The endocrine system: An introduction

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What does “endocrine” mean?

- The endocrine system is a collection of ductless glands that secrete chemical messengers into the blood called hormones.
  - Tissues that are not considered as endocrine glands such as kidneys, liver, and heart may act as such.
- “Endocrine" denotes internal secretion of biologically active substances.
- “Exocrine" denotes secretion outside of body (e.g. sweat glands).

What does “hormone” mean?

- The word “hormone” is derived from the Greek *hormao* meaning 'I excite or arouse‘.

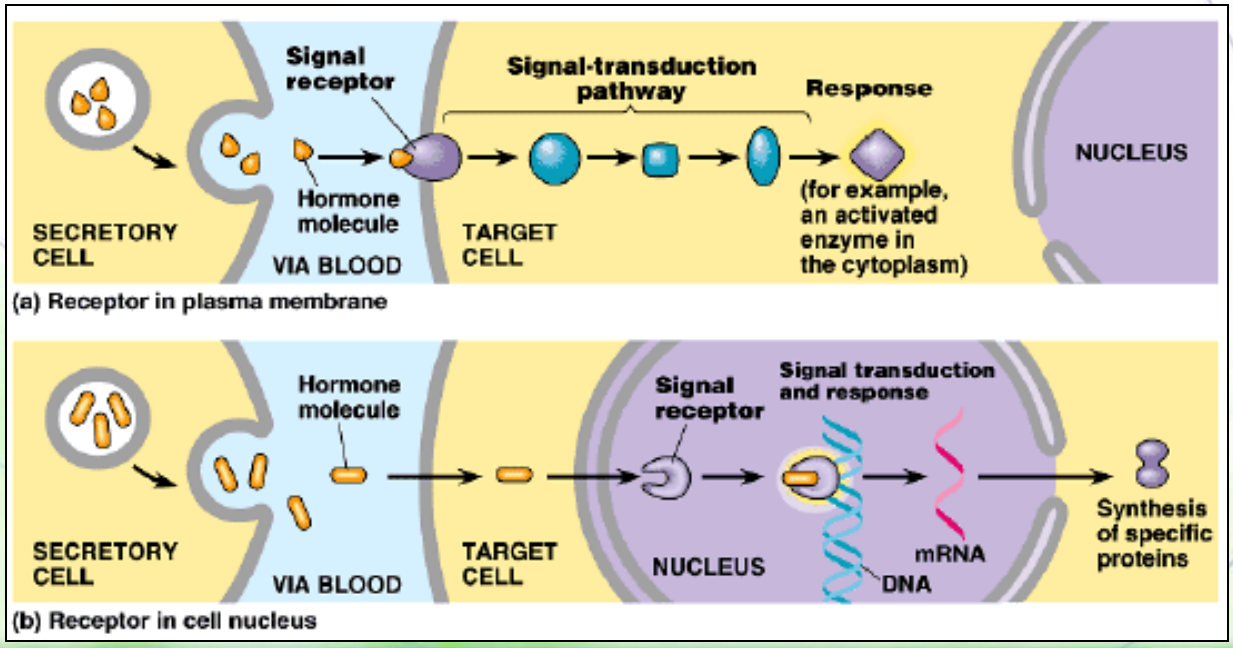
- Hormones are defined as substances released by endocrine glands and transported via bloodstream to tissues where they can act to regulate specific functions (*too restrictive; paracrine, autocrine*).
  - >50 known hormones produced by few, but act on many

Location of glands: examples

- Hormone producing cells are NOT randomly distributed
  - Spermatogenesis occurs in the seminiferous tubules that are next to the Leydig cells, which produce testosterone that is required for this process.
  - Hepatic production of glucose is regulated by the insulin/glucagon ratio; the pancreas, which produces both of these hormones, is in close proximity to the liver.
  - Hypothalamus and anterior pituitary are in close proximity so that high concentrations of hypothalamic-releasing hormones can reach the pituitary target via a special portal vascular system.
  - Adrenal cortex produces cortisol, which is required in the adrenal medulla for catecholamine synthesis, reaches the medulla by a special portal vascular system.

Hormone receptors

- Hormones cause cellular alterations via protein receptors.
- The cellular localization of hormonal receptors depends on the type of hormones
  - Lipid-soluble: intracellular
  - Water-soluble: extracellular

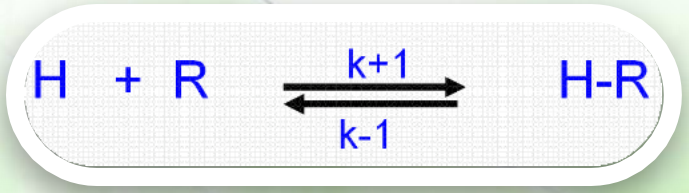


Receptors Discriminate Precisely

- Major challenge:
  - Hormone (10^{-18} to 10^{-9} mol/L) vs. structurally similar molecules (sterols, amino acids, peptides, and proteins) at 10^{-6} to 10^{-3} mol/L

Features

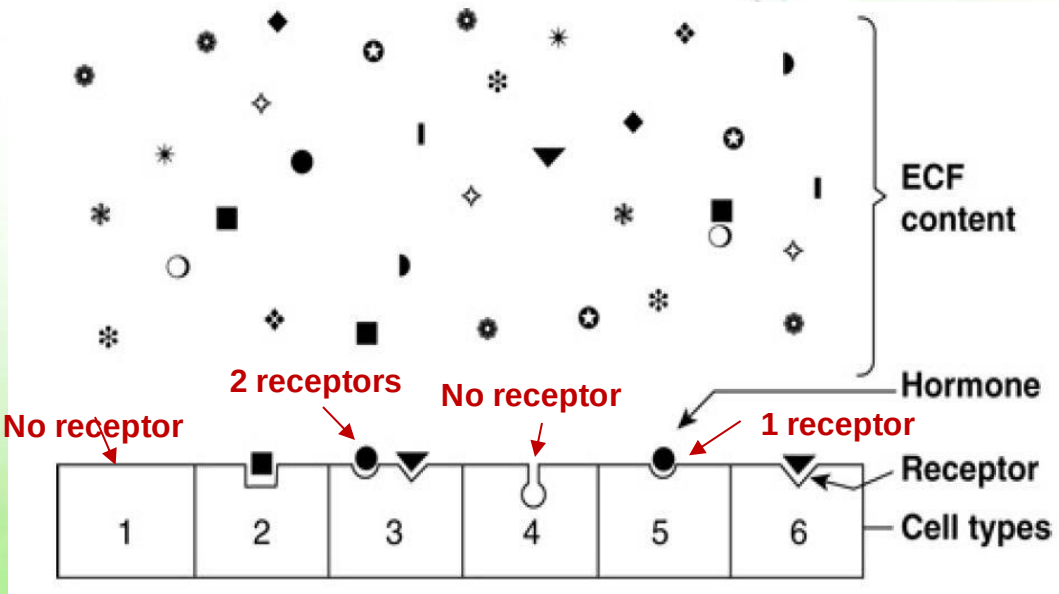
- Should be specific and displaceable by agonist/antagonist
- Should be saturable
- Concentration reflects needed biologic response
- Is usually 20-folds more than dissociation constant



$K_d = \{[H] X [R]\} / [H\text{-}R]$

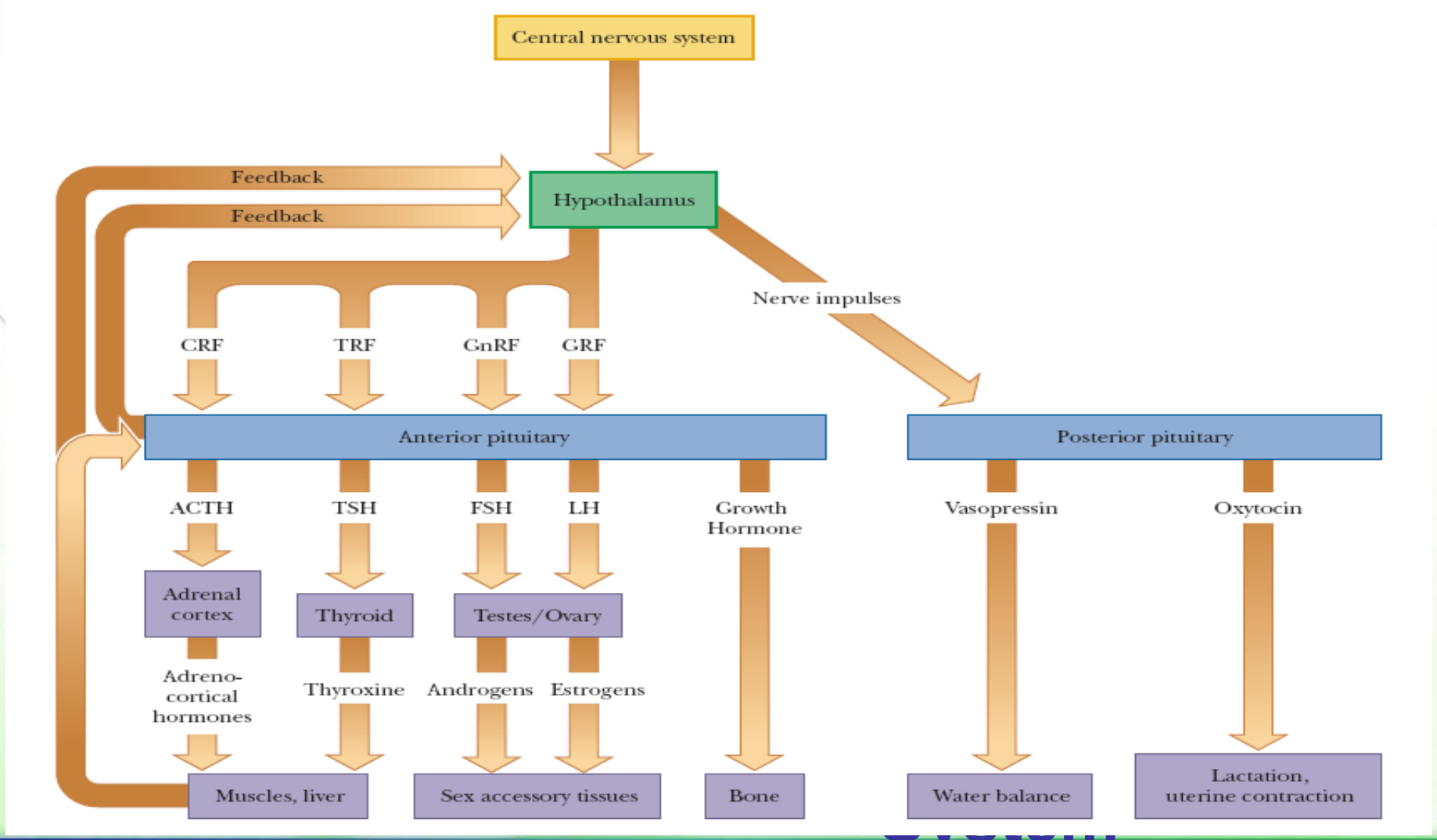
K_d values = 10^{-9} to 10^{-11} M

Specificity and selectivity of hormone receptors



Nervous vs./& endocrine systems

The endocrine system works in parallel and conjunction with the nervous system.



