ENDOCRINOLOGY PHYSIOLOGY

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Chemical messenger

- Is any compound that serves to transmit a message.

A chemical messenger may refer to:

- **Hormone**, Long range chemical messenger
- **Neurotransmitter**, communicates to adjacent cells
- **Neuropeptide**, a protein sequence which acts as a hormone or neurotransmitter

Chemical Messengers:

- **Hormones:** long-distance chemical signals that travel in the blood or lymph
- **Autocrines:** chemicals that exert effects on the same cells that secrete them
- **Paracrines:** locally acting chemicals that affect cells other than those that secrete them
- **Autocrines and paracrines** are local chemical messengers and will not be considered part of the endocrine system

Chemistry of Hormones

- ***Two main classes***
  1. Amino acid-based hormones
     - Amines, thyroxine, peptides, and proteins
  2. Steroids
     - Synthesized from cholesterol
     - Gonadal and adrenocortical hormones

Mechanisms of Hormone Action

- Hormone action on target cells
  1. Alter plasma membrane permeability of membrane potential by opening or closing ion channels
  2. Stimulate synthesis of proteins or regulatory molecules
  3. Activate or deactivate enzyme systems
  4. Induce secretory activity
  5. Stimulate mitosis

Hormonal signaling across this hierarchy involves the following:

- **Biosynthesis** of a particular hormone in a particular tissue

- Storage and secretion of the hormone

- **Transport** of the hormone to the target cell(s)

- **Recognition** of the hormone by an associated cell membrane or intracellular receptor protein.

- Relay and amplification of the received **hormonal** signal via a signal transduction process: This then leads to a cellular response. The reaction of the target cells may then be recognized by the original hormone-producing cells, leading to a down-regulation in hormone production. This is an example of a homeostatic negative feedback loop.

- **Degradation** of the hormone.

Hormones have the following effects on the body:

- stimulation or inhibition of growth
- mood swings
- induction or suppression of apoptosis (programmed cell death)
- activation or inhibition of the immune system
- regulation of metabolism
- preparation of the body for fighting, sex, fleeing, mating, and other activity
- preparation of the body for a new phase of life, such as puberty, parenting, and menopause
- control of the reproductive cycle
- hunger cravings
- A hormone may also regulate the production and release of other hormones. Hormone signals control the internal environment of the body through homeostasis.

G proteins, short for **guanine nucleotide-binding proteins,** are a family of proteins involved in second messenger cascades.

G proteins are so called because they function as "molecular switches," alternating between an inactive guanosine diphosphate (GDP) and active guanosine triphosphate (GTP) bound state, ultimately going on to regulate downstream cell processes.

Mechanisms of Hormone Action

- Two mechanisms, depending on their chemical nature
  1. **Water-soluble hormones (all amino acid–based hormones except thyroid hormone)**
     - Cannot enter the target cells
     - Act on plasma membrane receptors
     - Coupled by G proteins to intracellular second messengers that mediate the target cell's response

Mechanisms of Hormone Action

2. Lipid-soluble hormones (steroid and thyroid hormones)
   - Act on intracellular receptors that directly activate genes

Plasma Membrane Receptors and Second-Messenger Systems

- **cAMP signaling mechanism**
  1. *Hormone (first messenger) binds to receptor*
  2. *Receptor activates G protein*
  3. *G protein activates adenylate cyclase*
  4. *Adenylate cyclase converts ATP to cAMP (second messenger)*
  5. *cAMP activates protein kinases*

Plasma Membrane Receptors and Second-Messenger Systems

- **cAMP signaling mechanism**
  - ***Activated kinases phosphorylate various proteins, activating some and inactivating others***
  - ***cAMP is rapidly degraded by the enzyme phosphodiesterase***
  - ***Intracellular enzymatic cascades have a huge amplification effect***

