Hormones & Chemical Signaling

Part 2 – modulation of signal pathways and hormone classification & function

Communication

Modulation of Signal Pathways

- How are these pathways controlled?
  - Receptors are proteins!
    - Subject to
      - Specificity of binding
      - Competition for binding site
        - » Agonists and antagonists
      - Saturation of ligand
        - » Up regulation and down regulation of receptors
  - Pathways are mechanisms under homeostasis guidelines

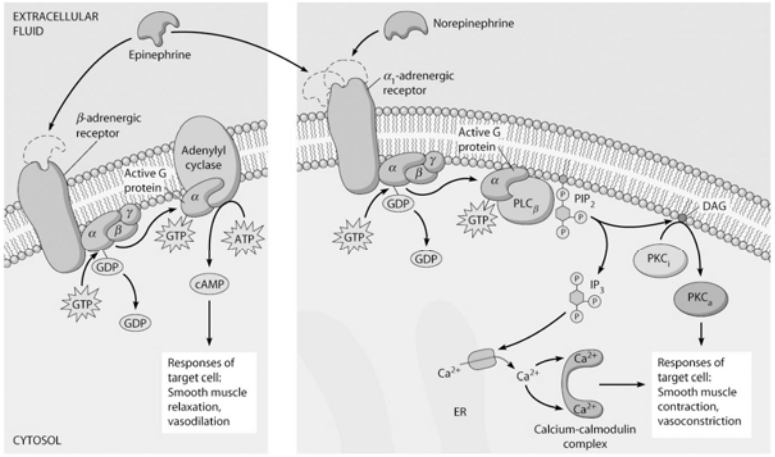
Communication

Modulation of Signal Pathways

- Specificity of Binding & Competition
  - Receptors have specific binding sites
  - Different compounds with similar molecular regions may bind to same site = competition
  - Ex. Epinephrine & norepinephrine have similar ligand structure and bind to a class of receptors called adrenergic receptors
    - Adrenergic receptors exhibit specificity
    - Adrenergic receptors are influence by competition

Communication

Modulation of Signal Pathways



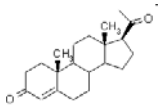
(a) cAMP pathway initiated by activation of β-adrenergic receptor

(b) Inositol-phospholipid-calcium pathway initiated by activation of α_1-adrenergic receptor

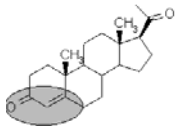
Communication

Modulation of Signal Pathways

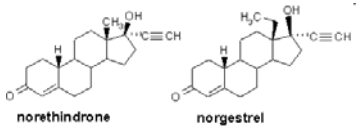
- Advances in medicines
  - Due to study of active sites and their properties
    - Slightly changing the non-binding areas may change the duration of action



progesterone



progesterone binding area (green)

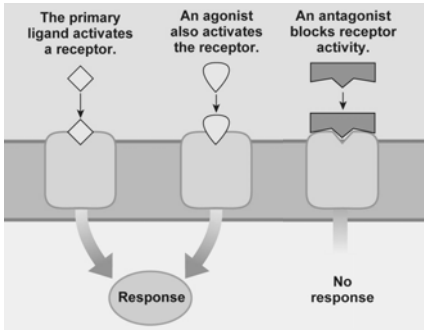


progesterone agonists (used in birth control medications)

Communication

Modulation of Signal Pathways

- Agonists vs. Antagonists
  - Agonists bind and cause activation
  - Antagonists bind and stop or prevent activation



Communication: Deadly Effects

- Muscarinic receptors

  - Bind acetylcholine (Ach) in the autonomic nervous system (ANS)
  - Also binds muscarine (a mushroom toxin) that
    - Mimics Ach (agonistic action) and can cause a severe parasympathomimetic to the point of death
- Nicotinic receptors
  - Bind Ach at neuromuscular junctions

  - Also binds curare (poison arrow frog toxin) and blocks the receptor (antagonistic action)
    - Causes paralysis and very potentially death

Communication

Modulation of Signal Pathways

- Up and Down-Regulation
  - Why?
    - To allow cells the ability to control the extent of signal pathway effect depending on
      - The concentration of signal in the ECF
      - The needs of the cell
      - Which form of diabetes would result in up and down regulation of insulin receptors?
    - Down-regulation vs desensitization
      - Down regulation is slower as cell needs to remove receptors from membrane
      - Desensitization is quicker as a binding agent can deactivate the receptor
        - » For ex. adding a phosphate can deactivate a receptor (β adrenergic receptors)

