Chapter 17.1

# Introduction to the Endocrine System

# and

# Hormone Chemistry

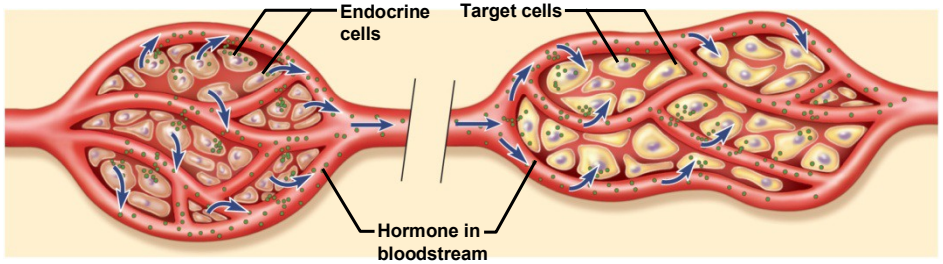
# Endocrine System

- **endocrine system**
  - glands secrete hormones (messenger molecules) into blood
  - blood transports hormones to target tissue
  - receptors on cells (i.e. target tissue) matched to specific hormones
  - if hormone is able to bind to receptor then hormone may change target tissue's metabolism

- **endocrine glands** – the source tissue for the hormone (single cells or multicelluar)

- **hormones** - chemical messengers /// transported in bloodstream and able to change target tissue's cellular metabolism

- **endocrinology** – the study of this system and the diagnosis and treatment of its disorders



(b) Endocrine system

## Key Steps (Know This!)

1. Hormone synthesized by endocrine gland.
2. Hormone released into blood.
3. Hormone circulates thoughout circulatory system
4. Hormone diffuses across capillary into interstitial fluid then diffuses to target cell with receptor.
5. Hormone binds to receptor
6. Hormone changes metabolism of target cell

# Some Endocrine Organs Are Hard to Classify

- Pancreas (mixed gland)
  - Exocrine – digestive enzymes
  - Endocrine – insulin / glucagon

- Hepatocytes (i.e. liver cells) defy rigid classification
  - releases hormones
  - releases bile into ducts
  - releases albumin and blood-clotting factors into blood (macromolecules not hormones)

# Nervous System VS Endocrine System

- **both serve internal communication**
  - nervous - both electrical and chemical
  - endocrine - only chemical
- **speed and persistence of response**
  - nervous - reacts quickly (1-10 msec), stops quickly
  - endocrine - reacts slowly (hormone release in seconds or days), effect may continue for weeks
- **adaptation to long-term stimuli**
  - nervous - response declines (adapts quickly)
  - endocrine - response persists (adapts slowly)
- **area of effect**
  - nervous - targeted and specific (one organ)
  - endocrine - general, widespread effects (many organs)

# Nervous System VS Endocrine System

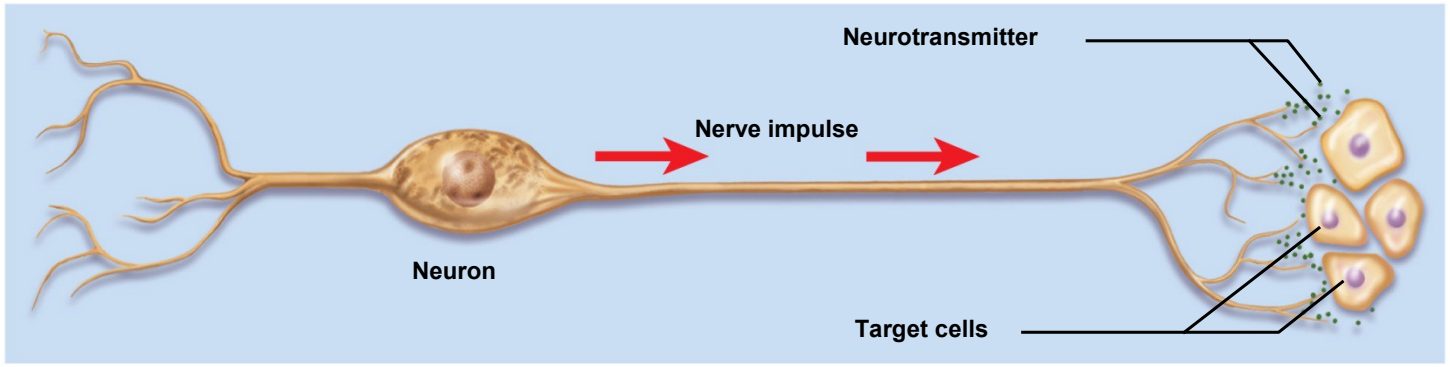
- Some molecules may function as either hormones or neurotransmitters // norepinephrine, cholecystokinin, thyrotropin-releasing hormone, dopamine and antidiuretic hormone

- Some hormones secreted by neuroendocrine cells (neurons) that release their secretion into the bloodstream // oxytocin and catecholamines

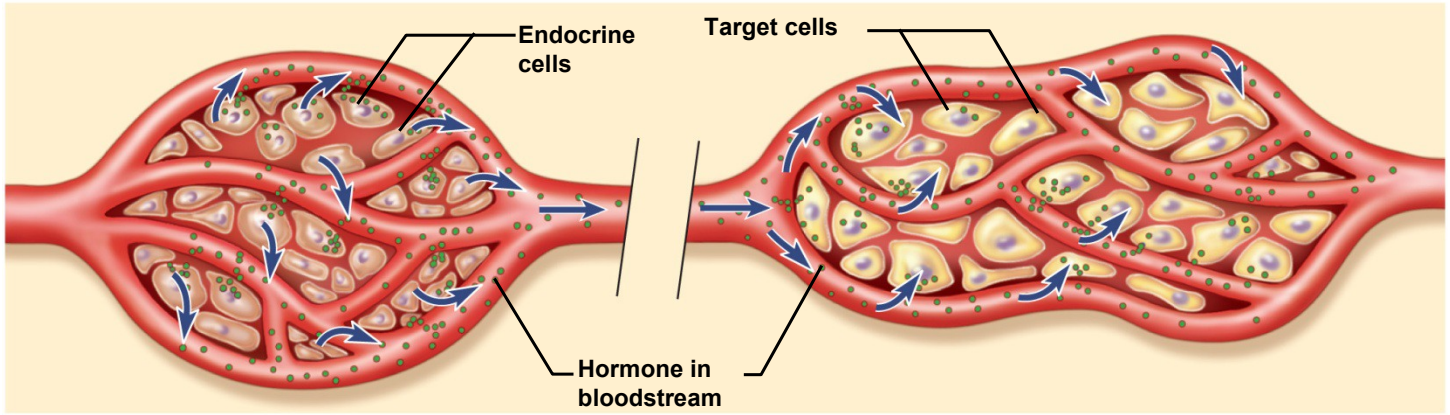
- Both systems may have effects that occur on same target cells // the neurotransmitter norepinephrine and the hormone glucagon both cause glycogen hydrolysis in liver

- Both systems may influence the function of the other system // neurons trigger hormone secretion or hormones stimulate or inhibit activity of neurons

