Al-Mustaqbal University College

Pharmacy Department / Second Stage

PHYSIOLOGY II

ENDOCRINE SYSTEM : L1

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COORDINATION OF BODY FUNCTIONS BY CHEMICAL MESSENGERS

The multiple activities of the cells, tissues, and organs of the body are coordinated by the interplay of several types of chemical messenger systems:

1. ***Neurotransmitters*** are released by axon terminals of neurons into the synaptic junctions and act locally to control nerve cell functions.
2. ***Endocrine hormones*** are released by glands or specialized cells into the circulating blood and influence the function of target cells at another location in the body.
3. ***Neuroendocrine hormones*** are secreted by neurons into the circulating blood and influence the function of target cells at another location in the body.
4. ***Paracrines*** are secreted by cells into the extracellular fluid and affect neighboring target cells of a different type.
5. ***Autocrines*** are secreted by cells into the extracellular fluid and affect the function of the same cells that produced them.
6. ***Cytokines*** are peptides secreted by cells into the extracellular fluid and can function as autocrines, paracrines, or endocrine hormones. Examples of cytokines include the *interleukins* and other *lymphokines* that are secreted by helper cells and act on other cells of the immune system. Cytokine hormones (e.g., *leptin*) produced by adipocytes are sometimes called *adipokines.*

In chemical signaling, a cell may target itself (**autocrine signaling**),

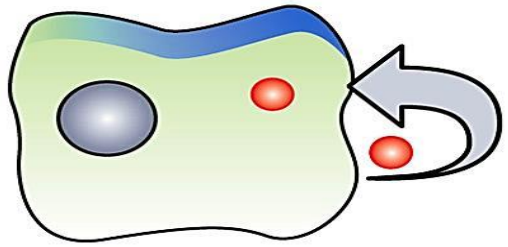
a cell connected by gap junctions,

a nearby cell (**paracrine signaling**),

or a distant cell (**endocrine signaling**).

Forms of Chemical Signaling

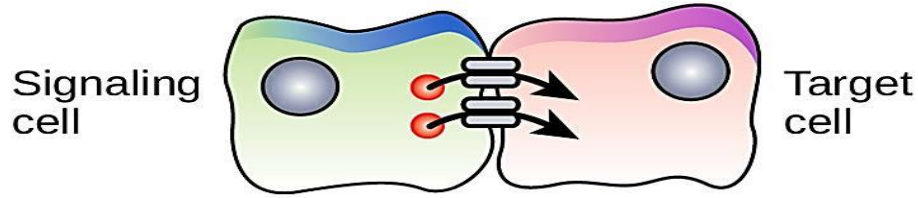
Autocrine	A cell targets itself.



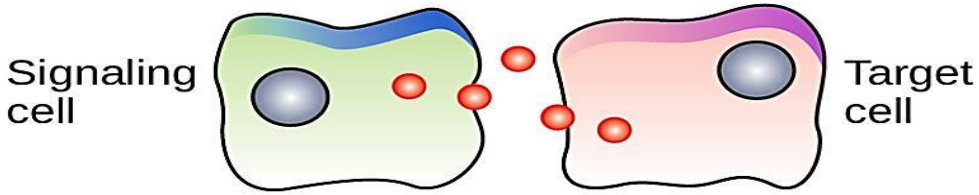
Such as interleukins play a key role in the development of inflammatory signals and pain sensation.

Interferons can act as autocrine signals in virus-infected cells.

Signaling across gap junctions	A cell targets a cell connected by gap junctions.

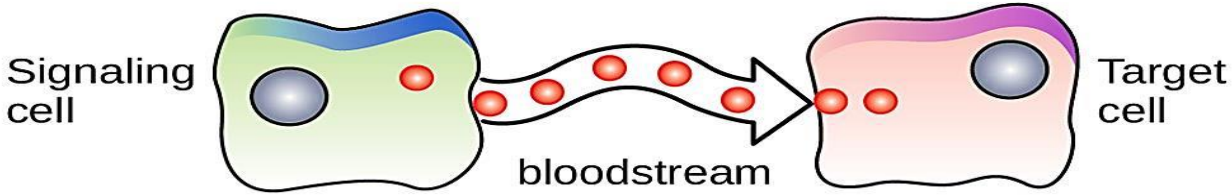


Paracrine	A cell targets a nearby cell.



