Introduction to Endocrinology

Coordination of Body Functions by Chemical Messengers.

The types of intercellular communication by chemical messengers in the extracellular fluid include the following:

• Neural, in which neurotransmitters are released at synaptic junctions and act locally • Endocrine, in which hormones released from specialized glands or cells reach the circulating blood and influence the function of target cells some distance away.

Neuroendocrine (neurocrine), in which secretion products from neurons (neurohormones) reach the circulating blood and influence the function of target cells some distance away

• Paracrine, in which cell secretion products diffuse into the extracellular fluid and affect neighboring target cells

• Autocrine, in which cell secretion products affect the function of the same cell by binding to cell surface receptors

• Cytokine, in which secreted cell proteins function as autocrines, paracrines, or endocrines and often act on a broad spectrum of target cells

Maintenance of Homeostasis and Regulation of Body Processes

Inmanyinstances, neuralandendocrinecontrolofbody processes is achieved through interactions between thesetwosystems. Thesesystems arelinked by neuroendocrine cells located in the hypothalamus whose axons terminate in the posterior pituitary gland and median eminence. The neurohormones secreted from theseneuroendocrine cells include antidiuretic hormone (ADH), oxytocin, andhypophysiotropic hormones (which control secretion of the anterior pituitary hormones). Hormones and neurohormones play a critical role in the regulation of almost all aspects of body function, including metabolism, growth and development, water and electrolyte balance, reproduction, and behavior.

Chemistry, Synthesis, Storage, and Secretion of Hormones

Local chemical messengers, not generally considered part of the endocrine system, include autocrines, which act on the cells that secrete them, and paracrines, which act on a different cell type nearby.

Hormones Classified According to Chemical Structure Chemically, hormones and neurohormones are of three types:

• Proteins and peptides. Included in this group are peptides ranging from as small as three amino acids (thyrotropin-releasing hormone) to proteins almost 200 amino acids long (growth hormone and prolactin).

• Steroids. These are derivatives of cholesterol and include the adrenocortical (cortisol, aldosterone) and gonadal (testosterone, estrogen, progesterone) hormones.

• Derivatives of the amino acid tyrosine. Included in this group are hormones from the thyroid gland (thyroxine, triiodothyronine) and adrenal medulla (epinephrine and norepinephrine).

Synthesis, Storage, and Secretion of Hormones Protein/Peptide Hormones Are Synthesized Like Most Proteins.

Protein/peptide hormones are synthesized on the rough endoplasmic reticulum in the same fashion as most other proteins. Typically, the initial protein formed by the endoplasmic reticulum is larger than the active hormone and is called a preprohormone. The signal sequence of this large protein is cleaved in the endoplasmic reticulum to form a prohormone. Subsequently, in the Golgi apparatus the prohormone is packaged in secretion granules along with proteolytic enzymes that cleave the prohormone into active hormone and other fragments. When the endocrine cell is stimulated, the secretion granules migrate from the cytoplasm to the cell membrane. Free hormone and co-peptides are then released into the extracellular fluid by exocytosis.

Steroid Hormones Are Synthesized from Cholesterol. In contrast to protein/peptide hormones, there is little hormone storage in steroid-producing endocrine cells. Typically, there are large stores of cholesterol esters in cytoplasmic vacuoles that can be rapidly mobilized for synthesis of steroid hormones after stimulation of the steroid-producing cell. Once the steroid hormone appears in the cytoplasm, storage does not take place, and the hormone diffuses through the cell membraneinto the extracellular fluid. Much of the cholesterol in steroid-producing cells is removed from the plasma, but there is also de novo synthesis of cholesterol from acetate.

Thyroid Hormones and Catecholamines Are Synthesized from Tyrosine.

As with steroid hormones, there is no storage of thyroid hormones in discrete granules, and once thyroid hormones appear in the cytoplasm of the cell they leave the cell via diffusion through the cell membrane. In contrast to steroid hormones, there are large stores of thyroxine and triiodothyronine as part of a large iodinated protein (thyroglobulin) that is stored in the lumens of thyroid follicles. In comparison, the other group of hormones derived from tyrosine, the adrenal medullary hormones epinephrine and

norepinephrine, are taken up into preformed vesicles and stored until secreted. As with protein hormones stored in secretion granules, catecholamines are released from adrenal medullary cells through exocytosis.