Endocrine vs. nervous systems

Criteria	Nervous	Endocrine
Range of effect	localized	widespread
Mediator	neurotransmitter	hormone
Effector cells	neurons	multiple tissues
Cellular targets	other neurons, muscle cells, glands	all tissues
Type of signal	chemical and electrical signals	chemical signals only
Mode of transmission	cell to cell only	Local and systemic
Onset of action	immediate response	gradual response (seconds – hours)
Duration of action	short lived (ms – minutes)	longer – lived effects (minutes – days)

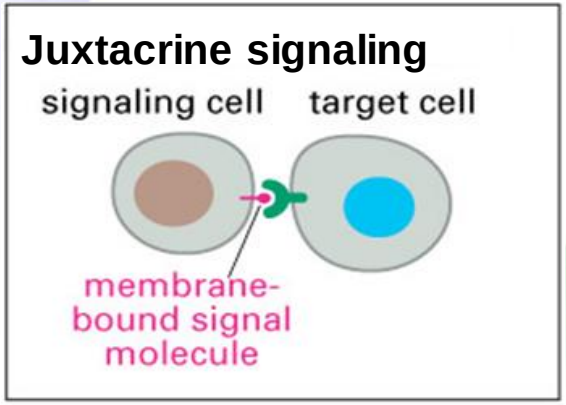
Types of hormones

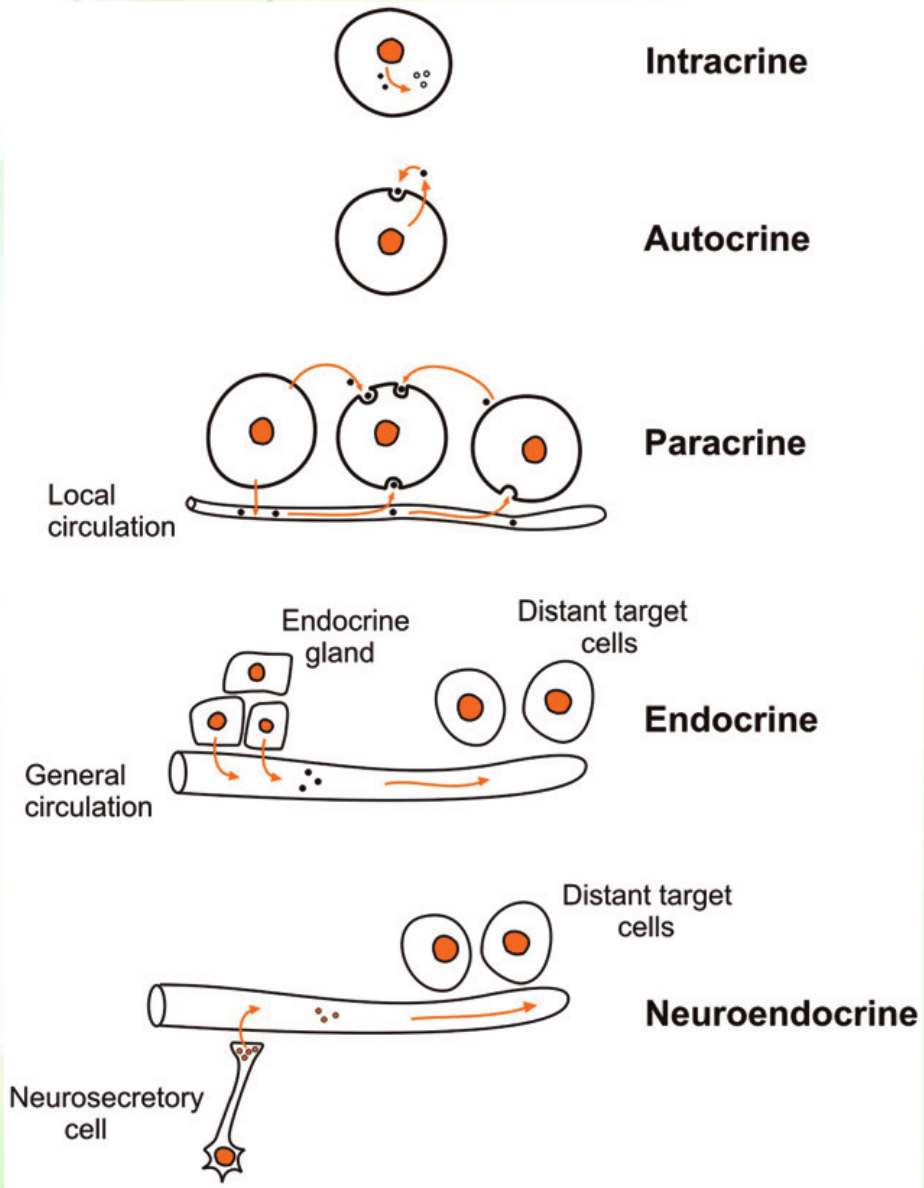
- True hormones: secreted into the blood by endocrine glands
  - thyroxine, epinephrine (adrenaline), estradiol, insulin
- Neurohormones: secreted by nerve cells. Many classic neurotransmitters (catecholamines, dopamine, acetylcholine, etc.) are similar to classic hormones with regard to synthesis, release, transport, and mechanism of action.
  - Catecholamines are neurotransmitters in one tissue and hormones in another.

Chemicals shared between Nervous and Endocrine Systems

	as Neurotransmitter	as Hormone
Endorphins	binds to pain receptors in brain	released from hypothalamus during times of stress
Enkephalins	blocks pain perception	blocks pain sensations
Dopamine	"feel good" neurotransmitter in limbic system & midbrain	inhibits secretion of prolactin
Estrogen, Progesterone	affects appetite center & body temp in hypothalamus and stimulates sexual arousal pathways	initiate secondary sex characteristics, follicular development & menstrual cycle
Testosterone	stimulates sexual arousal pathways and orgasm reflex	initiate secondary sex characteristics & spermatogenesis
Norepinephrine, Epinephrine	"feel good" neurotransmitter in limbic system and sympathetic branch	maintains sympathetic response
Prolactin	neurotransmitter in brain anterior pituitary	milk production
Leutinizing Hormone	neurotransmitter in brain anterior pituitary	maturation and development of reproductive system

Types of chemical signaling





Types of responses

- An endocrine mechanism is chemical communication between cells distant from each other. Mostly, hormones are transported via the bloodstream. Classical hormones act via this mechanism.
- A paracrine mechanism is chemical communication between neighboring cells within a tissue or organ.
- An autocrine mechanism is a chemical action on the same cell (or cell type).
- A neuroendocrine mechanism is a chemical communication between nerve cells and distant target cells.

Types of responses

- An intracrine mechanism is where the intracellular hormones sends the signal inside the producing cells itself
- A Juxtacrine mechanism is a mechanism by which the hormone is bound to the cell surface of one cell and interacts with the receptor on a neighboring, juxtaposed cell.
- A pheromonal mechanism entails secretion by one organism and sensation and response by a second one

Levels of regulation

- There are varied and sophisticated mechanisms that regulate hormone
  - synthesis,
  - release,
  - transport in circulation,
  - metabolism,
  - delivery to the surface or interior of target cells, and
  - intracellular signaling

The Target Cell Concept

- A target is any cell in which the hormone (ligand) binds to its receptor, regardless of the action.
  - 200 types of differentiated cells in humans, but only a few produce hormones!
  - All of 75 trillion cells in a human are targets to one or more

- One hormone → several cell types
- One cell type → several hormones
- One hormone → several effects

The Target Cell Concept

- Several factors determine the response of a target cell to a hormone:

Factors affect the concentration of the hormone at the target cell
✓ The rate of synthesis and secretion of the hormone
✓ The proximity of the target cell to the hormone source (dilution)
✓ The $\mathbf{K_d}$ of the hormone – receptor complex
✓ The rate of conversion of inactive form to the fully active form
✓ The rate of clearance from the plasma

The Target Cell Concept

- Several factors determine the response of a target cell to a hormone:

Factors affecting the target cell response
✓ The number, relative activity, and state of occupancy of receptors
✓ The metabolism (activation / inactivation) of the hormone in the target cell
✓ The presence of factors within target cells necessary for the response
✓ Up- or down-regulation of the receptors upon interaction with ligand ✓ Post-receptor desensitization of the cell

Bases of classification of hormones

- Solubility (and transport)
- Chemistry
- Synthesis
- Processing and modification
- Pharmacology-based

Solubility

- Water-soluble: such as modified amino acids, proteins or peptides, and eicosanoids
- Lipid-soluble such as steroids, thyroid hormones, and nitric oxide

Transport of hormones and their half-lives

- Steroid and thyroid hormones are less soluble in aqueous solution than protein and peptide hormones and over 90% circulate in blood as complexes bound to specific plasma globulins or albumin

- Bound and free hormones are in equilibrium

Free vs. bound hormone

- Hormone binding delays their metabolism and slows down their actions
- Thus, assays of total hormone concentrations do not reflect changes in free hormone concentrations
- Also, measurement of free and active hormone may be more important than measuring total hormone concentration
- Measurement of biologically relevant free hormone concentrations, however, is generally more difficult than measuring total hormone concentrations

Half-lives of hormones

- The rates of metabolism of hormones in the circulation vary but, in general, the half life (t1/2) of:
  - catecholamines from the adrenal medulla is in the order of seconds,
  - minutes for protein and peptide hormones and
  - hours for steroid and thyroid hormones

Factors affecting hormone concentration

- Rate of production: Synthesis and secretion of hormones
- Rate of delivery: An example of this effect is blood flow to a target organ or group of target cells - high blood flow delivers more hormone than low blood flow
- Rate of degradation and elimination: Hormones are metabolized and excreted from the body through several routes. Shutting off secretion of a hormone that has a very short half-life causes circulating hormone concentration to drop