# Nervous VS Endocrine Systems Communication

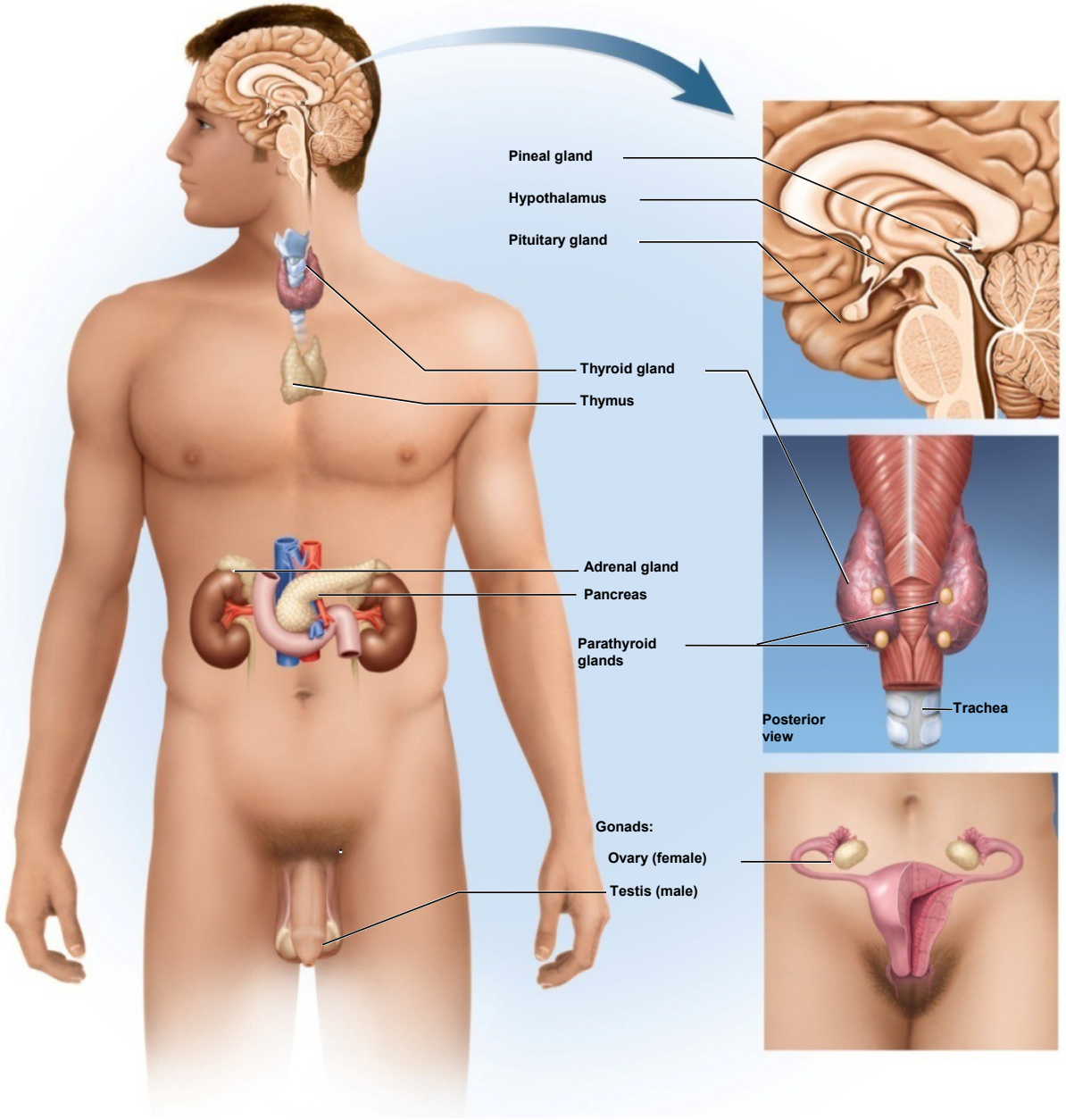



(a) Nervous system




(b) Endocrine system

# Major Endocrine Organs




Today, in the field of endocrinology there is a new paradigm. It is referred to as the democratization of the endocrine system.

This paradigm acknowledges every cell in the body may secrete molecules able to be transported in blood and capable of changing the cellular functions of other cells near and far.

The classical approach to learning endocrinology is to identify the structure and function of the major endocrine organs and then identify other tissues that also produce hormones.

## TABLE 17.5 Hormones from Sources Other than the Hypothalamus and Pituitary (continued)

| Source | Hormone | Target Organs and Tissues | Principal Effects |
|---|---|---|---|
| Pancreatic islets | Glucagon | Primarily liver | Stimulates amino acid absorption, gluconeogenesis, glycogen and fat breakdown; raises blood glucose and fatty acid levels |
| | Insulin | Most tissues | Stimulates glucose and amino acid uptake; lowers blood glucose level; promotes glycogen, fat, and protein synthesis |
| | Somatostatin | Stomach, intestines, pancreatic islet cells | Modulates digestion, nutrient absorption, and glucagon and insulin secretion |
| | Pancreatic polypeptide | Pancreas, gallbladder | Inhibits release of bile and digestive enzymes |
| | Gastrin | Stomach | Stimulates acid secretion and gastric motility |
| Ovaries | Estradiol | Many tissues | Stimulates female reproductive development and adolescent growth; regulates menstrual cycle and pregnancy; prepares mammary glands for lactation |
| | Progesterone | Uterus, mammary glands | Regulates menstrual cycle and pregnancy; prepares mammary glands for lactation |
| | Inhibin | Anterior pituitary | Inhibits FSH secretion |
| Testes | Testosterone | Many tissues | Stimulates fetal and adolescent reproductive development, musculoskeletal growth, sperm production, and libido |
| | Inhibin | Anterior pituitary | Inhibits FSH secretion |
| Skin | Cholecalciferol | — | Precursor of calcitriol (see kidneys) |
| Liver | Calcidiol | — | Precursor of calcitriol (see kidneys) |
| | Angiotensinogen | — | Precursor of angiotensin II (see kidneys) |
| | Erythropoietin | Red bone marrow | Promotes red blood cell production, increases oxygen-carrying capacity of blood |
| | Hepcidin | Small intestine, liver | Promotes iron absorption and mobilization |
| | Insulin-like growth factor I | Many tissues | Prolongs and mediates action of growth hormone |
| Kidneys | Angiotensin I | — | Precursor of angiotensin II, a vasoconstrictor |
| | Calcitriol | Small intestine | Increases blood calcium level mainly by promoting intestinal absorption of $Ca^{2+}$ |
| | Erythropoietin | Red bone marrow | Promotes red blood cell production, increases oxygen-carrying capacity of blood |
| Heart | Atrial natriuretic peptide and brain natriuretic peptide | Kidney | Lower blood volume and pressure by promoting $Na^+$ and water loss |
| Stomach and small intestine | Cholecystokinin | Gallbladder, brain | Bile release; appetite suppression |
| | Gastrin | Stomach | Stimulates acid secretion |
| | Ghrelin | Brain | Stimulates hunger, initiates feeding |
| | Peptide YY | Brain | Produces sense of satiety, terminates feeding |
| | Other enteric hormones | Stomach, intestines | Coordinate secretion and motility in different regions of digestive tract |
| Adipose tissue | Leptin | Brain | Limits appetite over long term |
| Osseous tissue | Osteocalcin | Pancreas, adipose tissue | Stimulates pancreatic beta cells to multiply, increases insulin secretion, enhances insulin sensitivity of various tissues, and reduces fat deposition |
| Placenta | Estrogen, progesterone | Many tissues of mother and fetus | Stimulate fetal development and maternal bodily adaptations to pregnancy; prepare mammary glands for lactation |