The most common example is the. Neurotransmitters

Endocrine	A cell targets a distant cell through the bloodstream.



Introduction

Two major regulatory systems make important contributions to homeostasis: the nervous system and the endocrine system. In order to maintain relatively constant conditions in the internal environment of the body, each of these systems influences the activity of all the other organ systems.

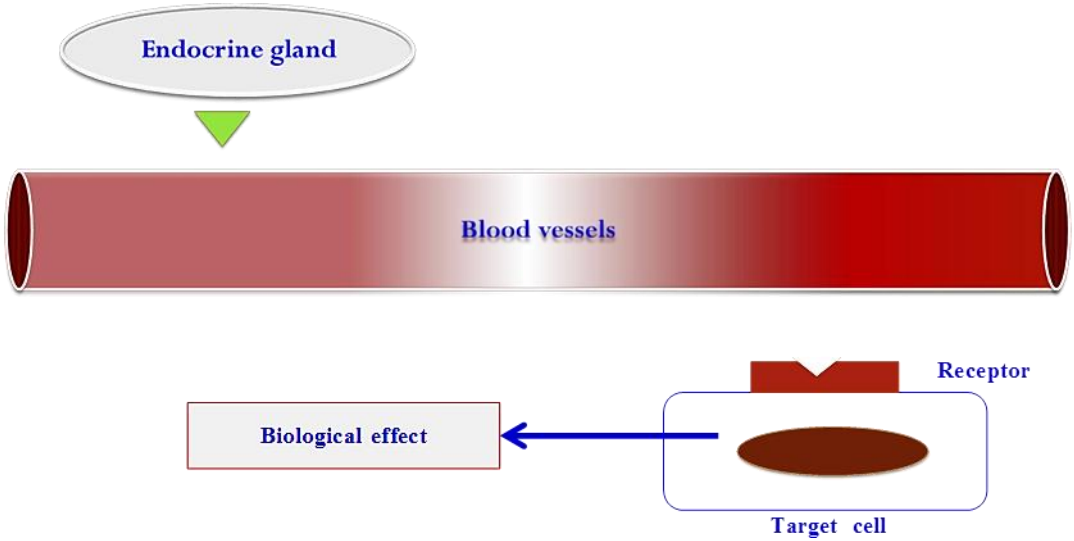
The nervous system coordinates fast, precise responses, such as muscle contraction. Electrical impulses generated by this system are very rapid and of short duration (milliseconds).

The endocrine system regulates metabolic activity within the cells of organs and tissues. In contrast to the nervous system, this system coordinates activities that require longer duration (hours, days) rather than speed.

Examples of such activities include growth; long-term regulation of blood pressure; and coordination of menstrual cycles in females.

The endocrine system carries out its effects through the production of hormones, **chemical messengers** that exert a regulatory effect on the cells of the body.

Secreted from endocrine glands, which are ductless structures, hormones are released directly into the blood. They are then transported by the circulation to the tissues upon which they exert their effects.



Biochemical classification of hormones

Hormones are classified into three biochemical categories :

- Steroids
- Proteins/peptides
- Amines

Steroid hormones are produced by the adrenal cortex, testes, ovaries, and placenta.

Synthesized from cholesterol, these hormones are lipid soluble; therefore, they cross cell membranes readily and bind to receptors found intracellularly.

However, because their lipid solubility renders them insoluble in blood, these hormones are transported in the blood bound to proteins.