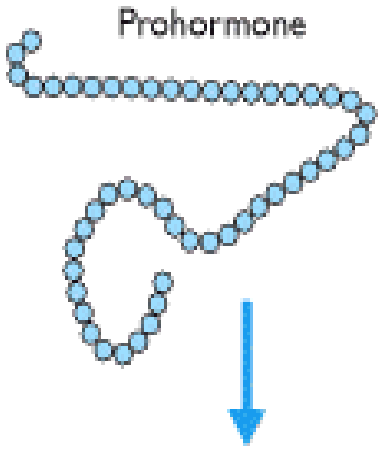
Other factors

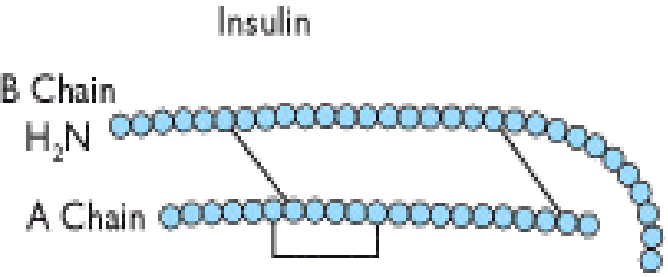
- Changes in binding proteins
- Age
- Gender
- Developmental stage
- Reproductive status
- Stage of temporal rhythm

Chemical Classification

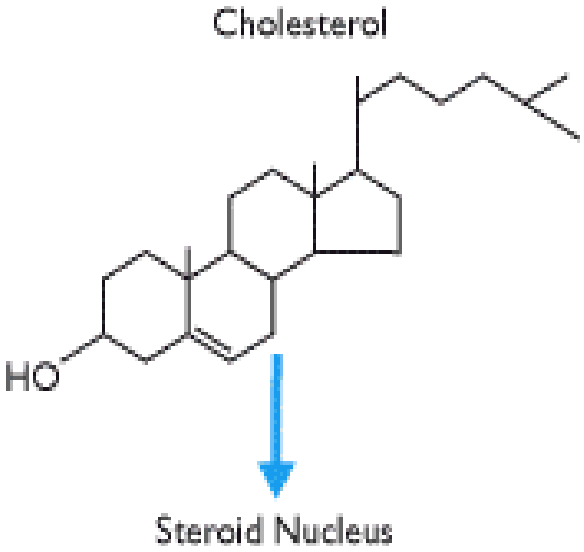
- Peptides. peptides or polypeptides (3 to 100 aa)
  - insulin, glucagon, adrenocorticotrophic hormone (ACTH)
- Amino acid derivatives. directly derived by modification of an amino acid
  - epinephrine and thyroxine (made from tyrosine), and serotonin (5-hydroxytryptamine; made from tryptophan)
- Steroids. derived from cholesterol by modification of the cholesterol ring system
  - estradiol, cortisol, calciferol (Vitamin D), and testosterone
- Eicosinoids. derivatives of the unsaturated fatty acid, arachidonic acid
  - prostaglandins, leukotrienes, and thromboxanes B
- Gasses. nitric oxide (NO) produced and released by endothelial cells, synthesized by NO synthase (NOS), which catalyzes NAPDH-dependent oxidation of l-arginine. Also, CO.