## TABLE 17.2 Names and Abbreviations for Hormones

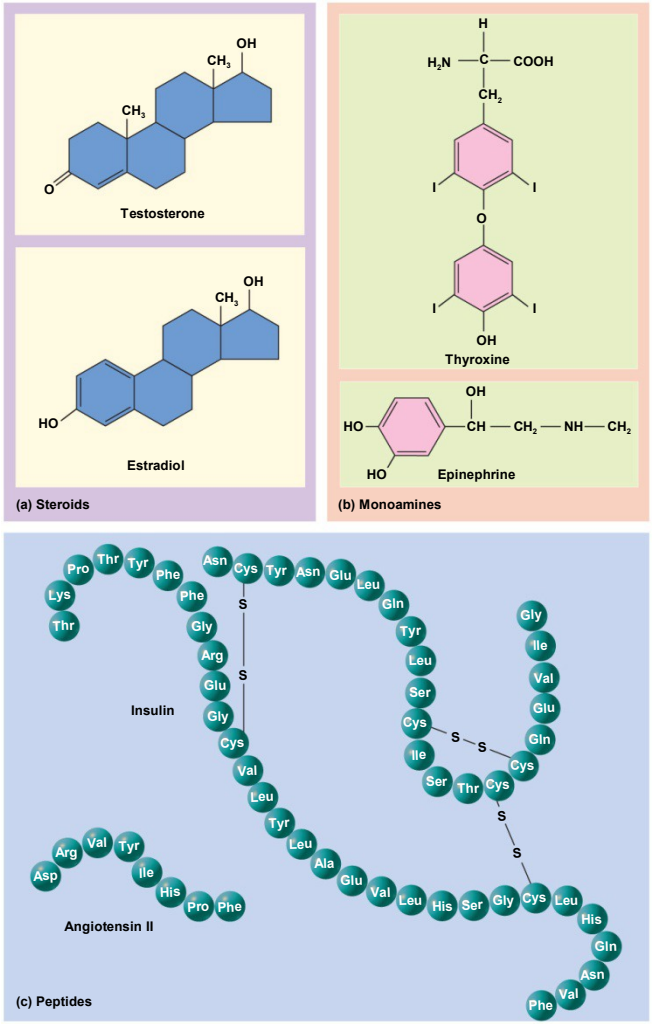
| Abbreviation | Name | Source |
|---|---|---|
| ACTH | Adrenocorticotropic hormone (corticotropin) | Anterior pituitary |
| ADH | Antidiuretic hormone (arginine vasopressin) | Posterior pituitary |
| ANP | Atrial natriuretic peptide | Heart |
| CRH | Corticotropin-releasing hormone | Hypothalamus |
| DHEA | Dehydroepiandrosterone | Adrenal cortex |
| EPO | Erythropoietin | Kidney, liver |
| FSH | Follicle-stimulating hormone | Anterior pituitary |
| GH | Growth hormone (somatotropin) | Anterior pituitary |
| GHRH | Growth hormone–releasing hormone | Hypothalamus |
| GnRH | Gonadotropin-releasing hormone | Hypothalamus |
| IGFs | Insulin-like growth factors (somatomedins) | Liver, other tissues |
| LH | Luteinizing hormone | Anterior pituitary |
| NE | Norepinephrine | Adrenal medulla |
| OT | Oxytocin | Posterior pituitary |
| PIH | Prolactin-inhibiting hormone (dopamine) | Hypothalamus |
| PRL | Prolactin | Anterior pituitary |
| PTH | Parathyroid hormone (parathormone) | Parathyroids |
| $T_3$ | Triiodothyronine | Thyroid |
| $T_4$ | Thyroxine (tetraiodothyronine) | Thyroid |
| TH | Thyroid hormone ($T_3$ and $T_4$) | Thyroid |
| TRH | Thyrotropin-releasing hormone | Hypothalamus |
| TSH | Thyroid-stimulating hormone (thyrotropin) | Anterior pituitary |

## Learning Objectives

- **Hormone chemistry?**
- **What are the different chemical properties of hormones?**
- **What are hormones mechanisms of actions?**

# Hormone Chemistry // Three Chemical Classes

- **Steroids**
  - derived from cholesterol
  - estrogens, progesterone, testosterone, cortisol, corticosterone, aldosterone, DHEA, and calcitriol
- **Peptides (and glycoproteins)**
  - created from chains of amino acids
  - secreted by pituitary and hypothalamus
  - oxytocin, antidiuretic hormone, releasing and inhibiting hormones, and anterior pituitary hormones

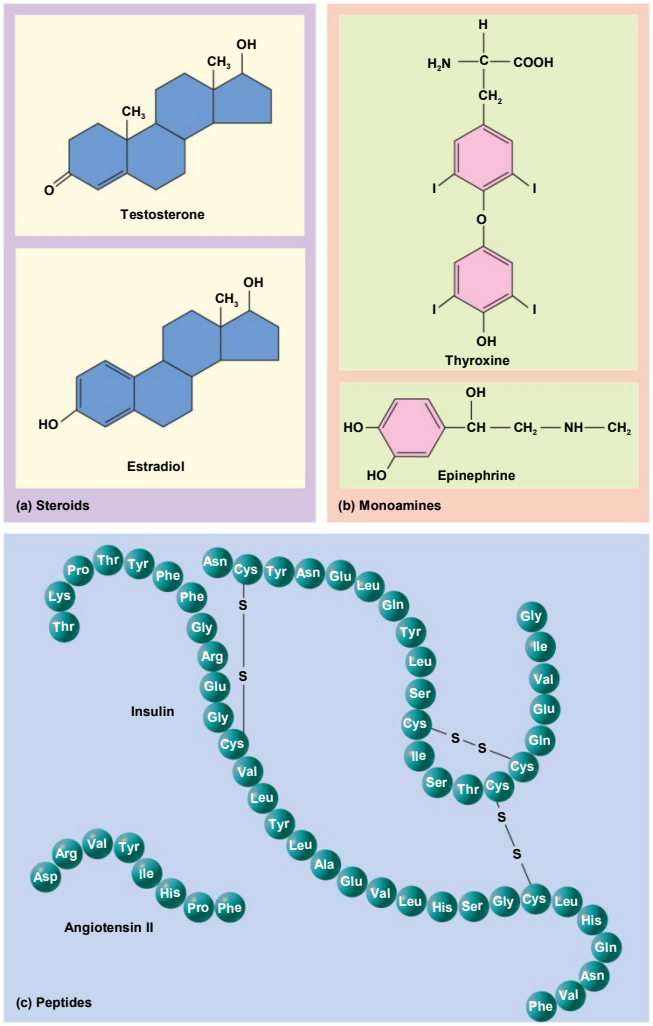


# Hormone Chemistry

– **Monoamines (biogenic amines)**

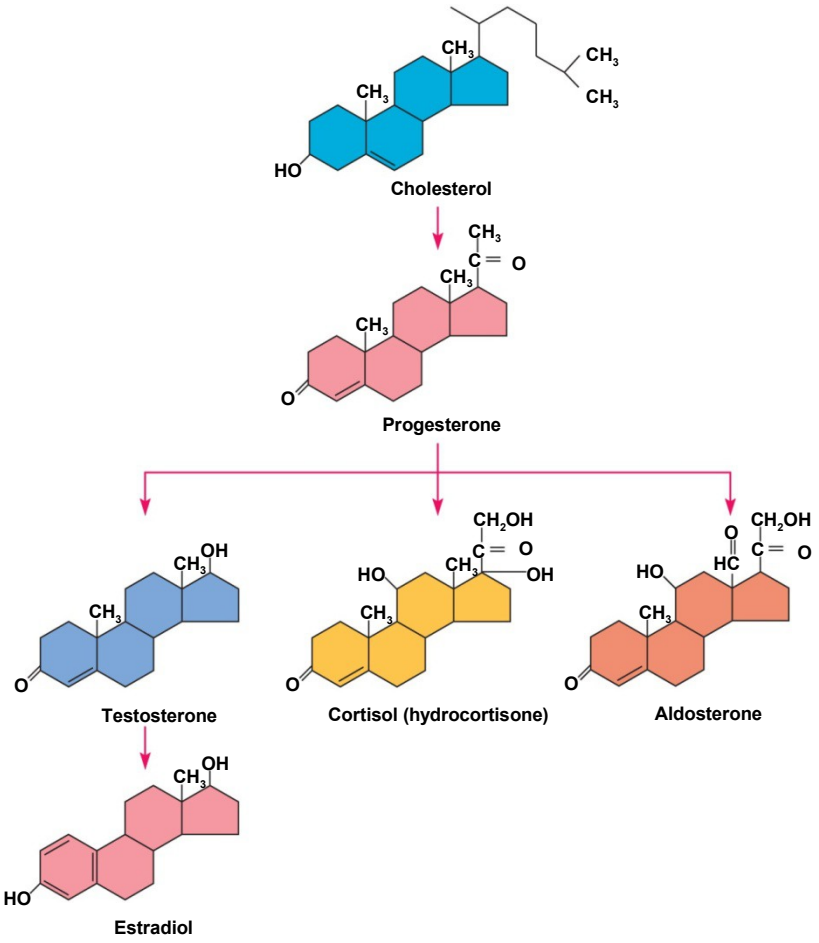
- derived from amino acids
- secreted by adrenal, pineal, and thyroid glands
- epinephrine, norepinephrine, melatonin, and thyroid hormone

