Introduction to Endocrine System-1

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Regulatory Systems

- Communicate and coordinate body functions

- *Nervous System*
  - Integrates tissue function by a network of cells and cell processes

- *Endocrine System*
  - Integrates organ function through chemicals that are secreted from endocrine tissues or «glands» into the extracellular fluid

Hormones

- Chemicals that are secreted from endocrine tissues, carried through the blood to distant target tissues, bind to specific, high-affinity receptors.

- Very low concentration (10^{-9} to 10^{-12} M)
- Accuracy and sensitivity are enabled by receptors
- Biological action is exerted by signal transduction pathways
  - Rapid response (e.g. increased heart rate by epinephrine)
  - Slow response (e.g. increases in protein synthesis caused by growth hormone)

Endocrine signalling

- Chemical signaling can occur through endocrine, paracrine, or autocrine pathways
- All three modes are in action to provide a complex regulatory system

Endocrine Glands

- Pituitary
- Hypothalamus
- Thyroid
- Parathyroids
- Testes
- Ovary
- Adrenal (cortex and medulla)
- Endocrine pancreas

- Gastrointestinal tract
- Liver
- Heart
- Kidney, etc.

- Neoplastic tissue

Paracrine Factors

- Somatostatin
  - Paracrine action → secreted by delta cells of the pancreatic islet cells and regulate insulin and glucagon secretion
  - Endocrine action → released by nerve terminals in the hypothalamus into the pituitary portal bloodstream and reaches to anterior pituitary. Inhibits the secretion of growth hormone

Chemical Classification of Hormones

- Peptide Hormones a large group of hormones made by a variety of endocrine tissues

- Very specialized tissues can synthesis catecholamins and steroid hormones due to necessary enzymatic steps (synthesis of thyroid hormone is more complex and restricted only to thyroid gland)

- Several glands make two or more hormones
  - Individual cells are specialized to secrete a single hormone

Circulation of Hormones

- Hormones can circulate either free or bound to carrier proteins

- Thyroid hormones (thyroxine [T4] and triiodothyronine [T3]), steroid hormones, insulin like growth factor types 1 and 2 (IGF-1 and IGF-2), and GH form complexes with circulating binding proteins
  - Reservoir of the hormone → minimizases fluctuations
  - Extends the half-life of the hormone in the circulation
  - Mostly hormones whose actions are long term

Measurement of circulating hormones

- A displacement curve is created by plotting the amount of radioactively labeled hormone complexed to the antibody as a function of the concentration of unlabeled hormone that is added

- Two assumptions
  - Specific binding of the hormone and antibody
  - No interference with normal binding of the hormone to the antibody

Hormone-hormone interactions

- Hormones can have complementary and antagonistic actions
  - Complex physiological functions necessitates the complementary action of several hormones
  - Complementary action: body's response to a short-term period of exercise
    - epinephrine (adrenaline), cortisol, glucagon
  - Counterpoised action: regulation of blood glucose level
    - Insulin, glucagon

Endocrine regulation

Feedback control of hormone secretion

Simple loop

1. Plasma glucose increase
2. Detection by beta cells of the pancreas
3. Insulin secretion
4. Decrease in glucose synthesis and internalization of glucose to muscles
5. Lower plasma glucose levels
6. Lowered insulin secretion by beta cells

Endocrine regulation

Feedback control of hormone secretion

Hierarchical loop: interaction between the CNS and the endocrine system

- E.g. extensive blood loss

1. Cerebral cortex stimulates the hypothalamus
2. Release of corticotropin-releasing hormone (CRH)
3. Stimulation of anterior pituitary by CRH via the pituitary portal system
4. Release of ACTH
5. Stimulation of adrenal cortical cells
6. Synthesis of cortizol
7. Regulation of vascular tone

- Involves two glands, the pituitary and the adrenal cortex, as well as specialized neuroendocrine tissue in the hypothalamus and the CNS
- Regulated by feedback on several levels

Peptide Hormones

- Specialized endocrine cells synthesize, store, and secrete peptide hormones
- Direction to endoplasmic reticulum

Peptide Hormones

- Processing in the endoplasmic reticulum (glycosylation, etc.)