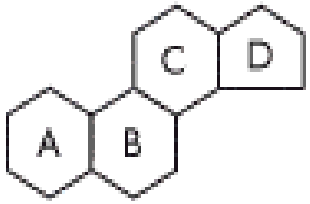
Protein and Peptide Hormones



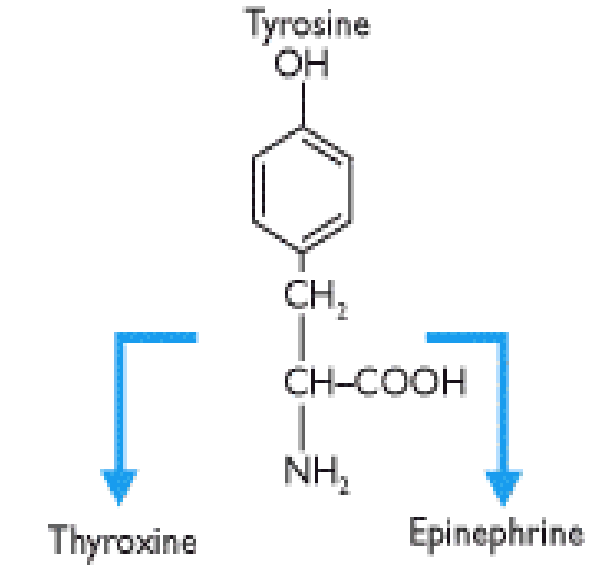


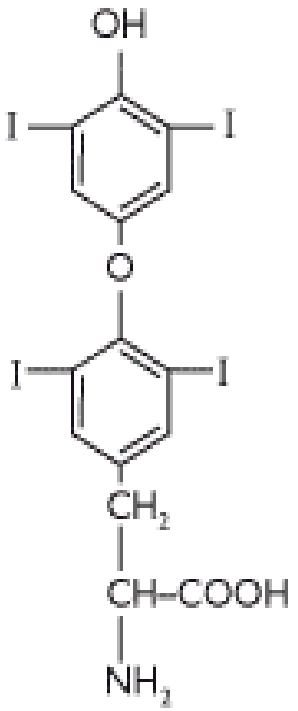
Steroid Hormones

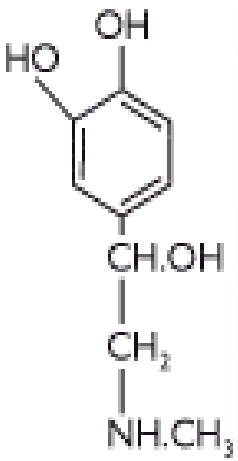


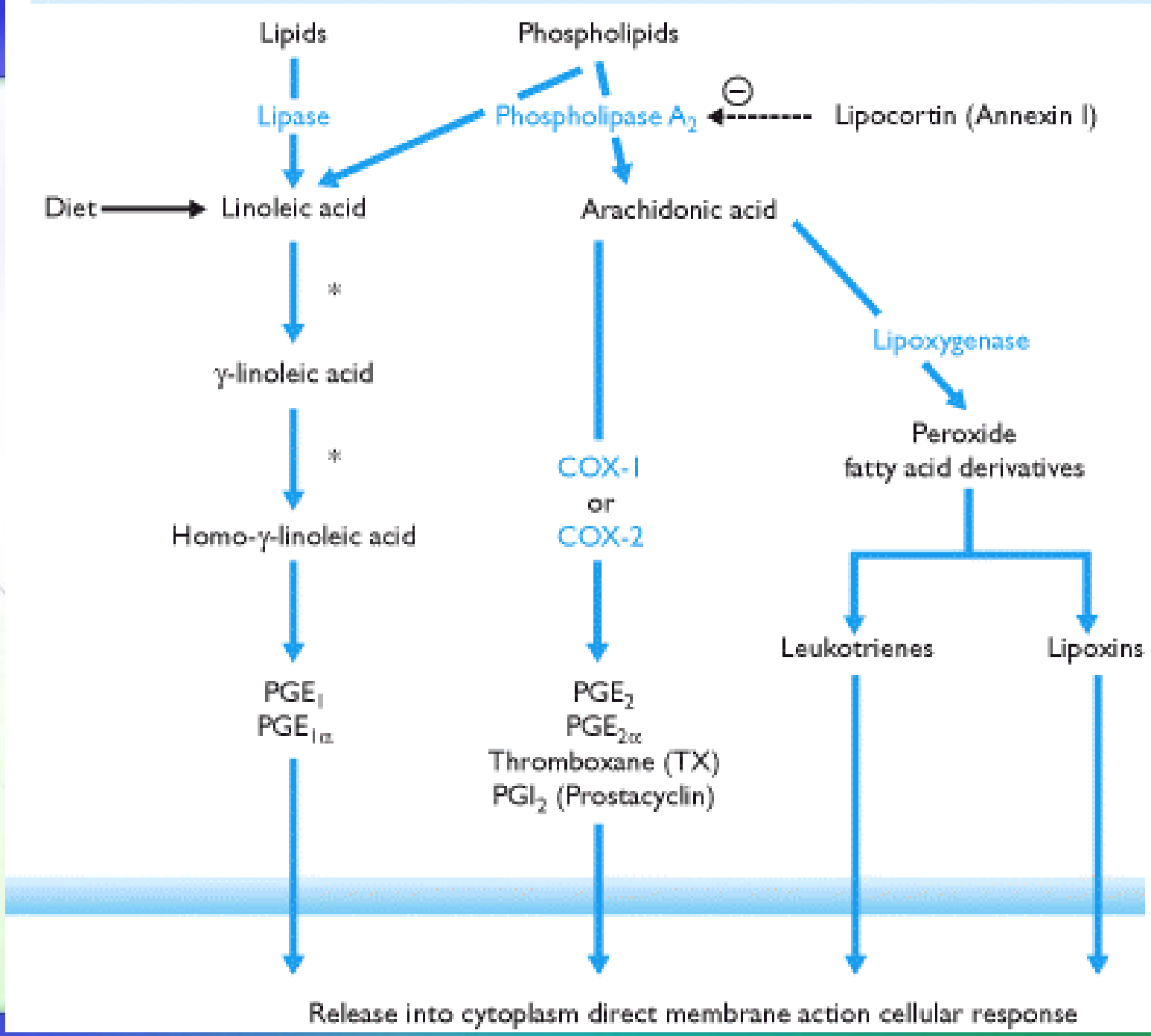


Tyrosine Derivatives

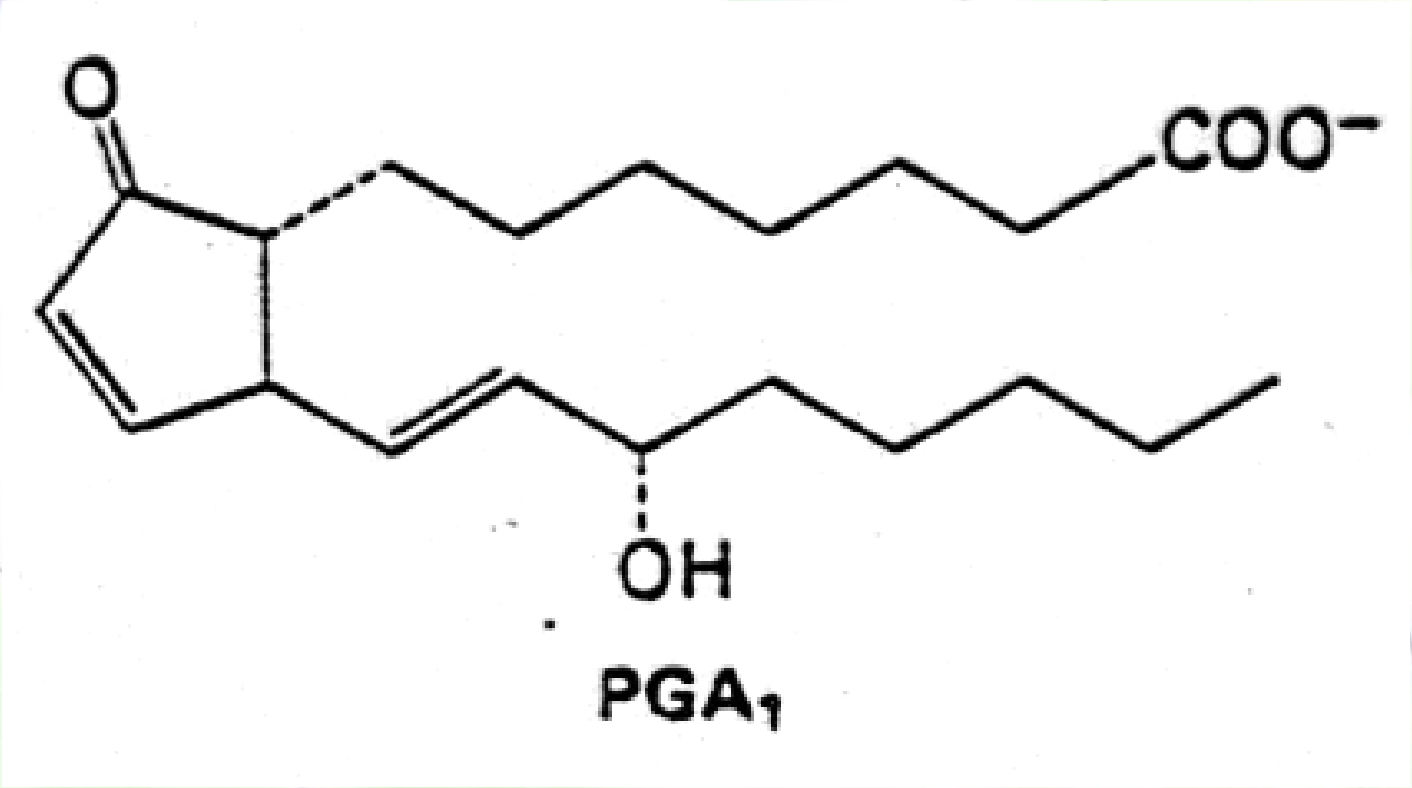







Lipids
Phospholipids
Lipase
Phospholipase A2
Lipocortin (Annexin I)
Diet
Linoleic acid
Arachidonic acid
*
γ-linoleic acid
*
Homo-γ-linoleic acid
COX-1
or
COX-2
Lipoxygenase
Peroxide
fatty acid derivatives
Leukotrienes
Lipoxins
PGE1
PGE1α
PGE2
PGE2α
Thromboxane (TX)
PGI2 (Prostacyclin)
Release into cytoplasm direct membrane action cellular response

Eicosanoids



Prostaglandin A1

Processing and modification

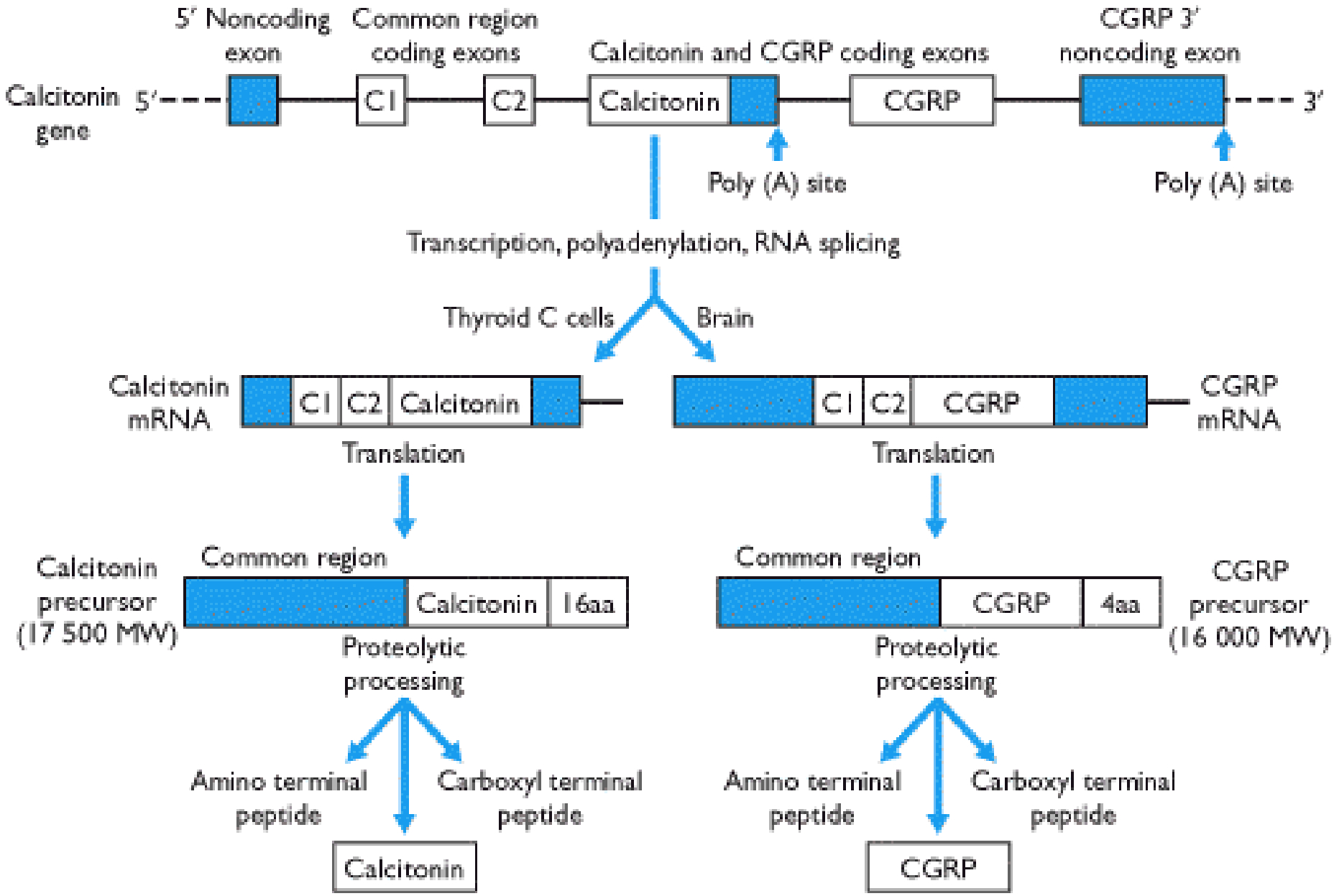
- Synthesized and secreted in final form
  - Aldosterone, hydrocortisone, estradiol, catecholamines (epinephrine & norepinephrine)
- Modified directly in target tissue
  - Insulin (synthesized as proinsulin and partially processed to insulin in the pancreas)
  - An extreme example are the products of the proopiomelanocortin (POMC) gene
- Modified indirectly by non-target tissue
  - Thyroxine T4 to T3 in the liver and pituitary
  - Testosterone to dihydrotestosterone (secondary sex tissues)
  - Vitamin D3 (skin) is converted to 25-hydroxycalciferol (liver(, then to 1,25-dihydroxycholecalciferol (kidney)

Hormone synthesis

- Protein and peptide hormones
  - Alternative splicing
  - Post-translational modification
  - Preprohormone
- Steroid hormones
- Amine hormones
- Eicosanoid hormones

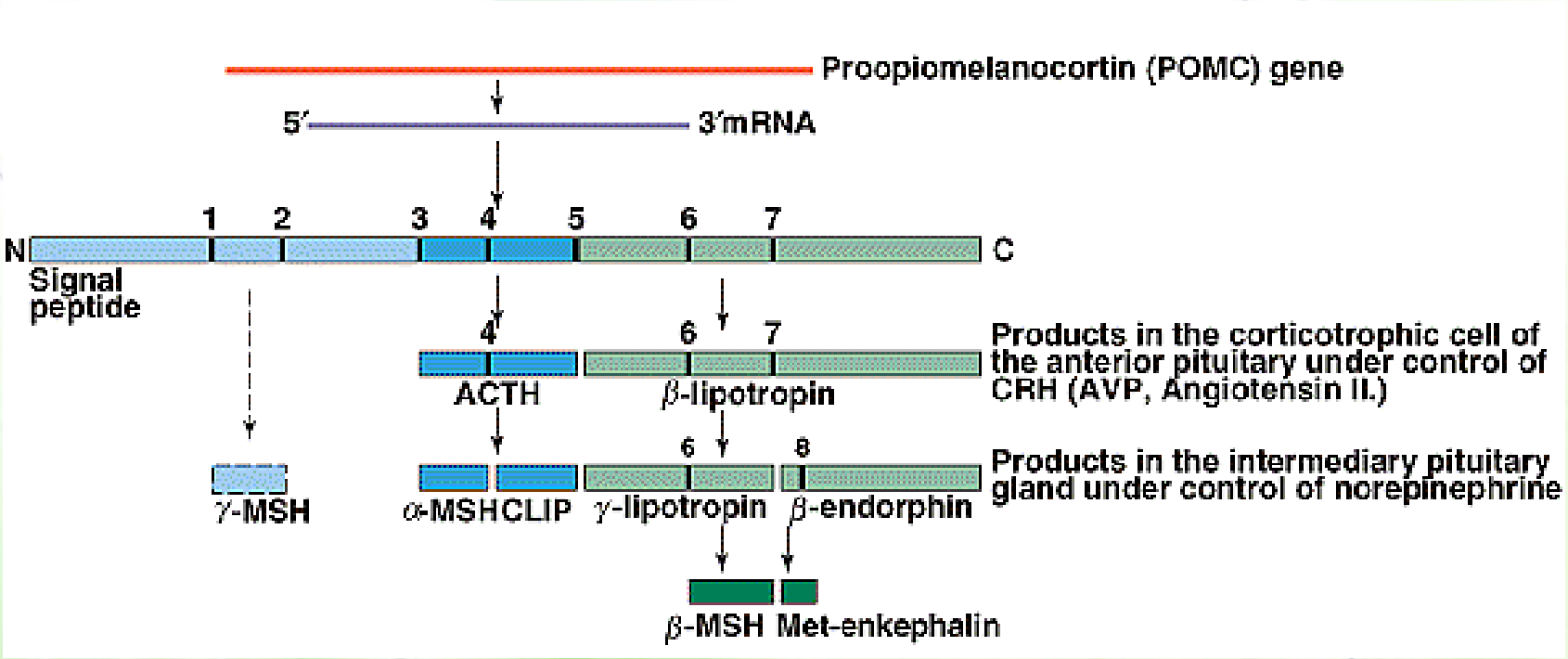
Alternative splicing

- As a result of alternative splicing of exons and post-translational modifications of the original amino acid sequence, more than one pro-hormone may be derived from a single gene.
- Alternative splicing and post-translational modification are typically tissue-specific.
  - Example: calcitonin and calcitonin-gene related peptide

