1 GH, PRL, TSH deficiencies TBX19 ACTH deficiency TTF-1/TTF-2/PAX-8 Thyroid dysgenesis SRY XY female Nuclear

receptors DAX-1/SF-1 Adrenal insufficiency, hypogonadism, and disorders of sex development (DSD) VDR Hereditary vitamin D-resistant rickets AR Androgen insensitivity syndrome or spinal and bulbar muscular atrophy ERα Tall stature and osteoporosis GR Glucocorticoid resistance TRβ Resistance to thyroid hormone PPARγ Lipodystrophic insulin resistance

 (Table 13.1.7). Constitutive activation of signal transduction may also result from G protein mutations. Here, specific amino acid sub- stitutions in Gsα inhibit its intrinsic GTPase activity, and the GTP- bound protein constitutively activates adenylate cyclase leading to cAMP accumulation. Somatic Gsα mutations occur in a proportion of pituitary GH secreting and thyroid adenomas; more widespread expression of a somatic Gsα mutation occurring early in develop- ment, leads to polyostotic fibrous dysplasia, café au lait skin pig- mentation, and hyperfunction of multiple endocrine glands, constituting the McCune–Albright syndrome. Similarly, germline loss-of-function mutations which reduce cellular Gsα activity, are associated with resistance to multiple hormones together with char- acteristic bone anomalies (Albright's hereditary osteodystrophy). FURTHER READING Braverman LE, Cooper D (eds) (2012). Werner & Ingbar's the thyroid; a fundamental and clinical text, 10th edition. Lippincott Williams & Wilkins, Philadelphia. Jameson JL, DeGroot LJ (eds) (2015). Endocrinology, 7th edition. Elsevier, Philadelphia. Lodish H, et al. (2016). Molecular cell biology, 8th edition. W.H. Freeman, San Francisco, CA. Melmed S, et al. (eds) (2016). Williams' textbook of endocrinology, 13th edition. Elsevier, Philadelphia. Strauss JF, Barbieri RL (eds) (2019). Yen & Jaffe's reproductive endocri- nology, 8th edition. Elsevier Saunders, Philadelphia. Table 13.1.7 Genetic defects in membrane receptors or signalling and endocrine disorders Gene Loss-of-function mutation Gain-of-function mutation G protein-coupled receptor TRH Central hypothyroidism GHRH GH deficiency with short stature GnRH Central hypogonadotropic hypogonadism KiSS 1 Central hypogonadotropic hypogonadism Precocious puberty NK3R (TACR3) Central hypogonadotropic hypogonadism Arginine vasopressin 2 (V2) Nephrogenic diabetes insipidus Nephrogenic syndrome of inappropriate antidiuresis Melanocortin 2 (ACTH) Family (isolated) glucocortisol deficiency Ca Familial hypocalciuric hypercalcaemia (FHH) Familial hypercalciuric hypocalcaemia TSH TSH resistance Familial nonautoimmune hyperthyroidism, familial pregnancy-limited hyperthyroidism, autonomous thyroid adenomas LH Leydig cell hypoplasia (males); primary amenorrhoea (females) Male-limited precocious puberty FSH Hypofertility (males); ovarian dysgenesis (females) FSH-independent spermatogenesis (males); spontaneous ovarian hyperstimulation syndrome (females) PTH/PTHrP Blomstrand chondrodysplasia Jansen's metaphyseal chondrodysplasia Melanocortin 4 Extreme obesity Tyrosine kinase receptor RET Hirschprung's disease MEN2: medullary thyroid carcinoma, phaeochromocytoma parathyroid neoplasia Insulin Insulin resistance Cytokine receptors GH Laron dwarfism Leptin Obesity Guanyly cyclase receptors CNP Acromesomelic dysplasia, type Maroteaux Skeletal overgrowth and macrodactyly Signalling pathway Gsα PTH, TSH, LH resistance Albright's hereditary osteodystrophy Somatotroph adenomas, thyroid adenomas, McCune–Albright syndrome Giα Ovary, adrenal, thyroid tumours AKT2 Insulin resistance

---

Revision #1
Created 2026-01-22 16:37:46 UTC by Omar Ayman
Updated 2026-01-22 16:37:46 UTC by Omar Ayman