1. Regulated pathway: transfer throughout golgi. Stored in secretory vesicle or granüle. external stimuli can trigger release or synthesis of hormone

2. Constitutive pathway: more directly from endoplasmic reticulum or cis-golgi. less responsive to triggers

- Exocytosis of the vesicular content

Peptide Hormones

- Peptide hormones bind to cell surface receptors and activate a variety of signal transduction systems

- Receptors bind to circulating hormone with very high affinity (10^{-8} to 10^{-12}M)

- The receptor provides the link between a specific extracellular hormone and the activation of a specific signal transduction system.

Peptide Hormones

G Proteins Coupled to Adenylyl Cyclase

1. activation of a heterotrimeric G protein (α_s or α_i)
2. activation (by α_s) or inhibition (by α_i) of a membrane-bound adenylyl cyclase
3. formation of intracellular cAMP from ATP, catalyzed by adenylyl cyclase
4. binding of cAMP to the enzyme protein kinase A (PKA)
5. separation of the two catalytic subunits of PKA from the two regulatory subunits
6. phosphorylation of serine and threonine residues on a variety of cellular enzymes and other proteins by the free catalytic subunits of PKA that are no longer restrained
7. modification of cellular function by these phosphorylations

- Termination of activation can be in two ways;
  - phosphodiesterases in the cell degrade cAMP
  - serine/threonine-specific protein phosphatases can dephosphorylate enzymes and proteins that had previously been phosphorylated by PKA

Peptide Hormones

G Proteins Coupled to Phospholipase C

1. activation of $G\alpha_q$
2. activation of a membrane-bound phospholipase C (PLC)
3. cleavage of phosphatidylinositol 4,5-biphosphate (PIP_2) by PLC → inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG)
4. binding of $IP_3$to a receptor on the cytosolic surface of the endoplasmic reticulum
5. release of Ca^{2+} from internal stores → rise of $[Ca^{2+}]i$ by several-fold
6. activation of Ca^{2+}-dependent kinases (e.g., Ca^{2+}-calmodulin–dependent protein kinases, protein kinase C [PKC])
7. alteration of cell function.

Peptide Hormones

G Proteins Coupled to Phospholipase A2

1. activation of $G\alpha_q$ or $G\alpha_{11}$
2. stimulation of membrane-bound PLA_2 by the activated $G\alpha$
3. cleavage of membrane phospholipids by PLA_2 to produce lysophospholipid and arachidonic acid
4. conversion—by certain enzymes—of arachidonic acid into a variety of biologically active eicosanoids (e.g., prostaglandins, prostacyclins, thromboxanes, and leukotrienes)

Peptide Hormones

Guanylyl Cyclase

1. Hormone binds to areceptor that is itself a guanylyl cyclase
2. Guanylyl cyclase converts cytoplasmic GTP to cGMP
3. Activation of cGMP dependent kinases, phosphatases or ion channels

Peptide Hormones

Receptor Tyrosine Kinases

1. Hormone receptor has tyrosine kinase activity
2. Hormone binding increases kinase activity
3. Kinase within the receptor autophosphorilates tyrosines as well as substrates within the cytosol

Peptide Hormones

Tyrosine Kinase–Associated Receptors

1. Hormone binding to receptor activates a cytoplasmic tyrosine kinase
2. Cascade of phosphorylation reactions

Amine Hormones

- Made from tyrosine and tryptophan
  - Epinephrine, norepinephrine:
    - principal active amine hormones
    - adrenal medulla
    - Stored in chromaffin vesicles
  - Dopamin:
    - synthesized in certain tissues, functional role outside the nervous system is not well clarified
  - Serotonin:
    - synthesized by endocrine cells that are located within the gut mucosa
    - regulate both motor and secretory function of the gut