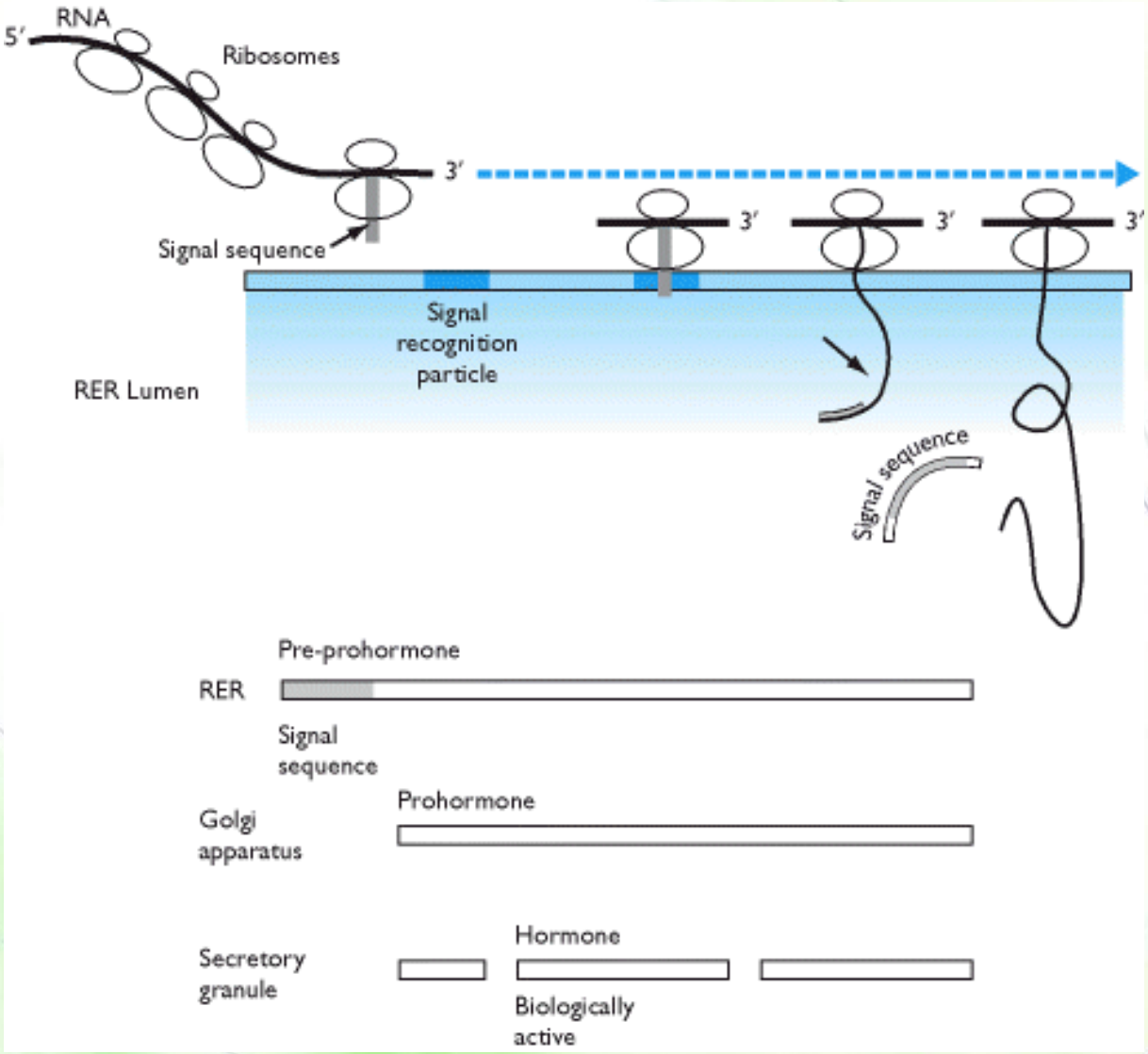

5′ Noncoding exon
Common region coding exons
Calcitonin and CGRP coding exons
CGRP 3′ noncoding exon
Calcitonin gene
5′
C1
C2
Calcitonin
CGRP
3′
Poly (A) site
Poly (A) site
Transcription, polyadenylation, RNA splicing
Thyroid C cells
Brain
Calcitonin mRNA
C1
C2
Calcitonin
C1
C2
CGRP
CGRP mRNA
Translation
Translation
Calcitonin precursor (17 500 MW)
Common region
Calcitonin
16aa
Common region
CGRP
4aa
CGRP precursor (16 000 MW)
Proteolytic processing
Proteolytic processing
Amino terminal peptide
Carboxyl terminal peptide
Amino terminal peptide
Carboxyl terminal peptide
Calcitonin
CGRP

Post-translational processing

- Post-translational processing of a pro-hormone may result in the formation of different biologically active peptide fragments (e.g. pro-opiomelanocortin)



Synthesis of a preproprotein hormone



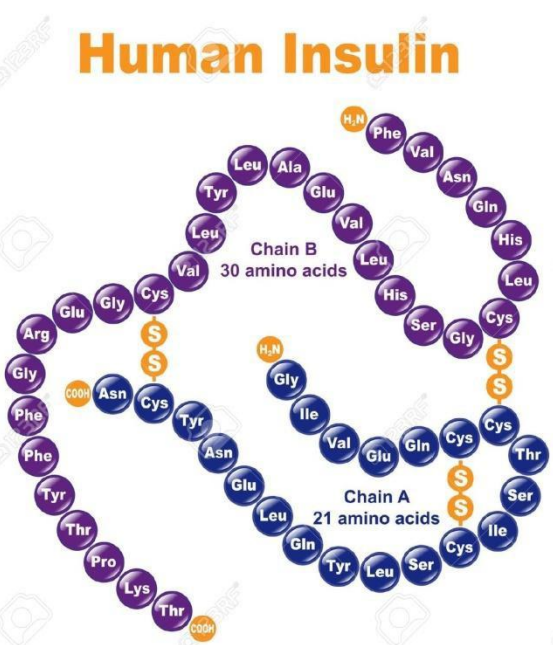
Preproinsulin

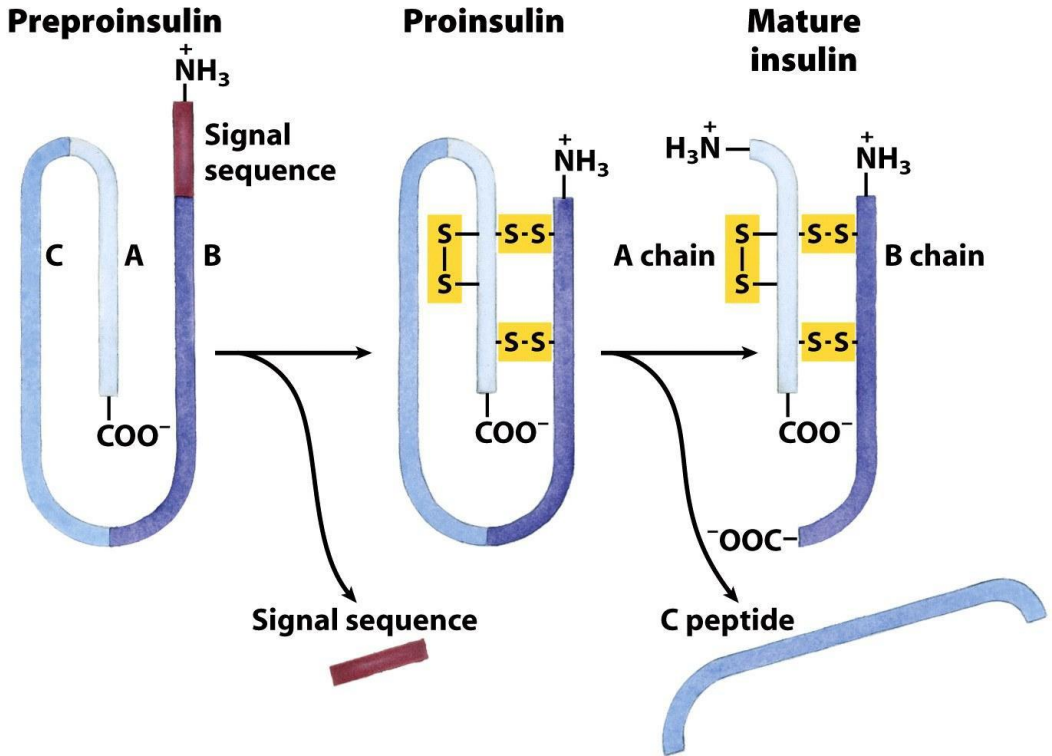
- Peptide & Protein Hormones
- From pre-pro-hormones

- A larger precursor preproinsulin
  - 23 aa signal sequence
  - 3 disulfide bonds