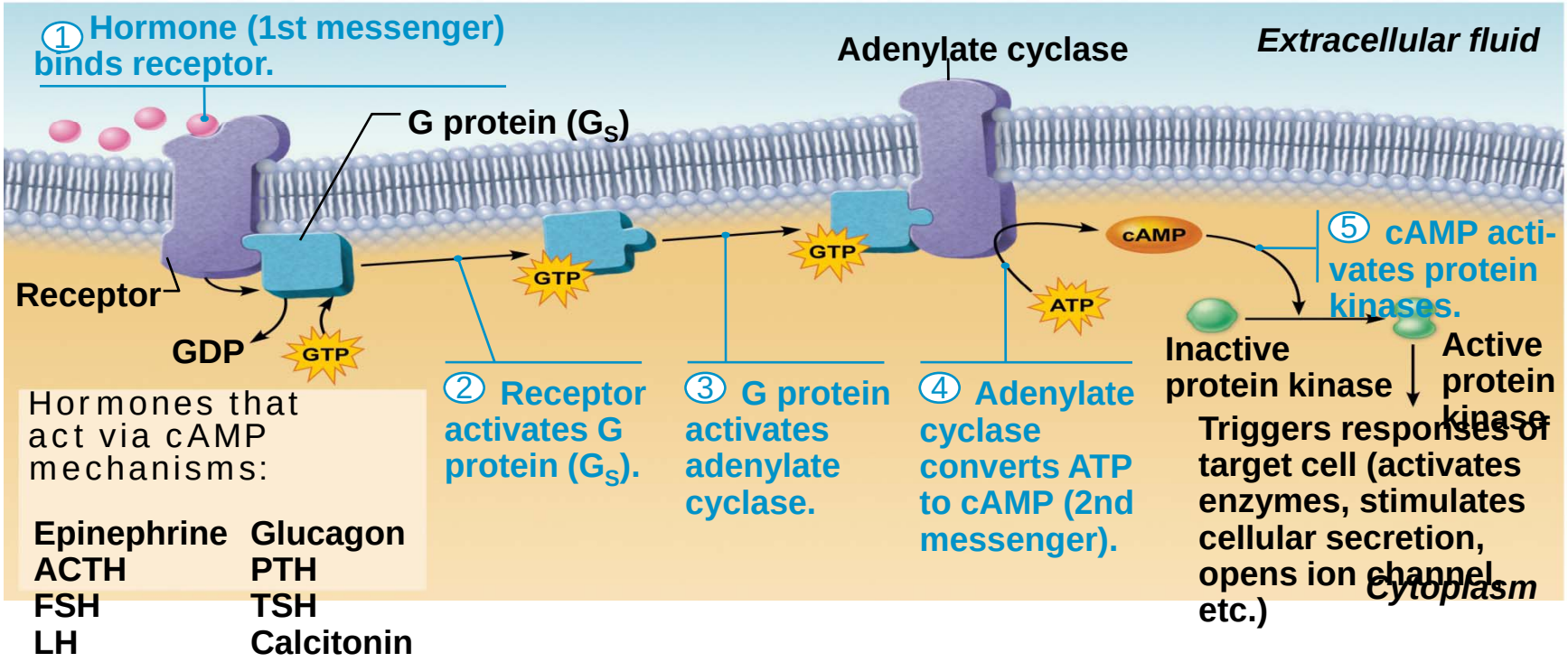
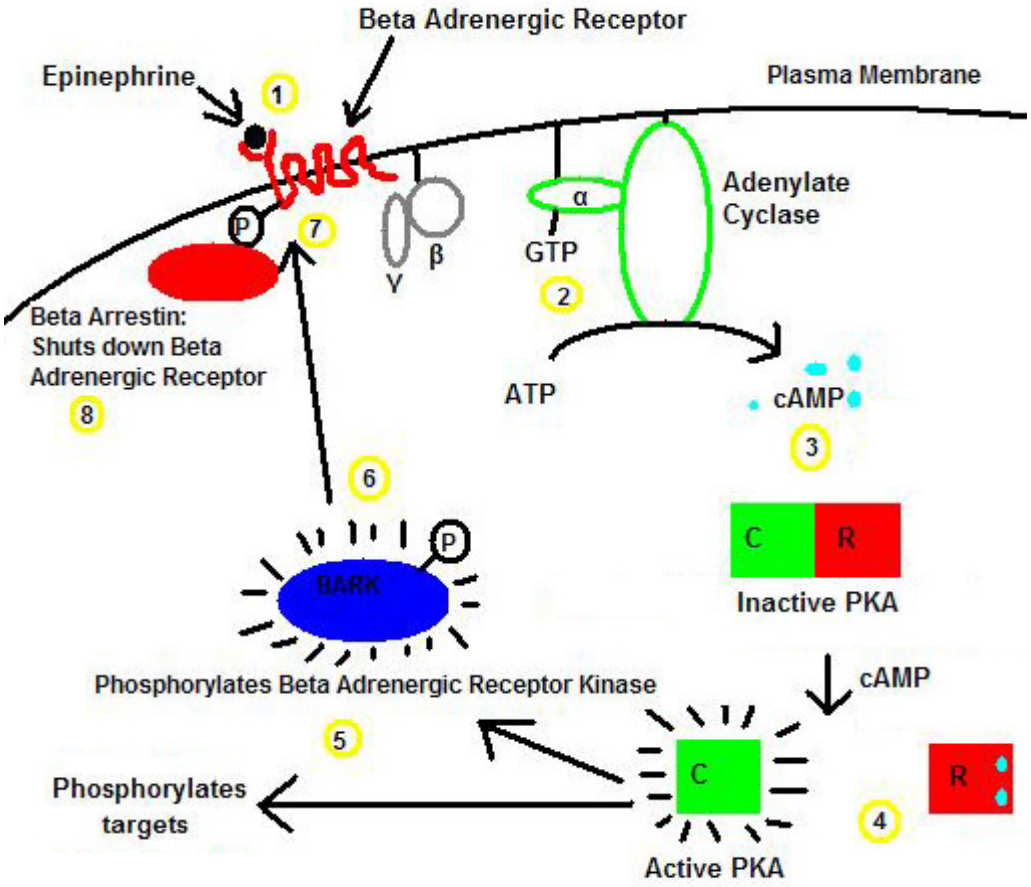
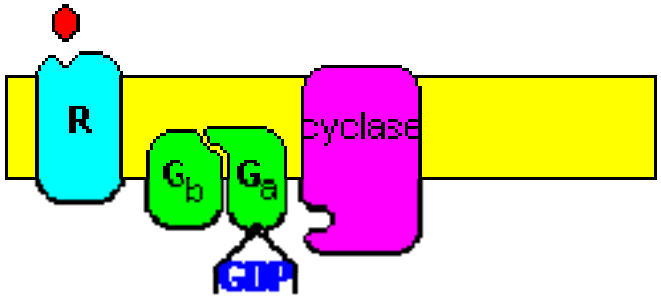