- *Note: all hormones are made from either cholesterol or amino acids (with carbohydrate added to make glycoproteins).*



# Hormone Synthesis: Steroid Hormones






- synthesized from cholesterol – differs in functional groups attached to 4-ringed steroid backbone

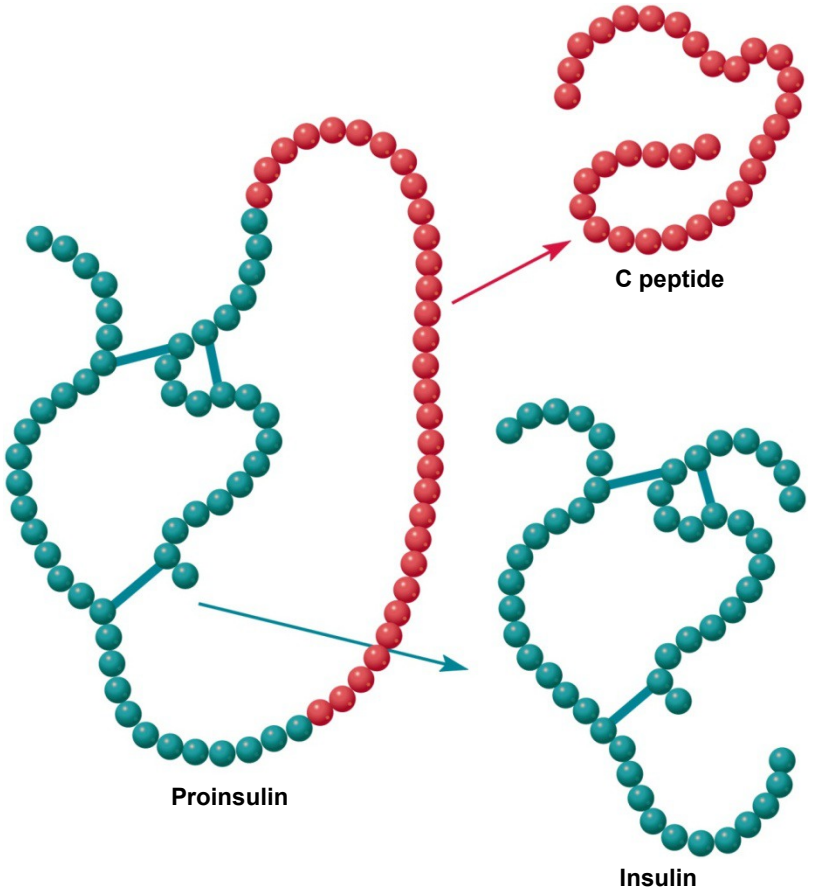
# Peptide Hormones

- synthesized using same metabolic pathways as any other protein
- first formed as an inactive **pre-prohormone**
- several amino acids in peptide function as a signal that guides it into cisterna of rough endoplasmic reticulum
- signal peptide removed to form **prohormone**
- Golgi does final transformation to **hormone** packaged for secretion

# Hormone Synthesis: Insulin

- begins as **pre-proinsulin**, then becomes **proinsulin**
- when **connecting peptide** is removed, two polypeptide chains are formed that make up insulin



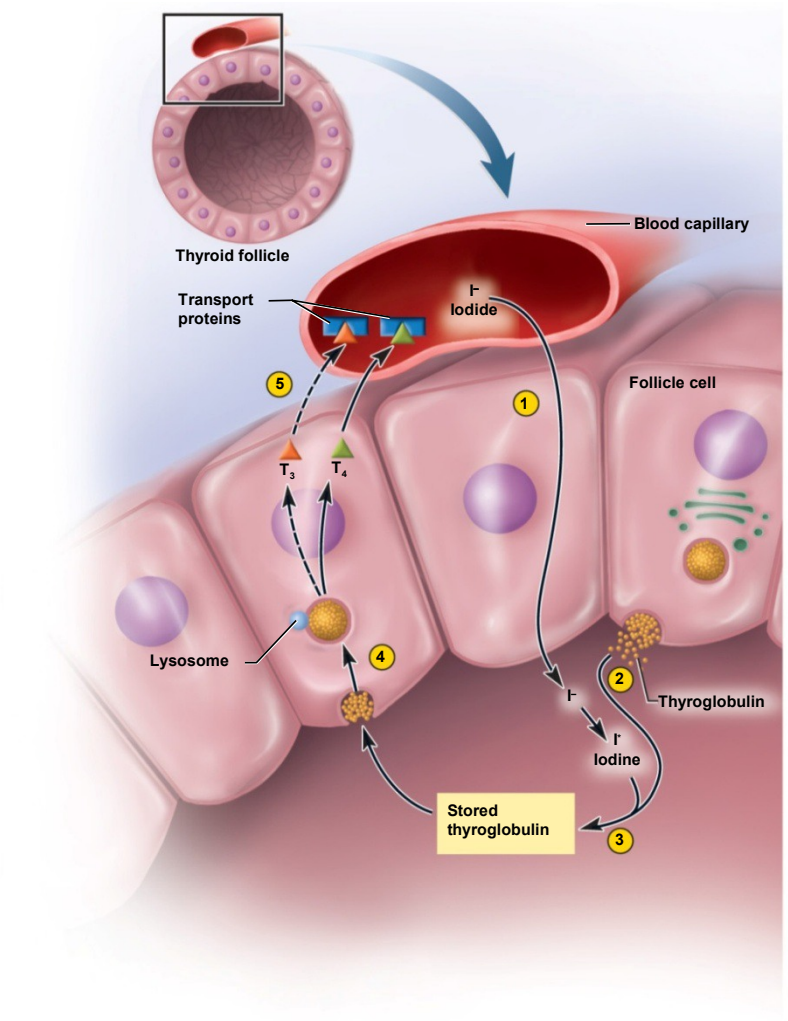


# Monoamines

- These are synthesized from amino acid
- E.g. /// **Melatonin** (the hormone released by the pineal gland) is synthesized from the amino acid tryptophan
- tryptophan first transformed into the brain neutrotransmitter seratonin which is then transformed into melatonin
- E.g. /// thyroid hormone is composed of 2 tyrosine molecules (tyrosine is an amino acid)

# Thyroid Hormone Synthesis

## (Note: this is not on exam)




1. Iodide absorption and oxidation
2. Thyroglobulin synthesis and secretion
3. Iodine added to tyrosines of thyroglobulin
4. Thyroglobulin uptake and hydrolysis
5. Release of $T_4$ and a small amount of $T_3$ into the blood