Communication

Modulation of Signal Pathways

- When the process has to stop
  - Enzymatic degradation of ligand
  - Removal of ligand by re-uptake
  - Endocytosis of receptor-ligand complex
    - Receptors can be reinserted into the membrane
- Why do we care about this process?
  - Disease & Disorders

Communication

Modulation of Signal Pathways

TABLE 6-3 Some Diseases or Conditions Linked to Abnormal Signaling Mechanisms

Genetically inherited abnormal receptors		
RECEPTOR	PHYSIOLOGICAL ALTERATION	DISEASE OR CONDITION THAT RESULTS
Vasopressin receptor (X-linked defect)	Shortens half-life of the receptor	Congenital diabetes insipidus
Calcium sensor in parathyroid gland	Fails to respond to increase in plasma Ca^{2+}	Familial hypercalcemia
Rhodopsin receptor in retina of eye	Improper protein folding	Retinitis pigmentosa
Toxins affecting signal pathways		
TOXIN	PHYSIOLOGICAL EFFECT	CONDITION THAT RESULTS
Bordetella pertussis toxin	Blocks inhibition of adenylate cyclase (i.e., keeps it active)	Whooping cough
Cholera toxin	Blocks enzyme activity of G proteins; cell keeps making cAMP	Ions secreted into lumen of intestine, causing massive diarrhea

Communication

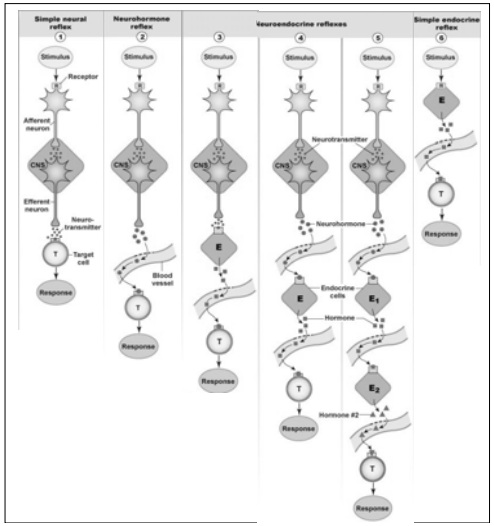
Pathways

- Controlled by homeostatic mechanisms regardless of type of pathway and resulting transduction of signal.

- What are the options for getting the signal to the cell for transduction?

Communication

Pathways



Communication

Pathways

- Similarities between neural and endocrine pathways?

TABLE 6-4 Comparison of Neural and Endocrine Control

PROPERTY	NEURAL REFLEX	ENDOCRINE REFLEX
Specificity	Each neuron terminates on a single target cell or on a limited number of adjacent target cells.	Most cells of the body are exposed to a hormone. The response depends on which cells have receptors for the hormone.
Nature of the signal	Electrical signal passes through neuron, then chemical neurotransmitters pass the signal from cell to cell. In a few cases, signals pass cell-to-cell through gap junctions.	Chemical signals are secreted in the blood for distribution throughout the body.
Speed	Very rapid.	Distribution of the signal and onset of action are much slower than in neural responses.
Duration of action	Usually very short. Responses of longer duration are mediated by neuromodulators.	Duration of action is usually much longer than in neural responses.
Coding for stimulus intensity	Each signal is identical in strength. Stimulus intensity is correlated with increased frequency of signaling.	Stimulus intensity is correlated with amount of hormone secreted.