- Proinsulin
  - Remove the C peptide

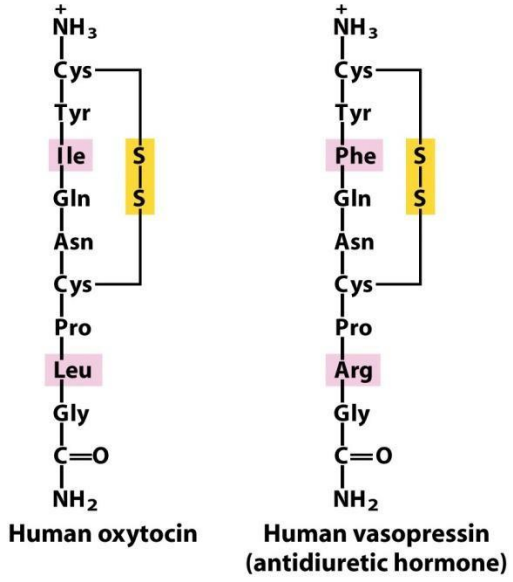
- Mature insulin
  - A and B chains

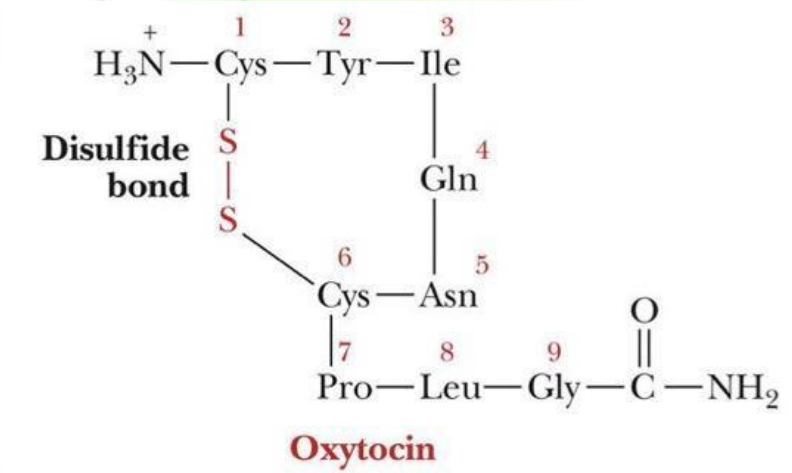


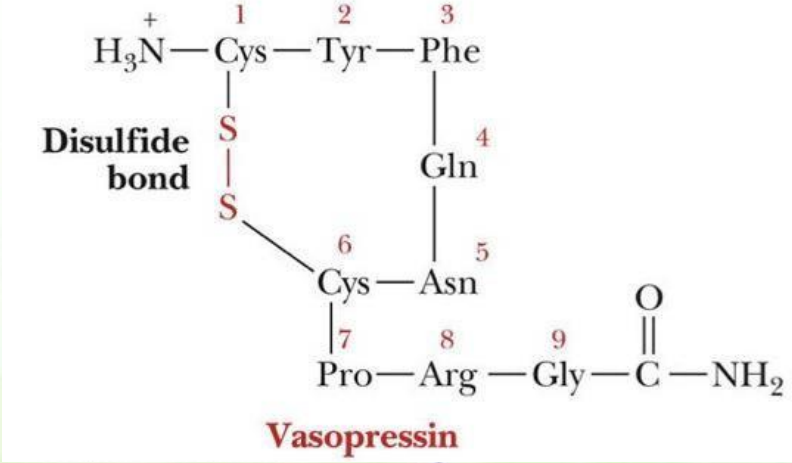


Synthesis of peptide hormones

- From precursor genes
  - Vasopressin and oxytocin
  - Synthesis in separate cell bodies of hypothalamic neurons

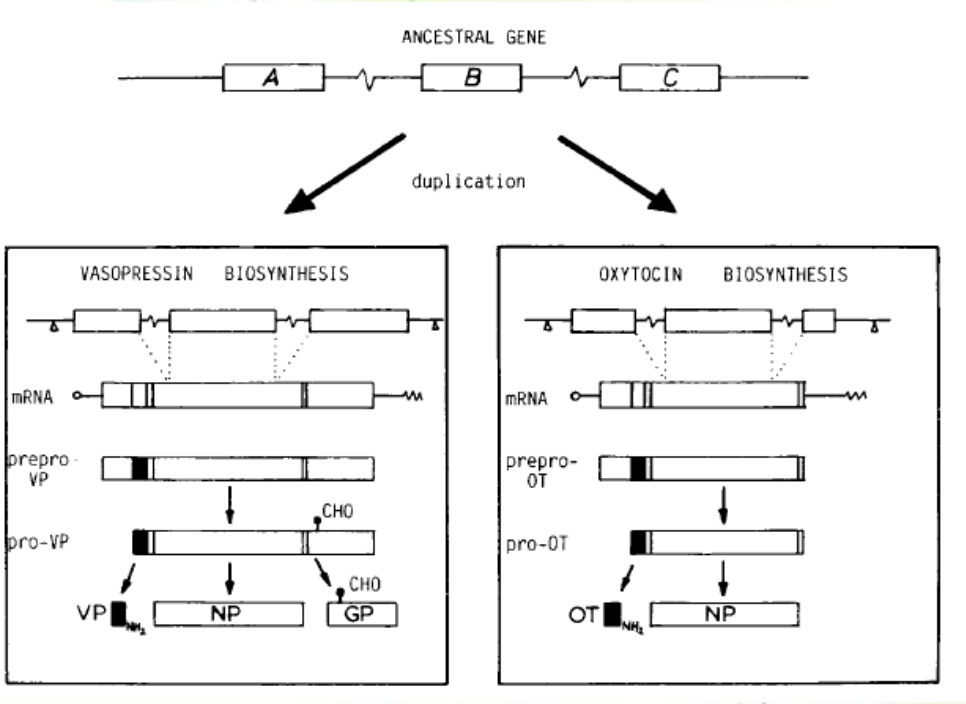






Gene structure of VP and OT

- The vasopressin precursor consists of the hormone, its carrier protein neurophysin, and a glycopeptide moiety of yet unknown function.
- The oxytocin precursor lacks the glycopeptide and consists only of the hormone and the respective carrier neurophysin.
- Both are synthesized as pre-pro-hormones.

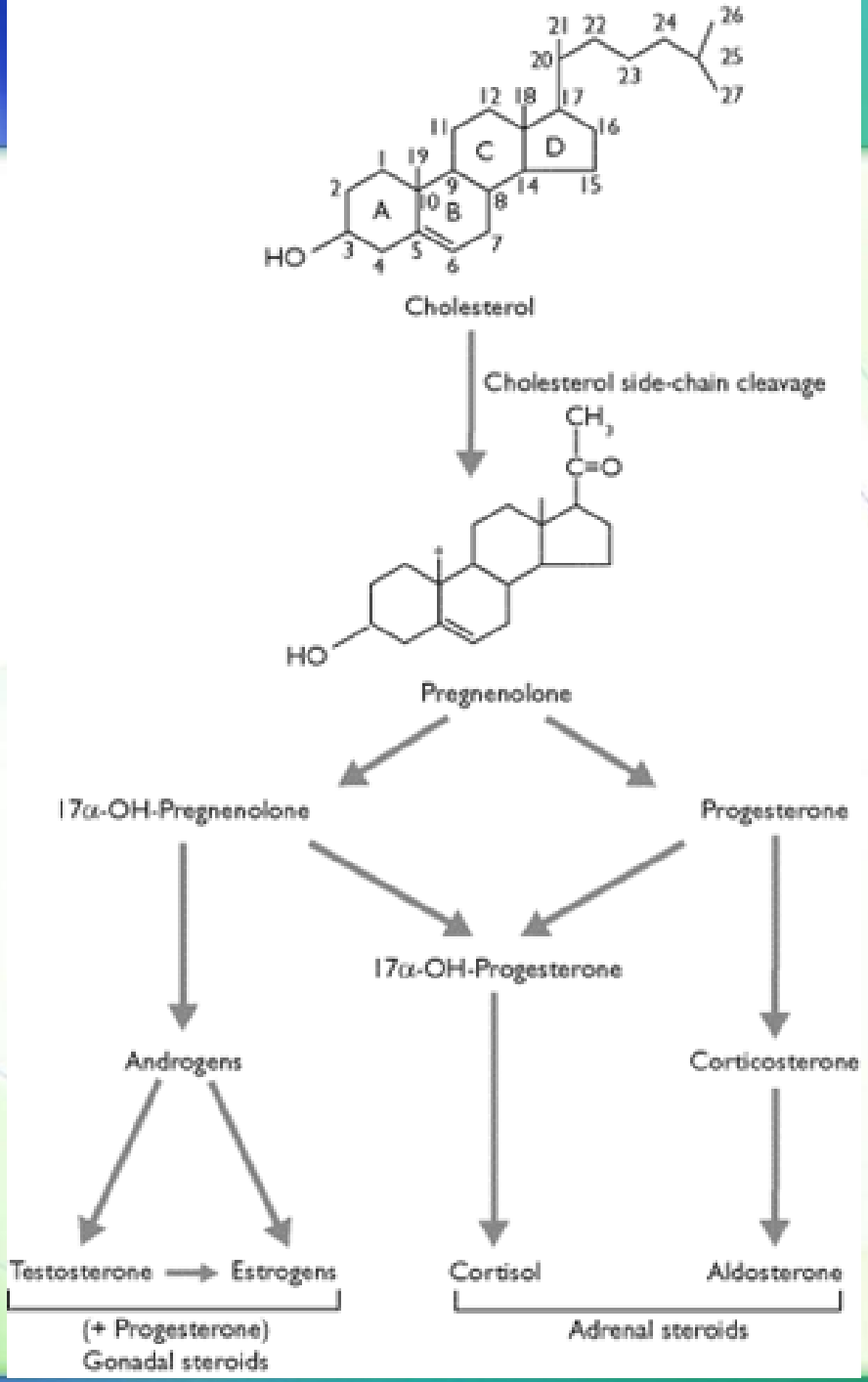


Protein vs. peptide hormones

Hormone	Structure
GHRH	44
TRH	3
GnRH	10
CRH	41
ADH	9
Vasopressin	9
Angiotensin I	10
Angiotensin II	8
Insulin	51
Glucagon	29

Synthesis of steroid hormones

- The synthesis of steroid hormones occurs in the mitochondria and smooth endoplasmic reticulum.
- They require specific enzymes that convert cholesterol into the appropriate steroid.
- Enzymes are expressed in different steroid-secreting cells and their expression is controlled by trophic hormones and/or other factors.
  - **A trophic hormone** is a **hormone** that has a growth effect, hyperplasia or hypertrophy, on the tissue it is stimulating. The term **trophic** is from Ancient Greek meaning "pertaining to food or nourishment", here used to mean "growth"; this is the same origin as atrophy.


Cholesterol
Cholesterol side-chain cleavage
Pregnenolone
17α-OH-Pregnenolone
Progesterone
17α-OH-Progesterone
Androgens
Corticosterone
Testosterone
Estrogens
(+ Progesterone)
Gonadal steroids
Cortisol
Aldosterone
Adrenal steroids

Amine hormones

- The amine hormones such as the catecholamines, melatonin and serotonin are formed by side-chain modifications of either a single tyrosine or tryptophan molecule.