# $T_3$ and $T_4$ Synthesis (not on exam)

- **Follicular cells**
  - absorb **iodide** ($I^-$) **ions** from blood and store in lumen as a reactive form of iodine
  - synthesize **thyroglobulin** and store in lumen // forms colloid // contains lots of tyrosine
  - tyrosine and iodine combine to form thyroxine ($T_4$) bound to thyroglobulin
  - stored in follicle

# $T_3$ and $T_4$ Synthesis (not on exam)

- **TSH**
  - stimulates follicular cells to remove $T_4$ from thyroglobulin for release into plasma
  - most $T_3$ is produced in liver or by target cells removing an iodine from circulating $T_4$
  - 95% $T_4$ and 5% $T_3$

# Hormone Transport

- Most monoamines and peptides are hydrophilic // mix easily with blood plasma

- Steroids and thyroid hormone are hydrophobic

  - Hydrophobic hormones need to bind to *transport proteins* (albumins and globulins which are synthesized by the liver)

  - "bound hormones"

    - have longer half-life
    - protected from liver enzymes and kidney filtration
    - transport proteins protect circulating hormones
    - being broken down by enzymes in the plasma and liver
    - being filtered out of the blood by the kidneys

  - after hydrophobic hormones detach from transporter then hormone may cross capillaries to reach target cell

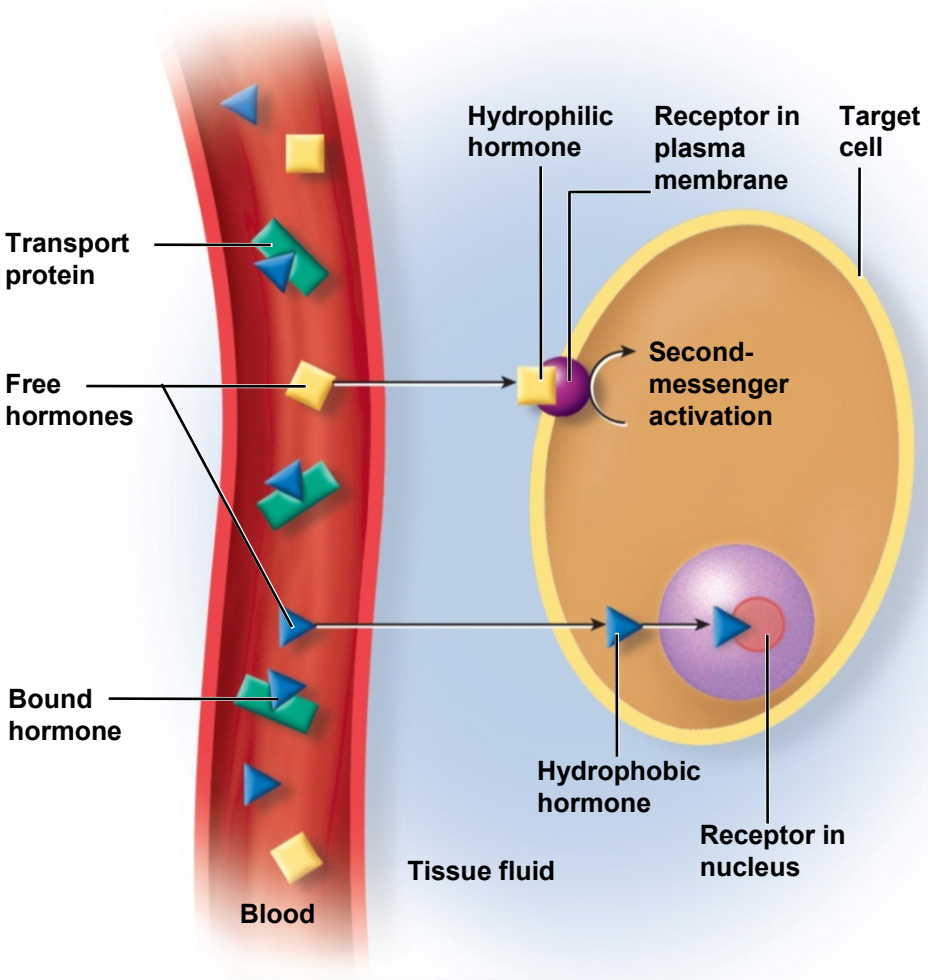
# Hormone Transport

- Thyroid hormone /// these are an exception to the rule /// protein based hormone but TH must bind to transport proteins in the plasma
  - albumin, thyretin and TGB (thyroxine-binding globulin)
  - more than 99% of circulating TH is protein bound
- Steroid hormones bind to globulins // transcortin is the transport protein for cortisol
  - Aldosterone // short half-life
    - 85% unbound
    - 15% binds weakly to albumin and others

# Hormone Receptors

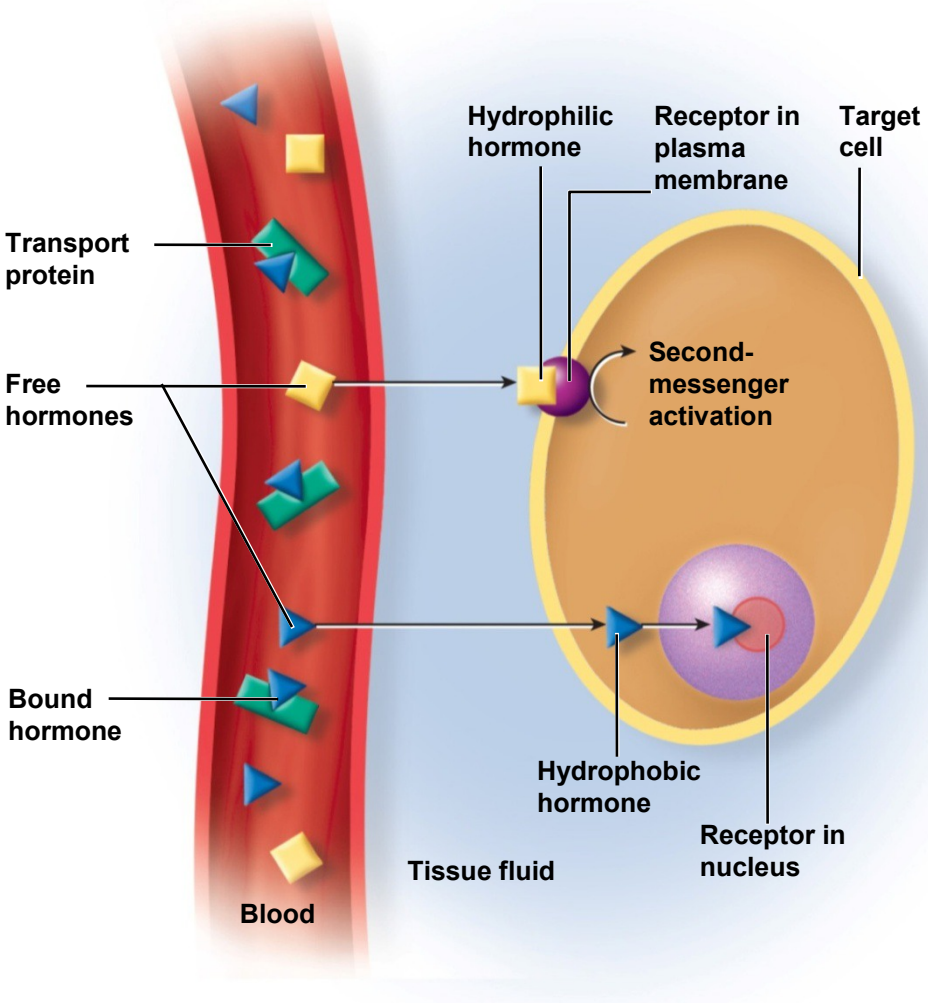
- A hormone may stimulate only those cells with a receptor that is matched to a" specific" hormone (i.e. think lock and key)
- Receptors are protein or glycoprotein molecules: // located on plasma membrane,
- If hydrophobic hormone then receptor for this hormone is in the cytoplasm, or in the nucleus
- A receptor functions as a switch /// turns on metabolic pathway when hormone binds to the receptor
- Any given target cell will have a few thousand receptors for any given hormone
- The receptor-hormone interactions exhibit specificity and saturation
  - specific receptor for each hormone
  - said to be "saturated" when all receptor molecules are occupied by hormone molecules