1 Hormone (1st messenger) binds receptor.
Adenylate cyclase
Extracellular fluid
G protein (G_S)
Receptor
GDP
GTP
GTP
GTP
ATP
cAMP
5 cAMP activates protein kinases.
Inactive protein kinase
Active protein kinase
Triggers responses of target cell (activates enzymes, stimulates cellular secretion, opens ion channel, etc.)
Cytoplasm
2 Receptor activates G protein (G_S).
3 G protein activates adenylate cyclase.
4 Adenylate cyclase converts ATP to cAMP (2nd messenger).
Hormones that act via cAMP mechanisms:
Epinephrine
ACTH
FSH
LH
Glucagon
PTH
TSH
Calcitonin

Figure 16.2


Beta Adrenergic Receptor
Epinephrine
1
Plasma Membrane
P
7
γ
β
α
GTP
2
Adenylate
Cyclase
Beta Arrestin:
Shuts down Beta
Adrenergic Receptor
8
ATP
cAMP
3
6
P
BARK
C
R
Inactive PKA
Phosphorylates Beta Adrenergic Receptor Kinase
cAMP
5
C
R
4
Phosphorylates
targets
Active PKA


R
cyclase
Gb
Ga
GDP

Plasma Membrane Receptors and Second-Messenger Systems

- PIP_2-calcium signaling mechanism
  - Used by some amino acid–based hormones in some tissues
  - Involves a G protein
  - G protein activates phospholipase C enzyme

Plasma Membrane Receptors and Second-Messenger Systems

- Phospholipase splits membrane phospholipid PIP_2 into two second messengers: diacylglycerol (DAG) and IP_3
- DAG activates protein kinases; IP_3 triggers release of Ca^{2+}
- Ca^{2+} alters enzymes or channels or binds to the regulatory protein calmodulin