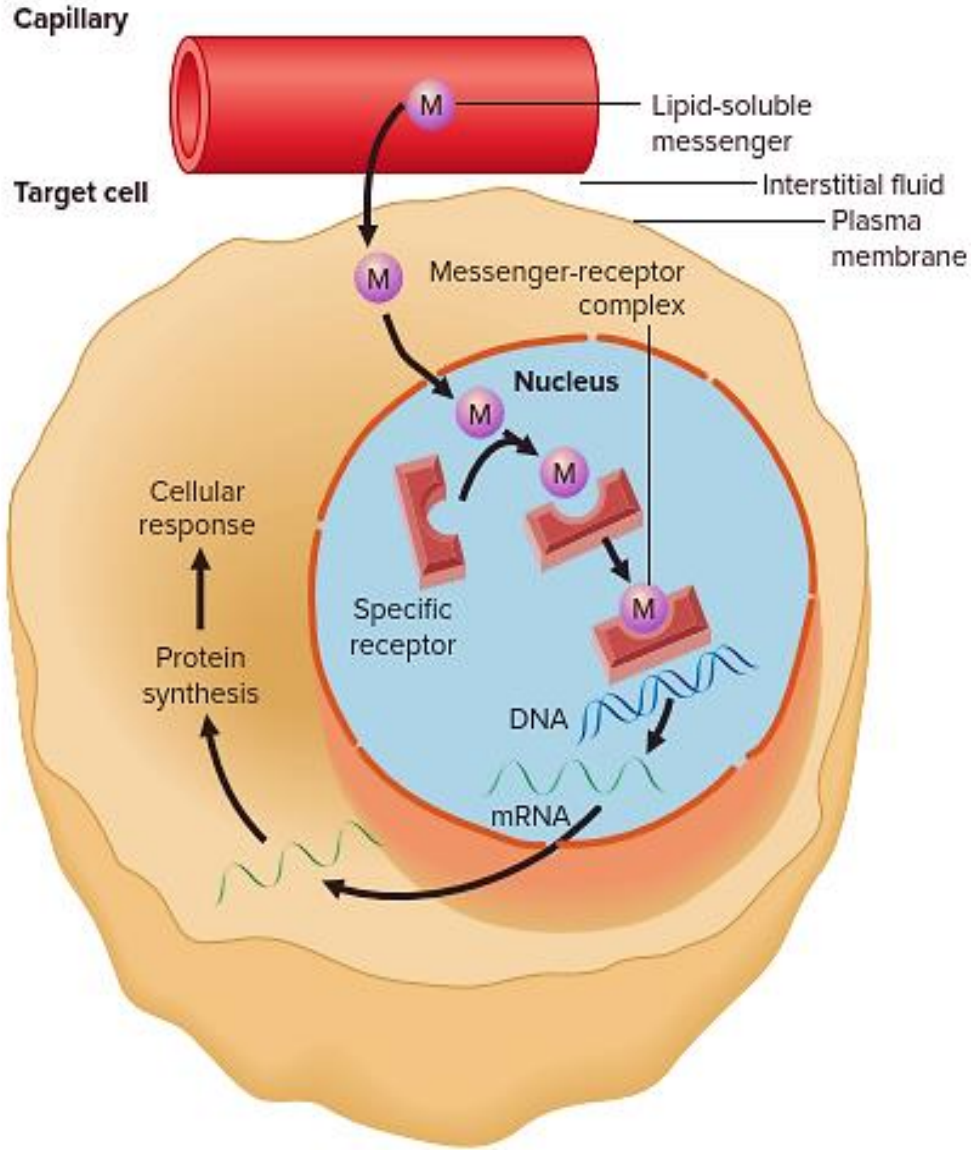
Furthermore, steroid hormones are not typically preformed and stored for future use within the endocrine gland. Because they are lipid soluble, they could diffuse out of the cells and physiological regulation of their release would not be possible.

Finally, steroid hormones are absorbed easily by the gastrointestinal tract and therefore may be administered orally.