Eicosanoid hormones

- The eicosanoid family of hormones are formed from lipids.
- The eicosanoids consist of the prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs).
- The principal eicosanoids are a group of molecules derived from the unsaturated C20 fatty acid, arachidonic acid.

A pharmacological classification of hormones

- Agonists
- Antagonists
- Partial agonists-partial antagonists
- Mixed agonists-antagonists

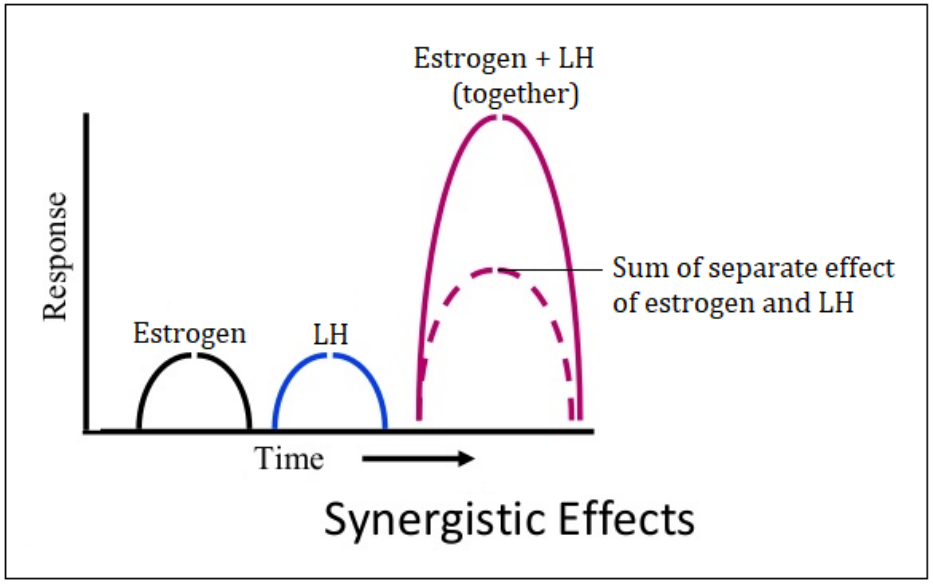
Hormone Interactions

- Hormones rarely act alone to maintain homeostasis

- Homeostasis usually involves several hormones working together in complex ways to regulate metabolic levels:
  - Synergistic effect
  - Antagonistic effect
  - Permissive effect
  - Integrative effect

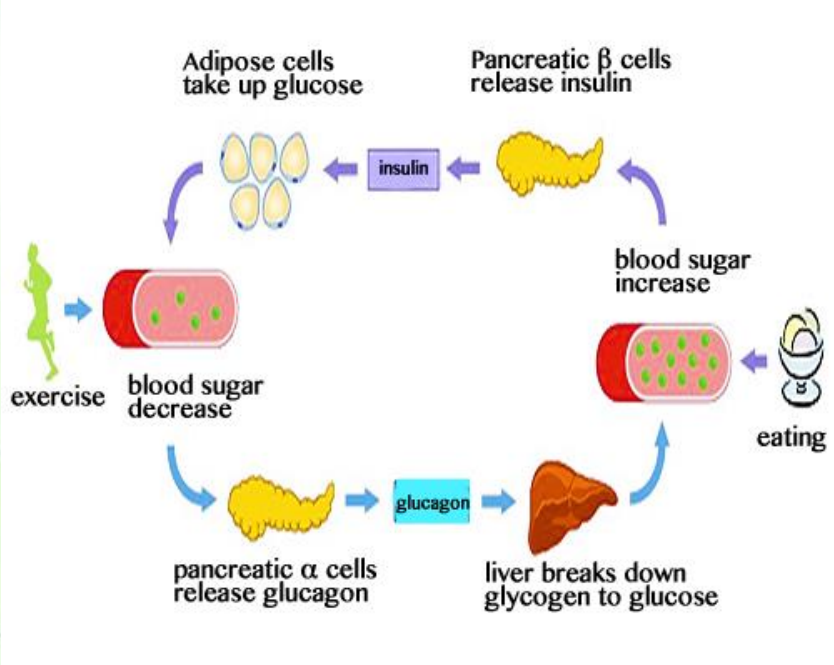
Synergistic effect

- hormones tend to cause the same effect
- Examples include:
  - ADH & aldosterone
  - Also, ovaries need both estrogen and FSH hormones for oocytes to develop



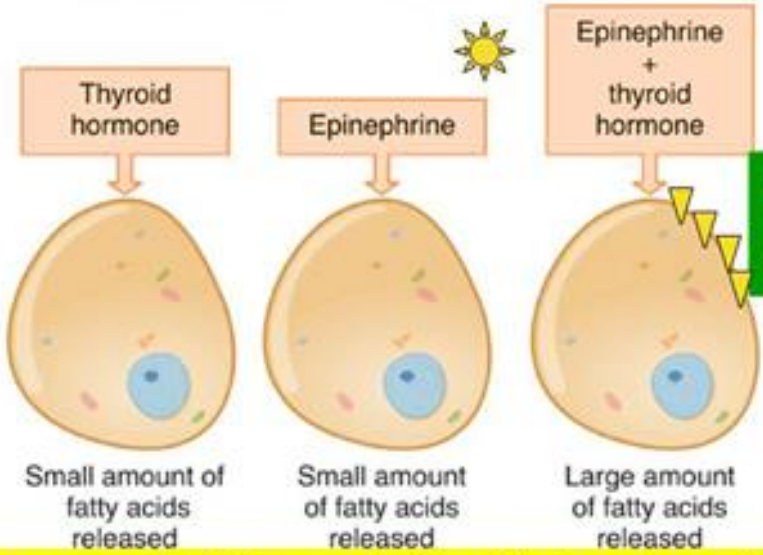
Antagonistic effect

- Hormones produce opposite effects
  - An example is insulin, which promotes synthesis of glycogen by liver cells and glucagons, which stimulates the breakdown of glycogen in the liver resulting in increased glucose

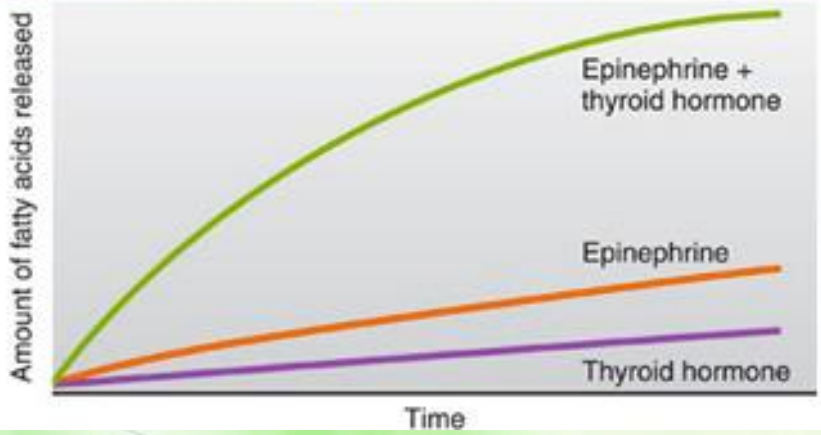


Permissive effect

- Hormones only affect “preprimed” tissues Examples include:
  - Two hormones acting together for a bigger effect (When epinephrine acts on fat cells to stimulate the breakdown of triglycerides for energy, it doesn’t have a big effect; but if small amounts of thyroid hormone T3 and T4 are also present then the same amount of epinephrine has a much bigger effect)
  - Sometimes the permissive hormone can stimulate the appearance of more receptors for another hormone
  - Other times a permissive hormone can promote the synthesis of an enzyme needed for the expression of other hormones

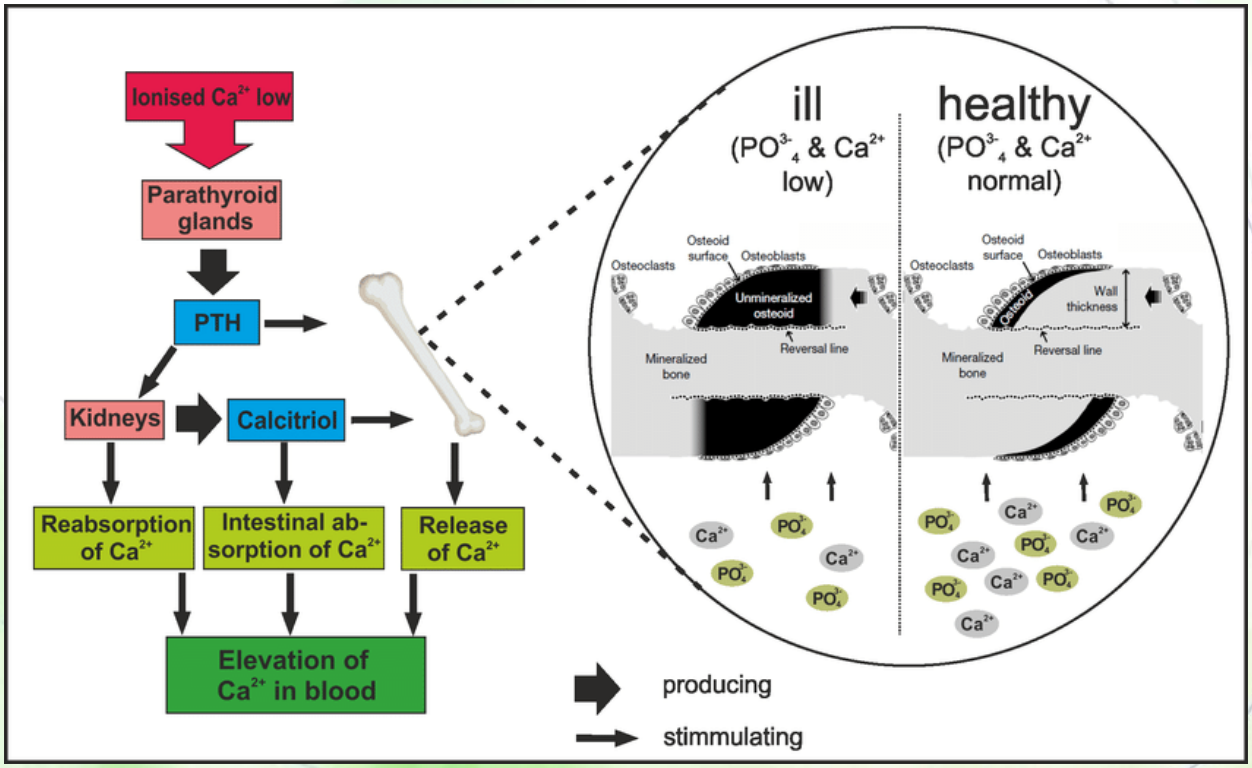


Thyroid hormone stimulates production of beta-adrenergic receptors



Integrative effect

- Integrative effects – hormones produce complementary effects on different tissues
  - PTH and calcitriol increase ECF calcium