Intracellular Receptors and Direct Gene Activation

- Steroid hormones and thyroid hormone
  1. Diffuse into their target cells and bind with intracellular receptors
  2. Receptor-hormone complex enters the nucleus
  3. Receptor-hormone complex binds to a specific region of DNA
  4. This prompts DNA transcription to produce mRNA
  5. The mRNA directs protein synthesis

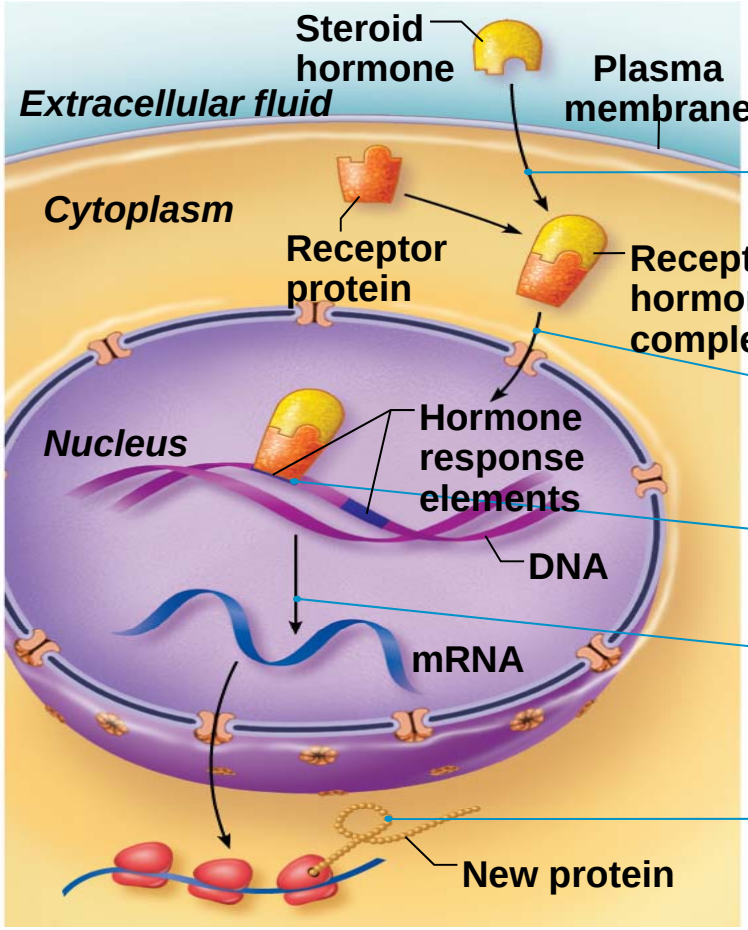

Steroid hormone
Plasma membrane
Extracellular fluid
Cytoplasm
Receptor protein
Receptor-hormone complex
Nucleus
Hormone response elements
DNA
mRNA
New protein
① The steroid hormone diffuses through the plasma membrane and binds an intracellular receptor.
② The receptor-hormone complex enters the nucleus.
③ The receptor- hormone complex binds a hormone response element (a specific DNA sequence).
④ Binding initiates transcription of the gene to mRNA.
⑤ The mRNA directs protein synthesis.

Figure 16.3

Target Cell Specificity

- Target cells must have specific receptors to which the hormone binds
  - ACTH receptors are only found on certain cells of the adrenal cortex
  - Thyroxin receptors are found on nearly all cells of the body

Target Cell Activation

- Target cell activation depends on three factors
  1. Blood levels of the hormone
  2. Relative number of receptors on or in the target cell
  3. Affinity of binding between receptor and hormone

Target Cell Activation

- Hormones influence the number of their receptors
  - Up-regulation—target cells form more receptors in response to the hormone
  - Down-regulation—target cells lose receptors in response to the hormone

Hormones in the Blood

- Hormones circulate in the blood either free or bound
  - Steroids and thyroid hormone are attached to plasma proteins
  - All others circulate without carriers
- The concentration of a circulating hormone reflects:
  - Rate of release
  - Speed of inactivation and removal from the body

Hormones in the Blood

- Hormones are removed from the blood by
  - Degrading enzymes
  - Kidneys
  - Liver
  - Half-life—the time required for a hormone's blood level to decrease by half

Interaction of Hormones at Target Cells

- Multiple hormones may interact in several ways
  - **Permissiveness:** one hormone cannot exert its effects without another hormone being present
  - **Synergism:** more than one hormone produces the same effects on a target cell
  - **Antagonism:** one or more hormones opposes the action of another hormone