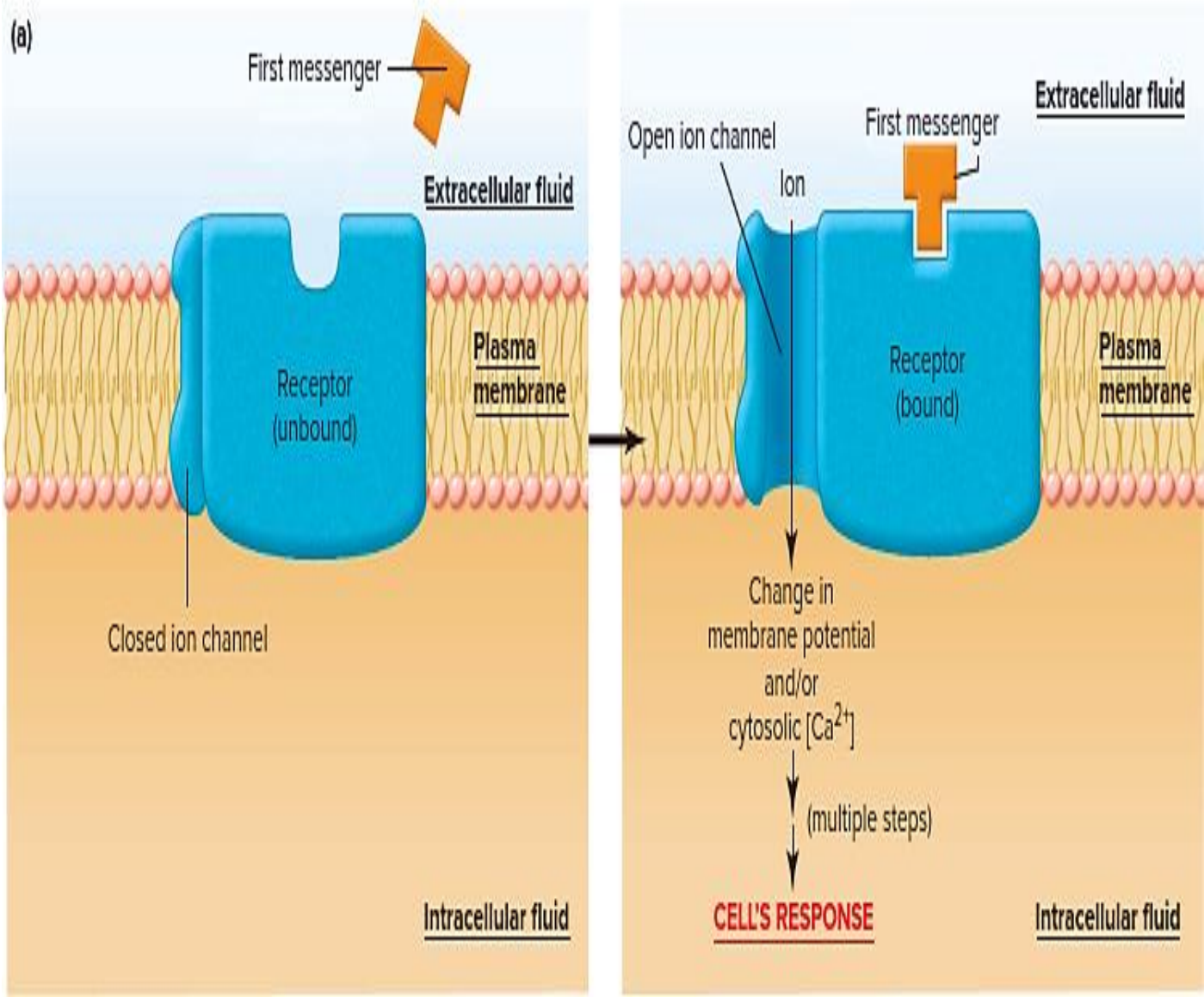
Protein/peptide hormones are derived from amino acids. These hormones are preformed and stored for future use in membrane-bound secretory granules. When needed, they are released by exocytosis.
Protein/peptide hormones are water soluble, circulate in the blood predominantly in an unbound form, and thus tend to have short half-lives.
Because these hormones are unable to cross the cell membranes of their target tissues, they bind to receptors on the membrane surface.
Protein/peptide hormones cannot be administered orally because they would be digested in the gastrointestinal tract. Instead, they are usually administered by injection (e.g., insulin).