Amine Hormones

- Secretion mediated by stimulation of the sympathetic division of ANS
- Amine hormones do not have a hierarchic feedback system
  - indirect feedback: a physiological end effect of that amine hormone (e.g., blood pressure) is sensed

Amine Hormones

- Serotonin
  - Made by neuroendocrine cells (not by a specific gland) located within the small intestine and larger bronchi
  - Carcinoid tumors:
    - release serotonin
    - can occur within the intestinal tract, in the bronchial tree, etc.
    - Carcinoid syndrome: spontaneous, intense flushing in a typical pattern involving the head and neck, associated with diarrhea, bronchospasm, and occasionally right-sided valvular heart disease

Amine Hormones

- Adrenoreceptors are G-coupled receptors
- Intracellular action of a specific catecholamine is determined by the complement of receptors present on the surface of a specific cell
  - Dopamine
    - Binding to DA-1 → $G\alpha_s$ → stimulation
    - DA-2 → $G\alpha_i$ → inhibition
- Adrenergic effect: glycogenolysis in the liver or muscle (predominantly a β effect), contraction (α1) or relaxation (β2) of vascular smooth muscle, a change in the inotropic or chronotropic state of the heart (β1), etc.

Steroid Hormones

- cortisol, aldosterone, estradiol, progesterone, and testosterone
- Precursor is cholestrol

- Adrenal cortex
  - cortisol
  - aldosterone
  - Androgens

- Gonads
  - estrogen and progesterone
  - testosterone

Steroid Hormones

- Most of the cholesterol used for steroid synthesis comes from LDL
- A small amount is synthesized from acetate

- LDL is internalized by receptor-mediated endocytosis
- Release of free cholestrol by lysosomal hydrolases
- Synthesis of pregnenolone (common precursor of all steroid hormones)
- Metabolization to major steroid hormones

- Poorly soluble in water
- In circulation steroid hormones associate with specific binding proteins (e.g., sex hormone–binding globulin) that transport steroids to target tissues

Steroid Hormones

- Intracellular receptor
- Enter target cell through simple diffusion across the plasma membrane
- High affinity binding →change of conformation→ active receptor-hormone complex
- Binding to DNA sequences : Hormone response elements (steroid response elements; SREs)
- Regulation of transcription
- Termination: receptor is modified to permits dissociation of the hormone

Steroid Hormones

- Receptors dimerize on binding to their target sites on DNA
- DNA binding domain is very similar for steroids
- Mutations cause non-specific effects (e.g., substitution of two amino acids in the glucocorticoid receptor causes the mutated glucocorticoid receptor to bind to DNA to estrogen receptor binding sites – estrogen like effect)

Steroid Hormones

1. Binding to SREs regulates the rate of transcription of the gene
2. Stabilization of mRNA molecules and increase their half-life

- SREs are preserved through different cell types, but can be recognized by different steroid receptors in different cell types
  - The same SRE is recognised by
    - Progesterone receptor in endometrium cell
    - Mineralocorticoid receptor in renal distal tubule
    - Glucocorticoid receptor

Thyroid hormones

- Bind to intracellular receptors that regulate metabolic rate
- The principal protein component is thyroglobulin
- By the iodination of tyrosine residues on the thyroglobulin T3 and T4 are formed, degraded within the lysosome of follicular cells and released into the circulation
- T4 is bound to a binding protein a d carried to its sites of action
- T3 has lower percentage in circulation (5%) but higher affinity – main effector of thyroid hormone signalling

Steroid and Thyroid Hormones

- Receptors can also bind to and modulate the activity of cytosolic proteins and can thereby regulate their activity or behavior through a nongenomic action

- Association of estrogen receptor (ERα) with phosphatidylinositol-3-kinase (PI3K), stimulates phosprylation ratio of catalytic subunit