Communication

Pathways

- The homeostatic pathways are

TABLE 6-5 Comparison of Neural, Neuroendocrine, and Endocrine Reflexes

	NEURAL	NEUROENDOCRINE	ENDOCRINE
Sensor or receptor	Special and somatic sensory receptors	Special and somatic sensory receptors	Endocrine cell
Afferent pathway	Afferent sensory neuron	Afferent sensory neuron	None
Integrating center	Brain or spinal cord	Brain or spinal cord	Endocrine cell
Efferent pathway	Efferent neuron (electrical signal and neurotransmitter)	Efferent neuron (electrical signal and neurohormone)	Hormone
Effector(s)	Muscles and glands, some adipose tissue	Most cells of the body	Most cells of the body
Response	Contraction and secretion primarily; may have some metabolic effects.	Change in enzymatic reactions, membrane transport, or cell proteins	Change in enzymatic reactions or membrane transport or cell proteins

Communication

Hormones

- What are they?
  - Chemical messengers secreted by specialized cells
    - from isolated endocrine cells which makes up the diffuse endocrine system
    - from neurons
    - from immune system cells producing cytokines
  - Where do they go?
    - Into blood (most)
    - Into environment (ectohormones or pheromones)

Communication

Hormones

- Involved in
  - Growth
  - Development
  - Metabolism
  - Reproduction
- Act by
  1. Altering rates of enzyme mediated reactions
  2. Control the movement of molecules across the plasma membrane
  3. Regulating the rate of gene expression (& therefore protein production)

Communication
Hormones

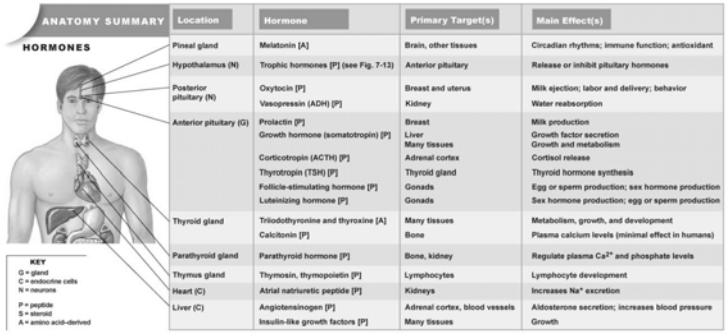
- How do hormones get from point A to B?
  - To be classified as hormone & not a paracrine or autocrine hormone
  - Travel in blood
    - May require water soluble (protein) transport mechanism if hormone is lipid soluble
- Hormones act by binding to receptor on target cells
- Hormones have to have a mechanism for ending the effect
  - Stop/reduce production of hormone
  - Degrate hormones
  - Enzymatic removal from receptor
  - Endocytosis of receptor-hormone complex

Communication
Hormone Classification

- Hormones are mainly classified by
  - Source
  - Structure

Communication
Hormone Classification

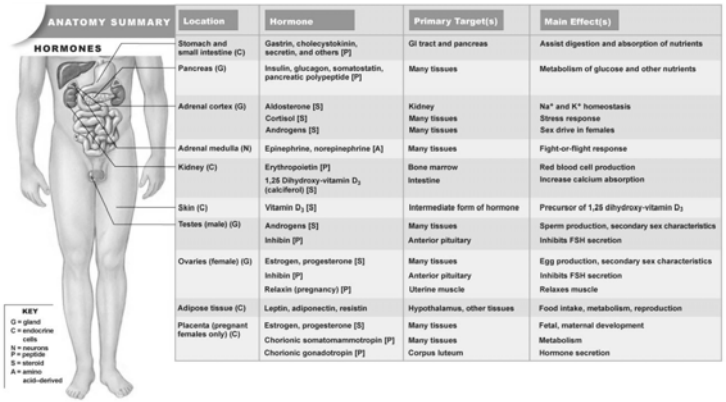
- Hormones classified by source



Location	Hormone	Primary Target(s)	Main Effect(s)
Pineal gland	Melatonin [A]	Brain, other tissues	Circadian rhythms; immune function; antioxidant
Hypothalamus (N)	Trophic hormones [P] (see Fig. 7-13)	Anterior pituitary	Release or inhibit pituitary hormones
Posterior pituitary (N)	Oxytocin [P]	Breast and uterus	Milk ejection; labor and delivery; behavior
	Vasopressin (ADH) [P]	Kidney	Water reabsorption
Anterior pituitary (G)	Prolactin [P]	Breast	Milk production
	Growth hormone (somatotropin) [P]	Liver Many tissues	Growth factor secretion Growth and metabolism
	Corticotropin (ACTH) [P]	Adrenal cortex	Cortisol release
	Thyrotropin (TSH) [P]	Thyroid gland	Thyroid hormone synthesis
	Follicle-stimulating hormone [P]	Gonads	Egg or sperm production; sex hormone production
	Luteinizing hormone [P]	Gonads	Sex hormone production; egg or sperm production
Thyroid gland	Triiodothyronine and thyroxine [A]	Many tissues	Metabolism, growth, and development
	Calcitonin [P]	Bone	Plasma calcium levels (minimal effect in humans)
Parathyroid gland	Parathyroid hormone [P]	Bone, kidney	Regulate plasma Ca^{2+} and phosphate levels
Thymus gland	Thymosin, thymopoietin [P]	Lymphocytes	Lymphocyte development
Heart (C)	Atrial natriuretic peptide [P]	Kidneys	Increases Na^+ excretion
Liver (C)	Angiotensinogen [P]	Adrenal cortex, blood vessels	Aldosterone secretion; increases blood pressure
	Insulin-like growth factors [P]	Many tissues	Growth