Amine hormones include the thyroid hormones and the catecholamines.
The thyroid hormones tend to be biologically similar to the steroid hormones.
They are mainly insoluble in the blood and are transported predominantly (>99%) bound to proteins. As such, these hormones have longer half-lives (triiodothyronine, T3, = 24 h; thyroxine, T4, = 7 days). Furthermore, thyroid hormones cross cell membranes to bind with intracellular receptors and may be administered orally. The catecholamines are biologically similar to protein/peptide hormones. These hormones are soluble in the blood and are transported in an unbound form. Therefore, the catecholamines have a relatively short half-life. Because these hormones do not cross cell membranes, they bind to receptors on the membrane surface. Finally, the catecholamines are stored intracellularly in secretory granules for future use.

Mechanism of action of lipid-soluble messengers.



Mechanisms of action of water-soluble messengers



Transport of hormones

Steroid and thyroid hormones are transported in the blood bound to plasma proteins. The serum concentrations of free hormone (H), plasma protein (P), and bound hormone (HP) are in equilibrium. When the concentration of the free form of a hormone decreases, then more of this hormone will be released from the binding proteins. The free hormone is the biologically active form. It binds to the target tissue to cause its actions and is involved with the negative feedback control of its secretion.

The binding of hormones to plasma proteins has several beneficial effects, including:

- Facilitation of transport
- Prolonged half-life
- Hormone reservoir

Steroid and thyroid hormones are minimally soluble in the blood. Binding to plasma proteins renders them water soluble and facilitates their transport. Protein binding also prolongs the circulating half-life of these hormones. Because they are lipid soluble, they cross cell membranes easily. As the blood flows through the kidney, these hormones would enter cells or be filtered and lost to the urine if they were not held in the blood by the impermeable plasma proteins.

“Clearance” of Hormones From the Blood.

Hormones are “cleared” from the plasma in several ways, including
(1) metabolic destruction by the tissues,
(2) binding with the tissues,
(3) excretion by the liver into the bile, and
(4) excretion by the kidneys into the urine.

For certain hormones, a decreased metabolic clearance rate may cause an excessively high concentration of the hormone in the circulating body fluids. For example, excessive steroid hormones accumulate when the liver is diseased because these hormones are conjugated mainly in the liver and then “cleared” into the bile.

Hormones that are bound to plasma proteins are cleared from the blood at much slower rates and may remain in the circulation for several hours or even days. The half-life of adrenal steroids in the circulation, for example, ranges between 20 and 100 minutes, whereas the half-life of the protein-bound thyroid hormones may be as long as 1 to 6 days

Functional classification of hormones

Hormones are classified into two functional categories:

- Trophic hormones
- Nontrophic hormones

A trophic hormone acts on another endocrine gland to stimulate secretion of its hormone. For example, thyrotropin, or thyroid-stimulating hormone (TSH), stimulates the secretion of thyroid hormones. Adrenocorticotropin, or adrenocorticotropic hormone (ACTH), stimulates the adrenal cortex to secrete the hormone cortisol. Both trophic hormones are produced by the pituitary gland; in fact, many trophic hormones are secreted by the pituitary. The pituitary gland is sometimes referred to as the "master gland" because its hormones regulate the activity of other endocrine glands.

A nontrophic hormone acts on nonendocrine target tissues. For example, parathormone released from the parathyroid glands acts on bone tissue to stimulate the release of calcium into the blood. Aldosterone released from the cortical region of the adrenal glands acts on the kidney to stimulate the reabsorption of sodium into the blood.

Hormone interactions

Multiple hormones may affect a single target tissue simultaneously. Therefore, the response of the target tissue depends not only on the effects of each hormone individually, but also on the nature of the interaction of the hormones at the tissue. The three types of hormone interactions include:

- Synergism
- Permissiveness
- Antagonism

When two hormones interact at the target tissue such that the combination of their effects is more than additive, synergism occurs. In other words, their combined effect is greater than the sum of their separate effects. For example, epinephrine, cortisol, and glucagon are three hormones that each increase the level of blood glucose. The magnitude of their individual effects on glucose levels tends to be low to moderate. However, the simultaneous activity of all three hormones results in an increase in blood glucose that is several times greater than the sum of their individual effects.