# Hydrophobic Hormone Mode of Action



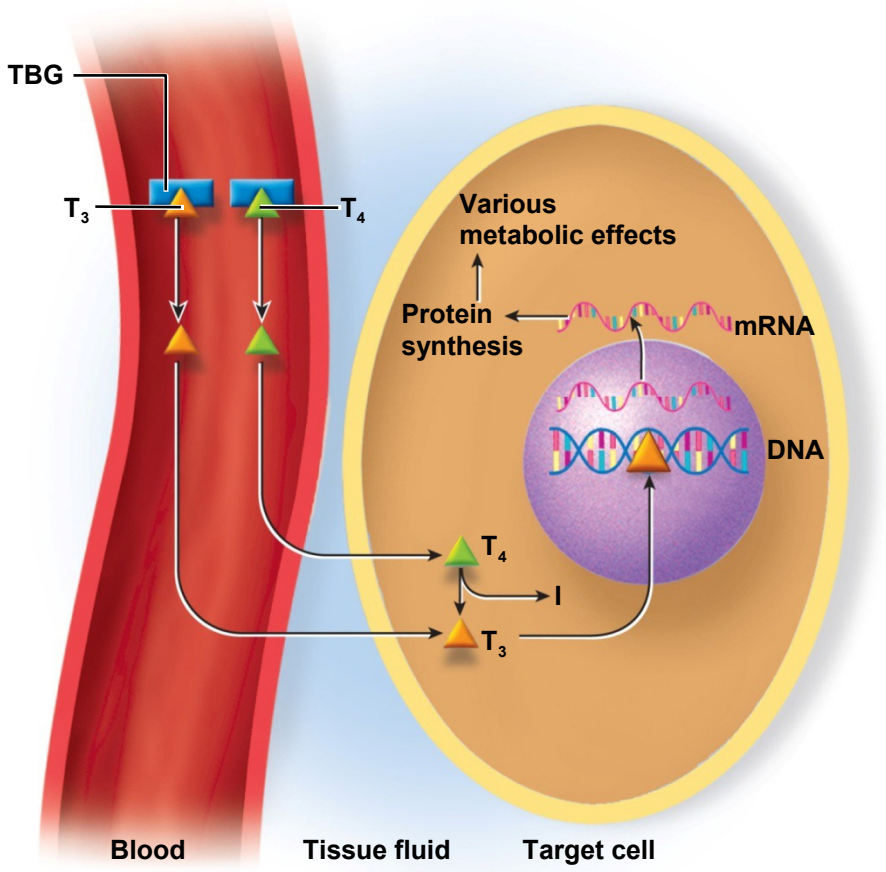

- hydrophobic hormones
  - penetrate plasma membrane and enter nucleus
  - act directly on the genes changing target cell physiology
  - estrogen, progesterone, thyroid hormone act on nuclear receptors
  - take several hours to days to show effect due to lag for protein synthesis

# Hydrophilic Hormone Mode of Action



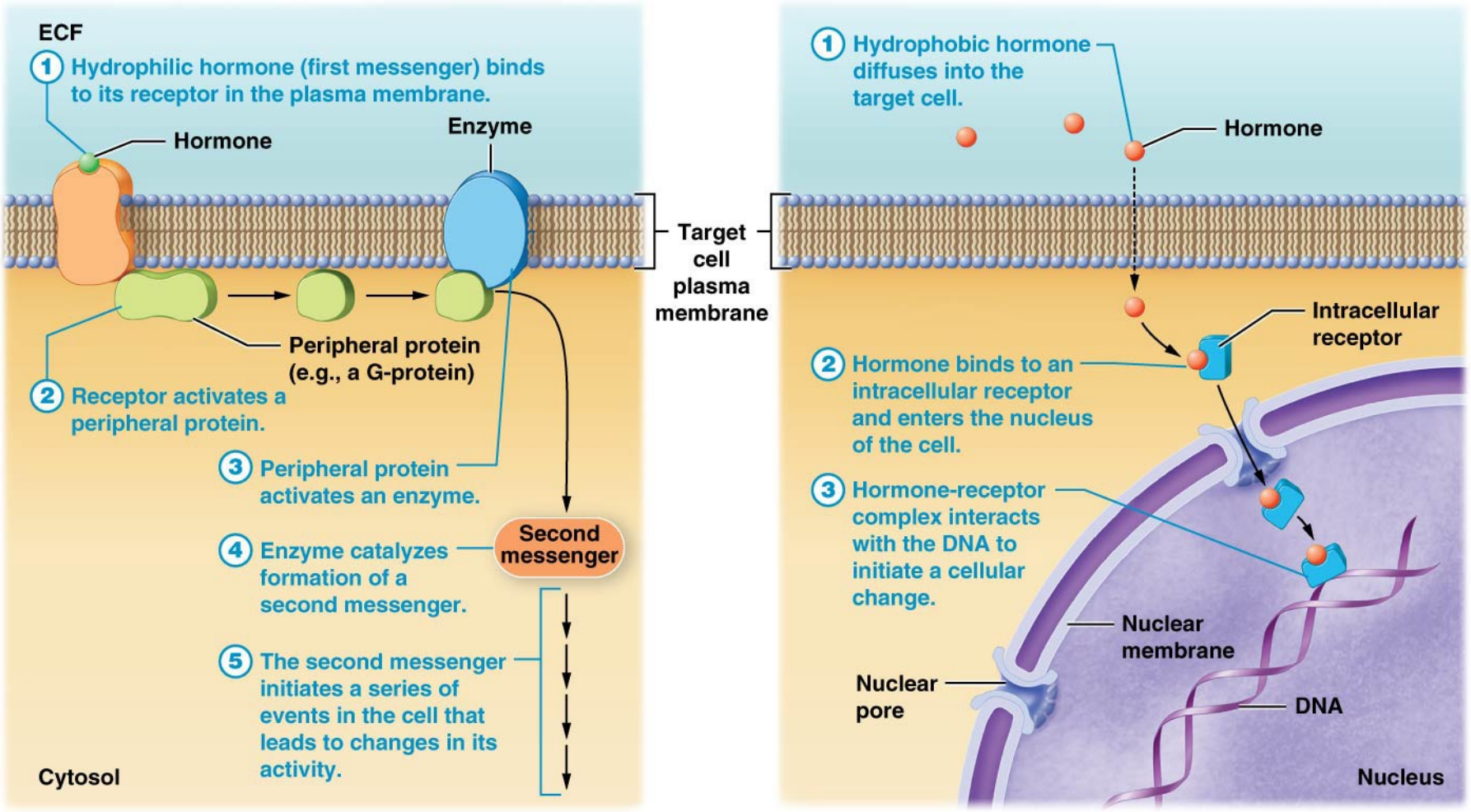

- hydrophilic hormones
  - cannot penetrate into target cell
  - must stimulate physiology indirectly
  - Second messenger systems // also called metabotrophic