Control of Hormone Release

- **Blood levels of hormones**
  - Are controlled by negative feedback systems
  - Vary only within a narrow desirable range
- **Hormones are synthesized and released in response to**
  1. Humoral stimuli
  2. Neural stimuli
  3. Hormonal stimuli

Humoral Stimuli

- Changing blood levels of ions and nutrients directly stimulates secretion of hormones
- Example: Ca^{2+} in the blood
  - Declining blood Ca^{2+} concentration stimulates the parathyroid glands to secrete PTH (parathyroid hormone)
  - PTH causes Ca^{2+} concentrations to rise and the stimulus is removed

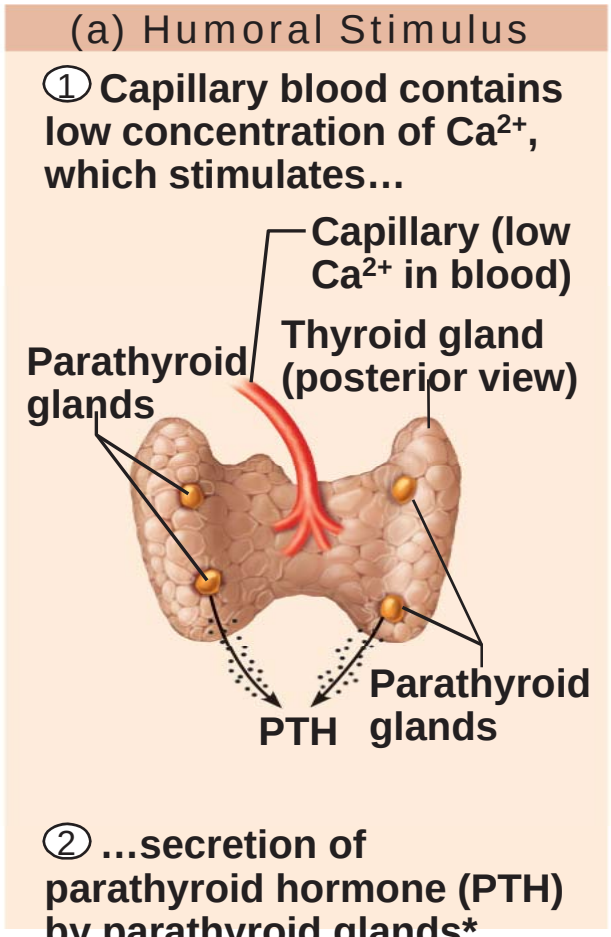

(a) Humoral Stimulus
① Capillary blood contains low concentration of Ca^{2+}, which stimulates…
Capillary (low Ca^{2+} in blood)
Thyroid gland (posterior view)
Parathyroid glands
Parathyroid glands
PTH
② …secretion of parathyroid hormone (PTH) by parathyroid glands*

Figure 16.4a

Neural Stimuli

- Nerve fibers stimulate hormone release
  - Sympathetic nervous system fibers stimulate the adrenal medulla to secrete catecholamines