Control of Hormonal Secretion and Negative Feedback

In most instances, the rate of hormonal secretion is controlled by negative feedback. In general, endocrine glands tend to oversecrete hormone, which in turn drives target cell function. When too much function of the target cell occurs, some factor about the function feeds back to the endocrine gland and causes a negative effect on the gland, decreasing its secretory rate

Mechanisms of Hormonal Action

Hormonal Receptors and Their Activation

Hormones control cellular processes by interacting with receptors on target cells. These receptors are (1) either on or within the cell membrane, as in the case of peptide/protein and catecholamine hormones, and (2) within the cell, in either the cytoplasm or nucleus, as is the case for steroid and thyroid hormones. Receptors are usually specific for a single hormone. The hormone-receptor interaction is coupled to a signalgenerating mechanism that then causes a change in intracellular processes by altering the activity or concentration of enzymes, carrier proteins, and so forth.

Mediating Hormonal Responses

Cell Responses to Protein/Peptide and Catecholamine Hormones Are Mediated by Second Messengers. In the case of peptide/protein and catecholamine hormones that do not readily pass the cell membrane, interaction with the receptor on or within the cell membrane often results in generation of a second messenger, which in turn mediates the hormonal response. Often, coupling G-proteins in the cell membrane link hormone receptors to the second messenger mechanisms. Second messenger mechanisms include the following:

- Adenylyl cyclase–cyclic adenosine monophosphate (cAMP). Hormone-receptor interaction may stimulate (or inhibit) the membrane-bound enzyme adenylyl cyclase. Stimulation of this enzyme results in synthesis of the second messenger cAMP. The cAMP activates protein kinase A, leading to phosphorylation that either activates or inactivates target enzymes.
- Plasma membrane phospholipids. Hormone-receptor interaction activates the membrane-bound enzyme phospholipase C, which in turn causes phospholipids in the cell membrane (especially those derived from

phosphatidylinositol) to split into the second messengers diacylglycerol and inositol triphosphate. Inositol triphosphate mobilizes calcium from internal stores, such as the endoplasmic reticulum, and the calcium in turn activates protein kinase C. Phosphorylation of enzymes by protein kinase C activates and deactivates enzymes mediating the hormone responses. In addition, the activity of protein kinase C is further enhanced by the second messenger diacylglycerol. Finally, diacylglycerol is hydrolyzed to arachidonic acid, which is the precursor for prostaglandins, which also influence hormonal responses.

Calcium-calmodulin.

Hormone-receptor interaction activates calcium channels in the plasma membrane, permitting calcium to enter cells. Calcium may also be mobilized from intercellular stores such as the endoplasmic reticulum. The calcium ions bind with the protein calmodulin, and this complex alters the activity of calcium-dependent enzymes and thus intercellular reactions.

Protein/peptide hormones may exert actions independent of G-protein-linked second messenger events, and other second messenger mechanisms may transduce hormonal responses. For example, the second messengercyclic GMP mediates the effects of atrial natriuretic peptide. Furthermore, in the case of the peptide hormone insulin, hormone binding to the cell surface receptor results in phosphorylation of an intracellular site of the receptor, which in turn alters enzymatic activity by phosphorylating (or dephosphorylating) other proteins in the cell. Cell Responses to Steroid and Thyroid Hormones Are Mediated by Stimulating Protein Synthesis. In contrast to protein/peptide hormones and catecholamines, steroid and thyroid hormones enter the cell and bind to intracellular receptors located in the cytoplasm or nucleus of the cell. The hormone-receptor interaction results in a conformational change in the receptor. This permits binding of the hormone-receptor complex to specific points on DNA strands in the chromosomes, which results in activation of specific genes, transcription, and translation of proteins that are essential for mediating the hormonal response. Because the transcription mechanism is involved in mediating the hormonal response, hours may be required for the biologic effects to become evident.