# Thyroid Hormone - Hydrophic




- Hydrophobic thyroid hormone <u>enters target cell by diffusion</u> (mostly as $T_4$ with little metabolic effect)
- <u>within target cell, $T_4$ is converted to more potent $T_3$</u>
- $T_3$ enters target cells and binds to receptors in chromatin
- activates genes
  - make a muscle protein (myosin) enhancing cardiac muscle response to sympathetic stimulation
  - strengthening heartbeat

**Mechanisms of action of hydrophilic and hydrophobic hormones. This figure presents examples of how these hormones can work.**

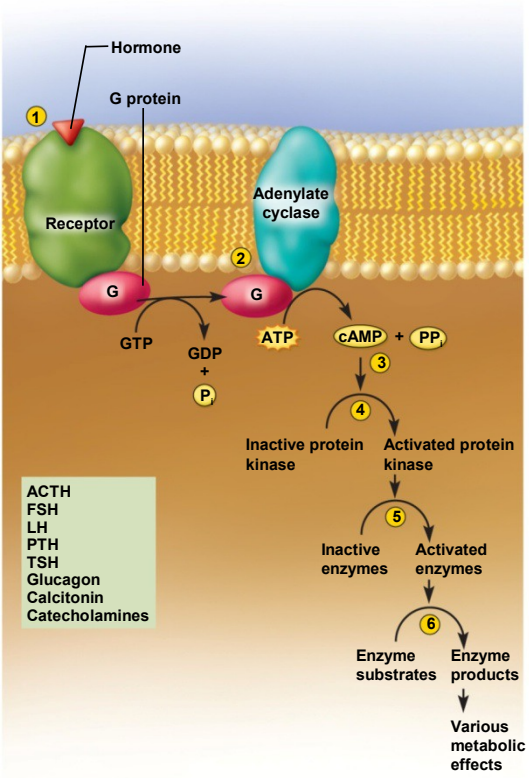



(a) Hydrophilic hormone and second-messenger system

(b) Hydrophobic hormone and intracellular receptor mechanism

# Peptides and Catecholamines Are Hydrophilic Molecules
## (Require Metabotrophic Receptors)

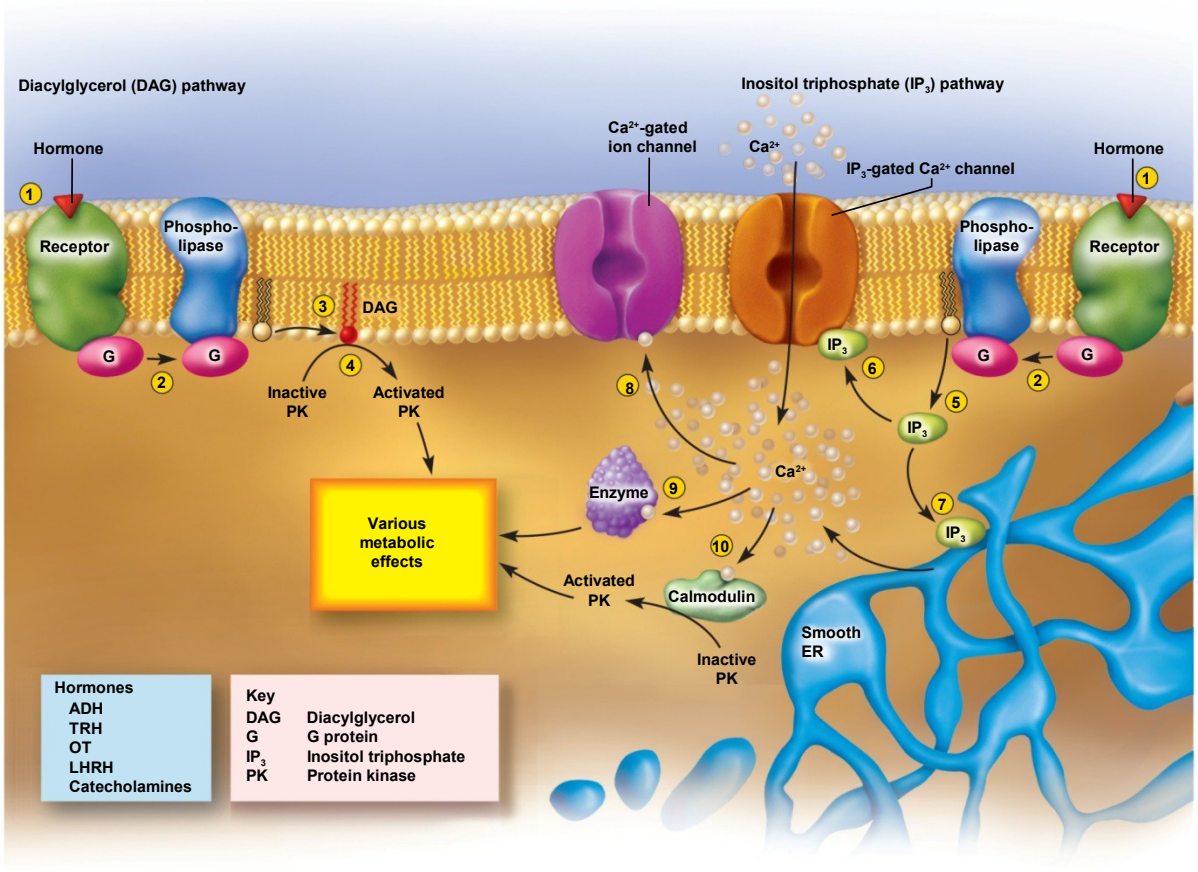





1. Hormone–receptor binding activates a G protein.
2. G protein activates adenylate cyclase.
3. Adenylate cyclase produces cAMP.
4. cAMP activates protein kinases.
5. Protein kinases phosphorylate enzymes. This activates some enzymes and deactivates others.
6. Activated enzymes catalyze metabolic reactions with a wide range of possible effects on the cell.

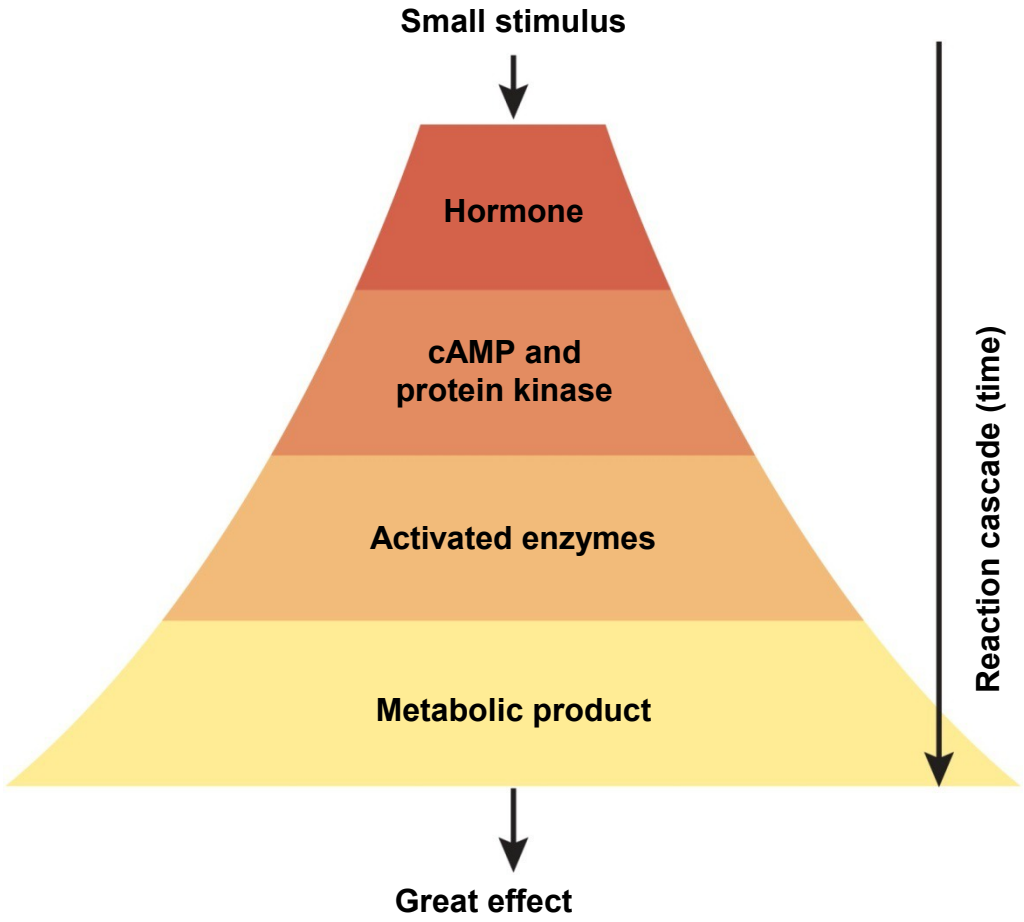
- hormone binds to cell-surface receptor
- receptor linked to second messenger system on other side of the membrane
- activates G protein which
- activates adenylate cyclase
- produces cAMP /// activates or inhibits enzymes
- possible metabolic reactions:
  - synthesis
  - secretion
  - change membrane potentials