Communication
Hormone Classification

- Hormones classified by source



Location	Hormone	Primary Target(s)	Main Effect(s)
Stomach and small intestine (C)	Gastrin, cholecystokinin, secretin, and others [P]	GI tract and pancreas	Assist digestion and absorption of nutrients
Pancreas (G)	Insulin, glucagon, somatostatin, pancreatic polypeptide [P]	Many tissues	Metabolism of glucose and other nutrients
Adrenal cortex (G)	Aldosterone [S]	Kidney	Na^+ and K^+ homeostasis
	Cortisol [S]	Many tissues	Stress response
	Androgens [S]	Many tissues	Sex drive in females
Adrenal medulla (N)	Epinephrine, norepinephrine [A]	Many tissues	Fight-or-flight response
Kidney (C)	Erythropoietin [P]	Bone marrow	Red blood cell production
	1,25 Dihydroxy-vitamin D_3 (calciferol) [S]	Intestine	Increase calcium absorption
Skin (C)	Vitamin D_3 [S]	Intermediate form of hormone	Precursor of 1,25 dihydroxy-vitamin D_3
Testes (male) (G)	Androgens [S]	Many tissues	Sperm production, secondary sex characteristics
	Inhibin [P]	Anterior pituitary	Inhibits FSH secretion
Ovaries (female) (G)	Estrogen, progesterone [S]	Many tissues	Egg production, secondary sex characteristics
	Inhibin [P]	Anterior pituitary	Inhibits FSH secretion
	Relaxin (pregnancy) [P]	Uterine muscle	Relaxes muscle
Adipose tissue (C)	Leptin, adiponectin, resistin	Hypothalamus, other tissues	Food intake, metabolism, reproduction
Placenta (pregnant females only) (C)	Estrogen, progesterone [S]	Many tissues	Fetal, maternal development
	Chorionic somatomammotropin [P]	Many tissues	Metabolism
	Chorionic gonadotropin [P]	Corpus luteum	Hormone secretion

Communication
Hormone Classification

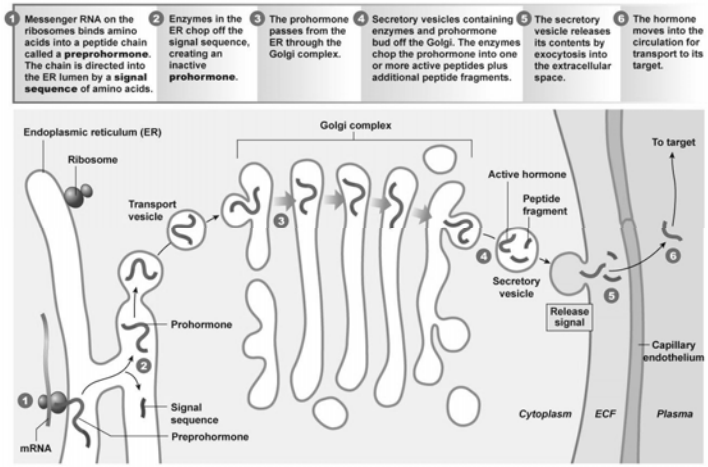
- Hormones classified by structure
  - – Peptide/protein hormones
  - – Steroid hormones
  - – Amino acid based hormones
    - Derived from tyrosine and may be
      - – Catecholamines
      - – Thyroid hormones