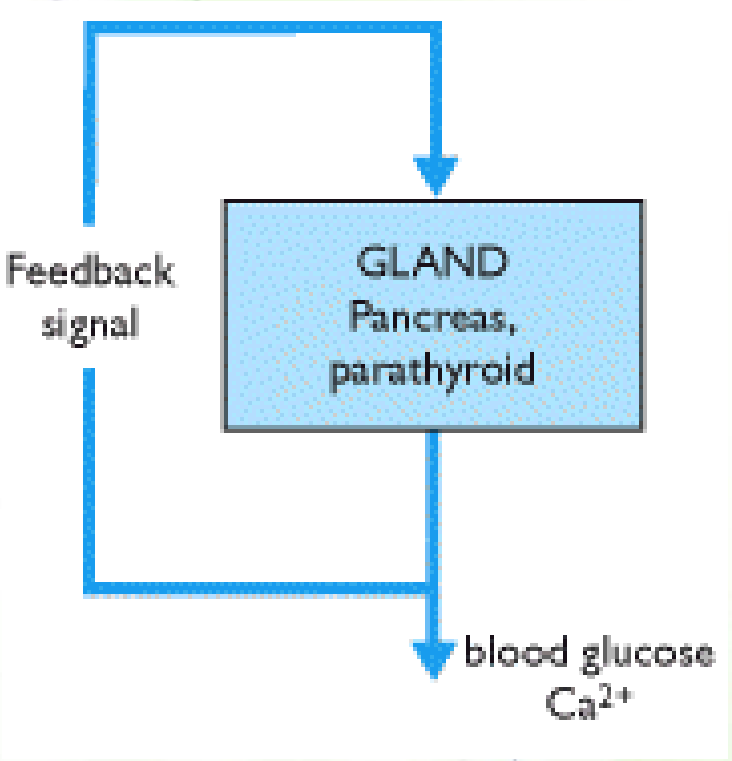


Feedback circuits

- Feedback circuits are at basis of most control mechanisms in physiology
- Feedback loops are used extensively to regulate secretion of hormones
- Negative feedback is much more common than positive dieback mechanisms

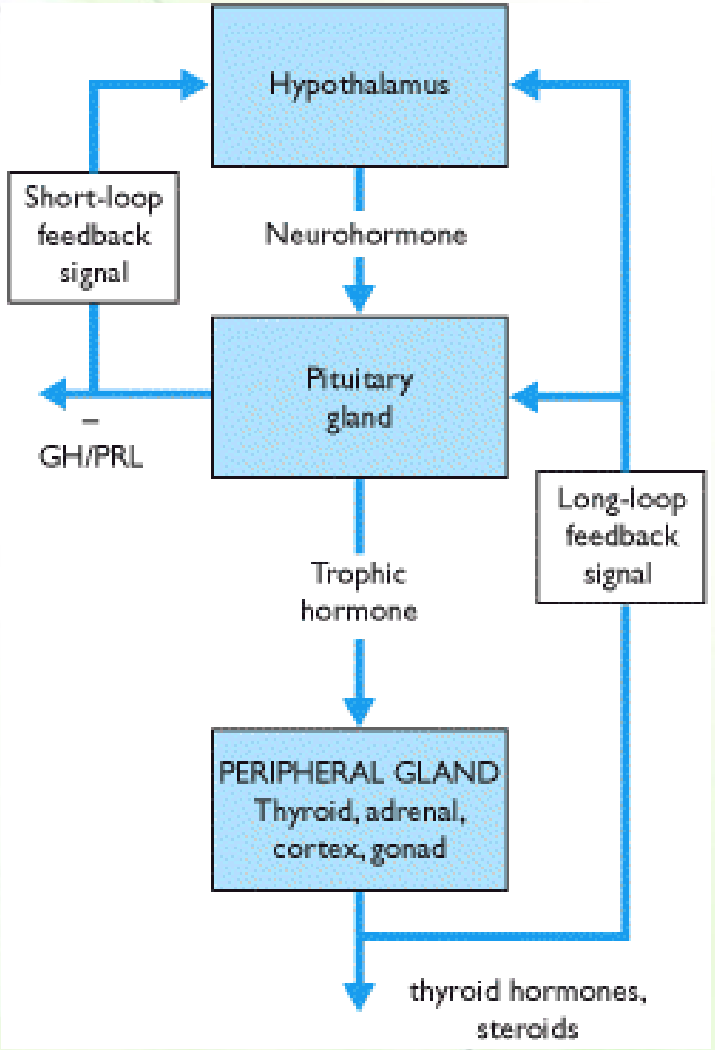
Simple Feedback Control of Hormone Production

- Glucose from the ingested lactose or sucrose is absorbed in the intestine and the level of glucose in blood rises
- Elevation of blood glucose concentration stimulates endocrine cells in the pancreas to release insulin
- Insulin has the major effect of facilitating entry of glucose into many cells of the body - as a result, blood glucose levels fall
- When the level of blood glucose falls sufficiently, the stimulus for insulin release disappears and insulin is no longer secreted



Simple Feedback Control of Hormone Production

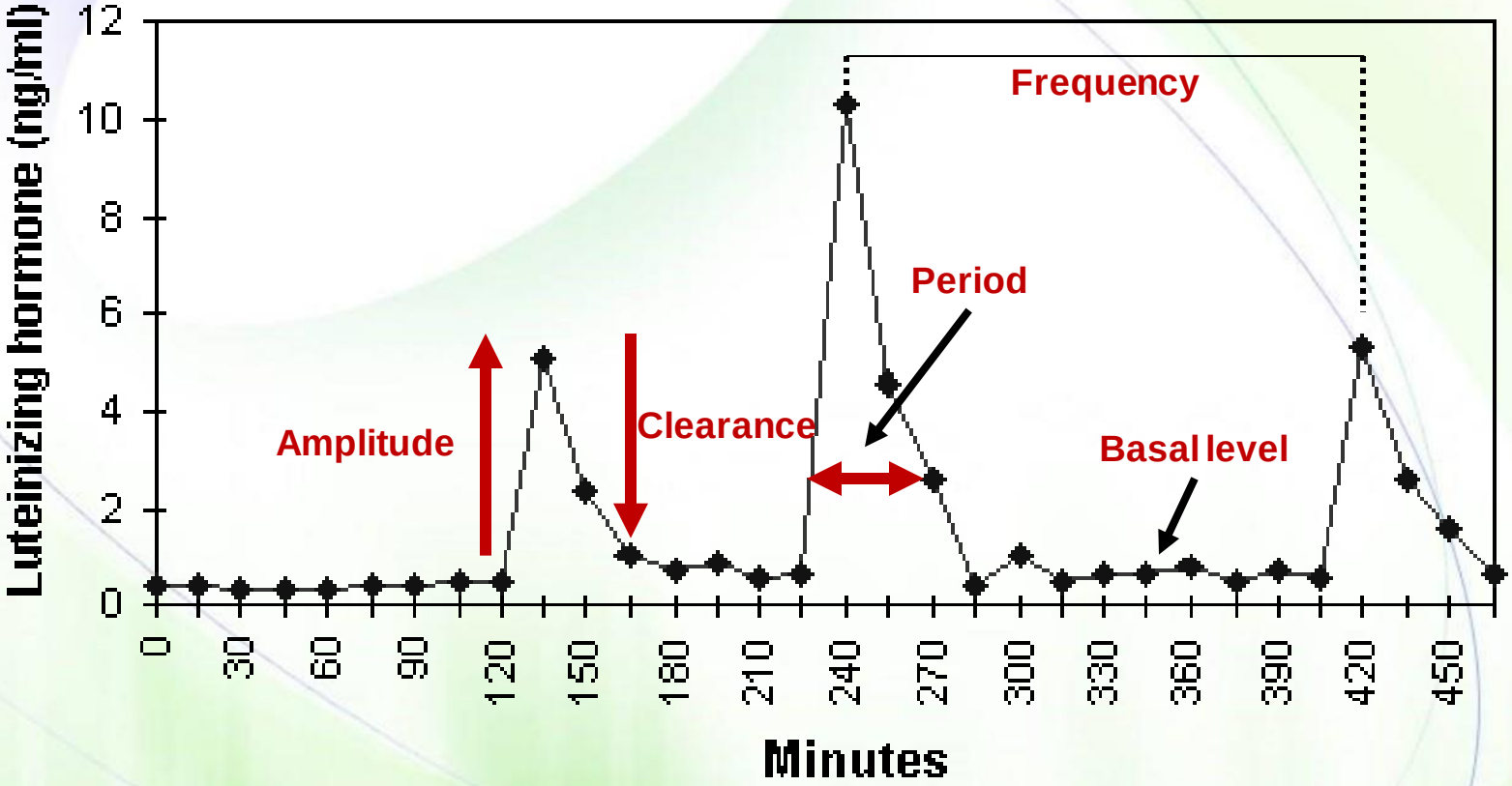
- The integration of feedback loops involving several hormones may be complex
- An example is feedback loops involving the hypothalamo-pituitary axis that detects changes in the concentration of hormones secreted by peripheral endocrine glands



Pulsatile secretion

- One important consequence of the feedback controls secretion of hormones in "pulses“
- Pulses reflect the coordinated actions of groups of releasing cells
- Each pulse has an amplitude and period
- Groups of pulses have a frequency
- Basal levels of hormone often reflect the spacing between pulses and its relation to hormonal clearance

Example: luteinizing hormone



Other examples

- Nerve impulses to adrenal medulla controls the release of epinephrine
- Blood Ca++ regulate the secretion of parathyroid hormone
- ACTH (hormone from anterior pit) stimulates the release of cortisol by the adrenal cortex

Elements of an Endocrine System

- Hormones are secreted by regulator cells in an endocrine gland and transported to target cells where signals are transduced via cellular molecules that include
  - receptors,
  - amplifiers (enzymes),
  - transducers (proteins and second messengers),
  - effector proteins