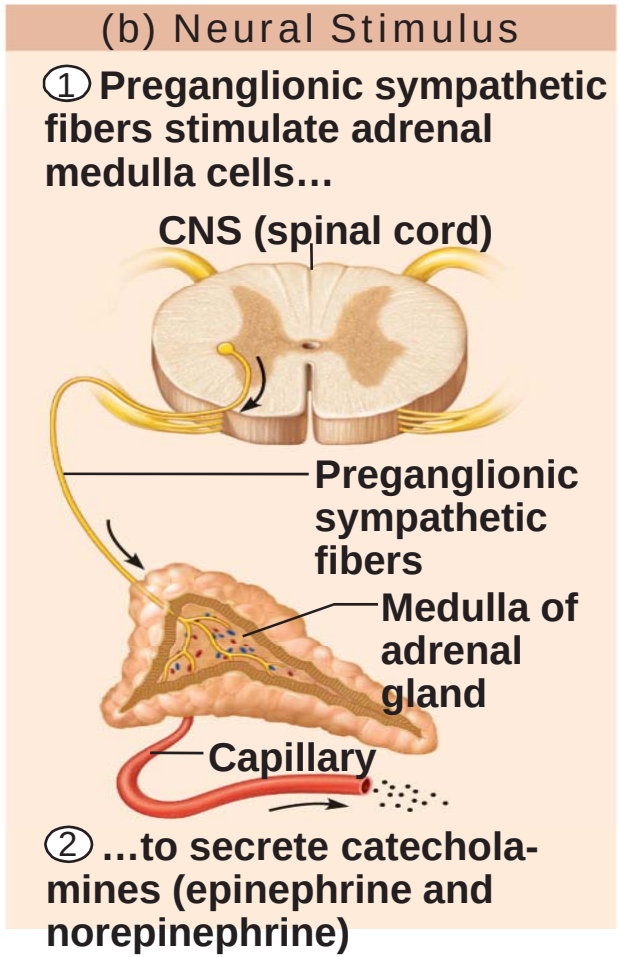

(b) Neural Stimulus
① Preganglionic sympathetic fibers stimulate adrenal medulla cells…
CNS (spinal cord)
Preganglionic sympathetic fibers
Medulla of adrenal gland
Capillary
② …to secrete catecholamines (epinephrine and norepinephrine)

Figure 16.4b

Hormonal Stimuli

- Hormones stimulate other endocrine organs to release their hormones
  - Hypothalamic hormones stimulate the release of most anterior pituitary hormones
  - Anterior pituitary hormones stimulate targets to secrete still more hormones
  - Hypothalamic-pituitary-target endocrine organ feedback loop: hormones from the final target organs inhibit the release of the anterior pituitary hormones

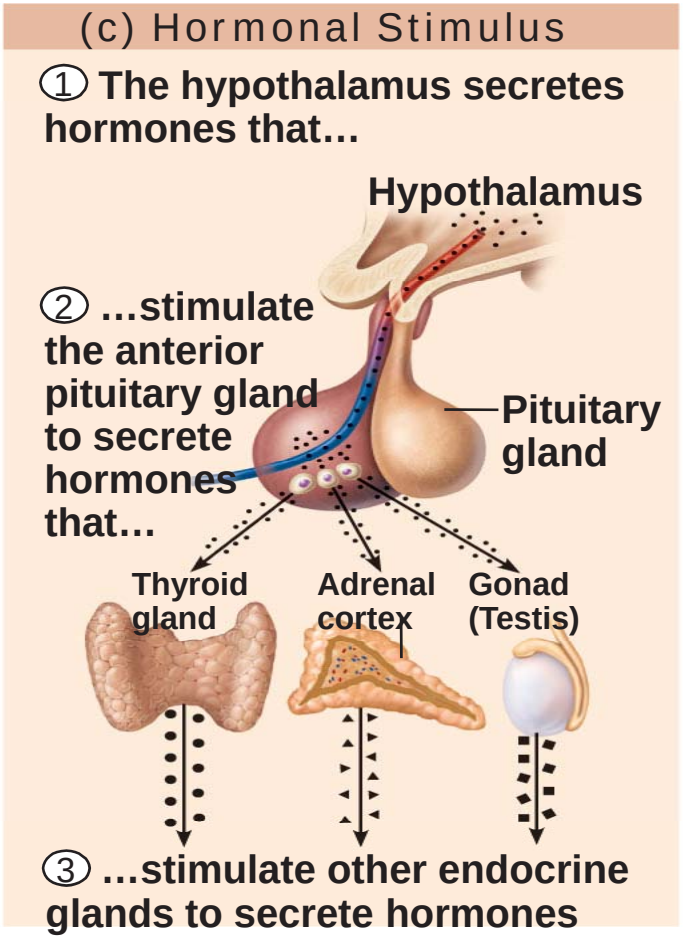

(c) Hormonal Stimulus
① The hypothalamus secretes hormones that…
Hypothalamus
② …stimulate the anterior pituitary gland to secrete hormones that…
Pituitary gland
Thyroid gland
Adrenal cortex
Gonad (Testis)
③ …stimulate other endocrine glands to secrete hormones

Figure 16.4c

Nervous System Modulation

- The nervous system modifies the stimulation of endocrine glands and their negative feedback mechanisms
  - Example: under severe stress, the hypothalamus and the sympathetic nervous system are activated
    - As a result, body glucose levels rise