Communication
Hormone Classification

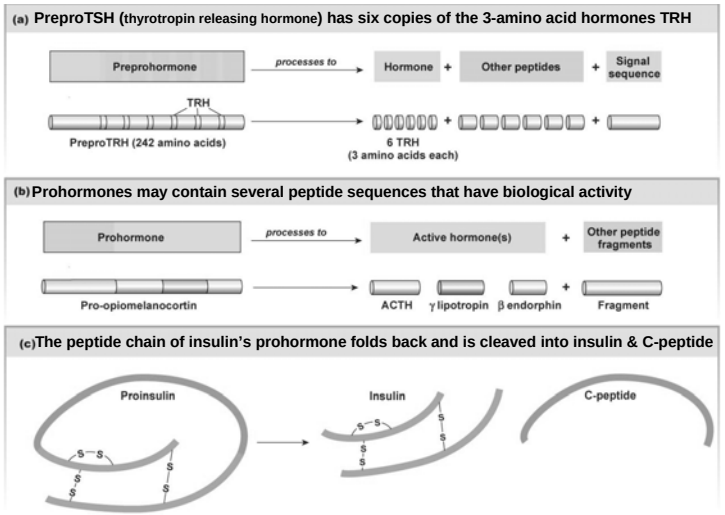
- Peptide/protein hormones
  - – Classification that includes most hormones
  - – If a hormone is not a steroid hormone or an amino acid derived hormone, then it is a protein/peptide hormone!
    - Concerns with these hormones
      - – How they are made, stored and released
      - – How they are transported in blood
      - – The mechanism of action
      - – How long they last

Communication
Hormone Classification

- Peptide/protein hormones & how they are made, stored and released



Communication
Hormone Classification



Communication
Hormone Classification

- Peptide/protein hormones
  - Cellular action mechanism
    - Lipophobic – must bind to receptors on membrane's ECF surface
    - Most work via cAMP messenger system
    - Some via receptor-enzyme complexes
      - Enzyme attached and activated by binding is tyrosine kinase (recall these enzymes phosphorylate various substrates)
        - » Insulin binds, tyrosine kinase activated and phosphorylates glucose to glucose 6-phosphate

Communication
Hormone Classification

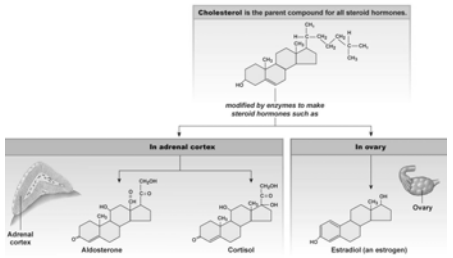
- Peptide/protein hormones
  - Duration
    - Depends on method of hormone action termination
    - Depends on molecule (some synthetic hormones have been modified to last longer)

Communication
Hormone Classification

- Steroid Hormones
  - Lipophilic – creates problems
    - No storage
    - Production is on an "as needed" basis
    - Can have the precursors in cytoplasm ready to go
    - Require protein transports in blood
      - prolongs duration of hormone
      - Blocks entrance into cell… it must disengage from carrier this follows law of mass action…

Communication
Hormone Classification

- Steroid hormones
  - Based on cholesterol
  - Produced using SER in the
    - Adrenal cortex
    - Gonads
    - Placenta
  - Secretion is by simple diffusion



Communication

Hormone Classification

- Steroid Hormones
  - Cellular mechanism of action
    - Diffuses into cytosol and or into the nucleus
    - Acts as a transcription factors in the nucleus to alter gene activity by
      - Repressing or activating rates of transcription
      - Lag period due to the processes that have to occur
    - Transcription factors have DNA binding domains (DBDs) that tells them where to bind on the DNA (there are approx. 2000 known human transcription factors with specific DBDs
    - How are they regulated?
      - Negative feedback loop – increased transcription factors cause a decrease in production
      - Phosphorylation – may stop transcription
      - Ligand binding to transcription factors or cofactors that regulate the transcription factors…

- New(er) research indicates that some steroid hormones have membrane receptors and signal transduction pathways similar in process to peptide/protein hormones
  - Nongenomic actions also attributed to aldosterone and estrogen

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1: Thyroid. 1996 Oct;6(5):497-504.

Nongenomic actions of thyroid hormone.

Davis PJ, Davis FB.

Department of Medicine, Albany Medical College, New York 12208, USA.