# Other Second Messengers



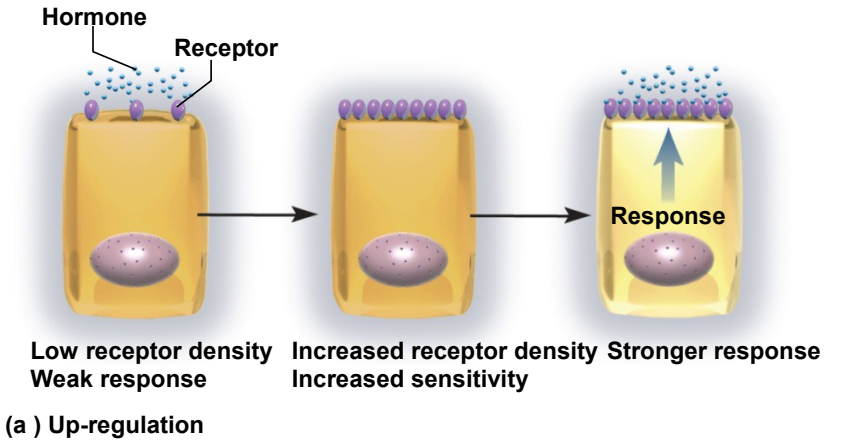

- diacylglycerol (diglyceride) second-messenger system
- inositol triphosphate second-messenger system

# Enzyme Amplification




- hormones are extraordinarily **potent molecules**
- one hormone molecule can trigger the synthesis of many enzyme molecules.
- very small stimulus produces very large effect
- hormone circulating concentrations can be very low but may cause great effect

# How Can Target Tissue Change Sensitivity to Hormones?




- target cell sensitivity <u>adjusted by changing the number of receptors</u>
- **up-regulation** means number of receptors is increased // sensitivity is increased
- **down-regulation** reduces number of receptors
  - cell less sensitive to hormone
  - happens with long-term exposure to high hormone concentrations
    - bind to other receptors
    - converted to different hormone

# Control of Pituitary Secretion

- **Hormone rate of secretions are not constant**
  - regulated by hypothalamus and other brain centers
  - negative feedback from hormone's target organs
- **Hypothalamic and Cerebral Control**
  - **anterior lobe secretions –** controlled by releasing hormones or inhibiting hormones from hypothalamus
  - E.g. // in cold weather, pituitary stimulated by hypothalamus to release TSH // leads to increase in metabolism and more Na-K-ATPase pumps placed in plasma membrane = more heat production // homeostatic mechanism

# Control of Pituitary Secretion

- Posterior lobe control – different mechanisms for oxytocin and ADH /// oxytocin = neuroendocrine reflex // ADH = blood tonicity

- Oxytocin:

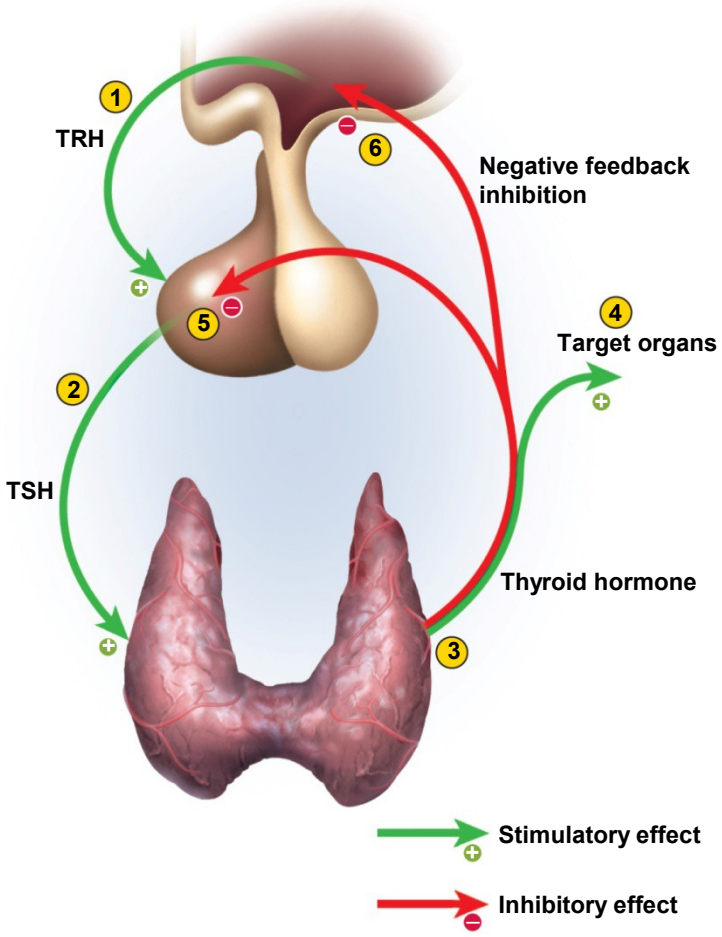
  - neuroendocrine reflex - hormone release in response to nervous system signals

  - suckling infant→ stimulates nerve endings → hypothalamus → posterior lobe → oxytocin → milk ejection

  - Also - hormone release in response to higher brain centers // milk ejection reflex -- can be triggered by a baby's cry

  - Note: emotional stress can affect secretion of gonadotropins, disrupting ovulation, menstruation, and fertility

# Negative and Positive Feedback Regulations




- negative feedback // thyroid regulation
  - increased target organ hormone levels inhibits release of hormones
- positive feedback // childbirth
  - stretching of uterus
  - increases OT release
  - causes contractions
  - causing more stretching of uterus
  - until delivery

# Hormone Interactions

- most cells sensitive to more than one hormone and exhibit interactive effects

- synergistic effects
  - multiple hormones act together for greater effect // synergism between FSH and testosterone on sperm production

- permissive effects
  - one hormone enhances the target organ's response to a second later hormone // estrogen prepares uterus for action of progesterone

- antagonistic effects
  - one hormone opposes the action of another // insulin lowers blood glucose and glycogen raises it

# Hormone Clearance

- hormone signals must be turned off when they have served their purpose

- most hormones are taken up and degraded by liver and excred in the bile // or by the kidney and excreted in the urine

- metabolic clearance rate (MCR)
  - rate of hormone removal from the blood
  - half-life - time required to clear 50% of hormone from the blood
  - faster the MCR, the shorter is the half-life