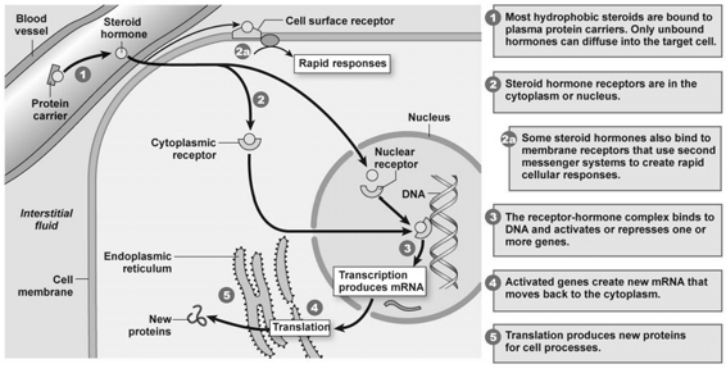
Nongenomic actions of thyroid hormone are by definition independent of nuclear receptors for the hormone and have been described at the plasma membrane, various cell organelles, the cytoskeleton, and in cytoplasm. The actions include alterations in solute transport (Ca2+, Na+, glucose), changes in activities of several kinases, including protein kinase C, cAMP-dependent protein kinase and pyruvate kinase M2 (PKM2), effects on efficiency of specific mRNA translation and mRNA t1/2, modulation of mitochondrial respiration, and regulation of actin polymerization (promotion of formation of F-actin). Iodothyronines also can regulate nongenomically the state of contractile elements in vascular smooth muscle cells (VSMC). The physiologic significance at the cellular level of certain of these actions has been demonstrated, for example, in the cases of myocardiocyte Na+ current, red cell Ca2+ content, and the control by hormone-induced alterations in actin solubility of cell surface activity of iodothyronine 5'-monodeiodinase activity and the intracellular distribution of protein disulfide isomerase activity. The physiologic significance of these actions at the organ or system level is less clear, but extranuclear effects of thyroid hormone on myocardial Na+ channel, sarcoplasmic reticulum Ca(2+)-ATPase activity, and contractile state of VSMC may each contribute to acute effects of thyroid hormone on cardiac output that have recently been described clinically. The molecular mechanisms for nongenomic actions are incompletely understood; relevant binding sites and signal transduction pathways have been described for hormone actions on plasma membrane Ca(2+)-ATPase activity, and PKM2 monomer is known to bind T3 and, as a result, prevent activation of the kinase via tetramer formation. Nongenomic actions of thyroid hormone may have different structure-activity relationships of iodothyronines from those effects that depend upon nuclear receptors; they may have different time courses and may invoke complex signal transduction pathways before the action is detected.

PMID: 8936679 [PubMed - indexed for MEDLINE]

Communication

Hormone Classification

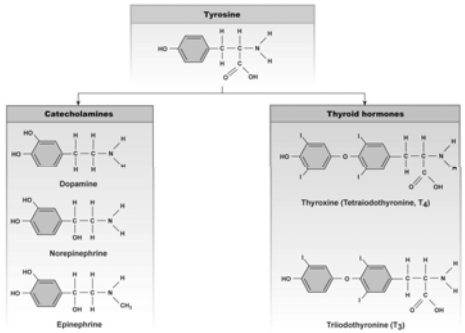
- Steroid Hormone Action



Communication

Hormone Classification

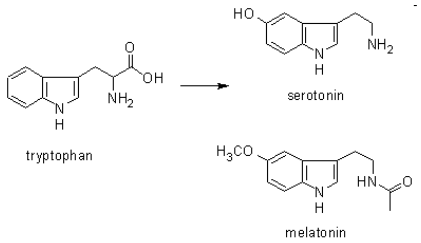
- Amino acid derived hormones may be
  - Derived from tyrosine
  - Produces
    - T_3 & T_4
    - Epinephrine & norepinephrine



Communication

Hormone Classification

- Amino acid derived hormones may be
  - Derived from tyrptophan
  - Produces
    - Melatonin
    - Serotonin*



**serotonin is classified as a neurohormone as it is synthesized and secreted by neurons of the GI tract for regulation of motility and CNS*

Communication

Hormone Controls

- Hormones are controlled by reflex pathways most utilizing negative feedback loops!
  - May have multiple controls though