In **permissiveness**, one hormone enhances the responsiveness of the target tissue to a second hormone; in other words, the first hormone increases the activity of the second. For example, the normal maturation of the reproductive system requires reproductive hormones from the hypothalamus, pituitary, and gonads as well as the presence of thyroid hormone. Although thyroid hormone by itself has no effect on the reproductive system, if it is absent the development of this system is delayed. Therefore, thyroid hormone is considered to have a permissive effect on the reproductive hormones.

When the actions of one hormone oppose the effects of another, the result is **antagonism**. For example, insulin decreases blood glucose and promotes the formation of fat. Glucagon, on the other hand, increases blood glucose and promotes the degradation of fat. Therefore, the effects of insulin and glucagon are antagonistic.

Mechanisms of hormone action

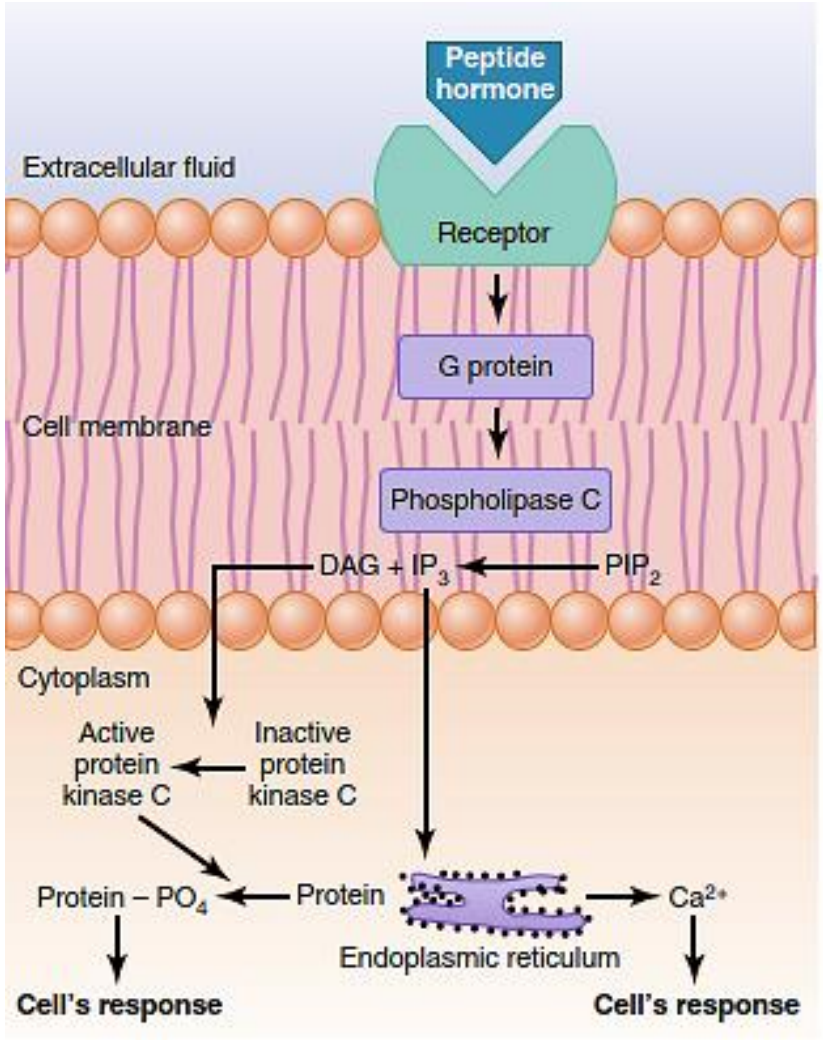
The binding of a hormone to its receptor initiates intracellular events that direct the hormone's action. Ultimately, all hormones produce their effects by altering intracellular protein activity. However, the mechanism by which this occurs depends on the location of the hormone receptor. Receptors are typically located on the cell surface or in the cell nucleus. As a result, most hormones carry out their effects by means of two general mechanisms:

- Signal transduction and second messenger systems
- Gene activation

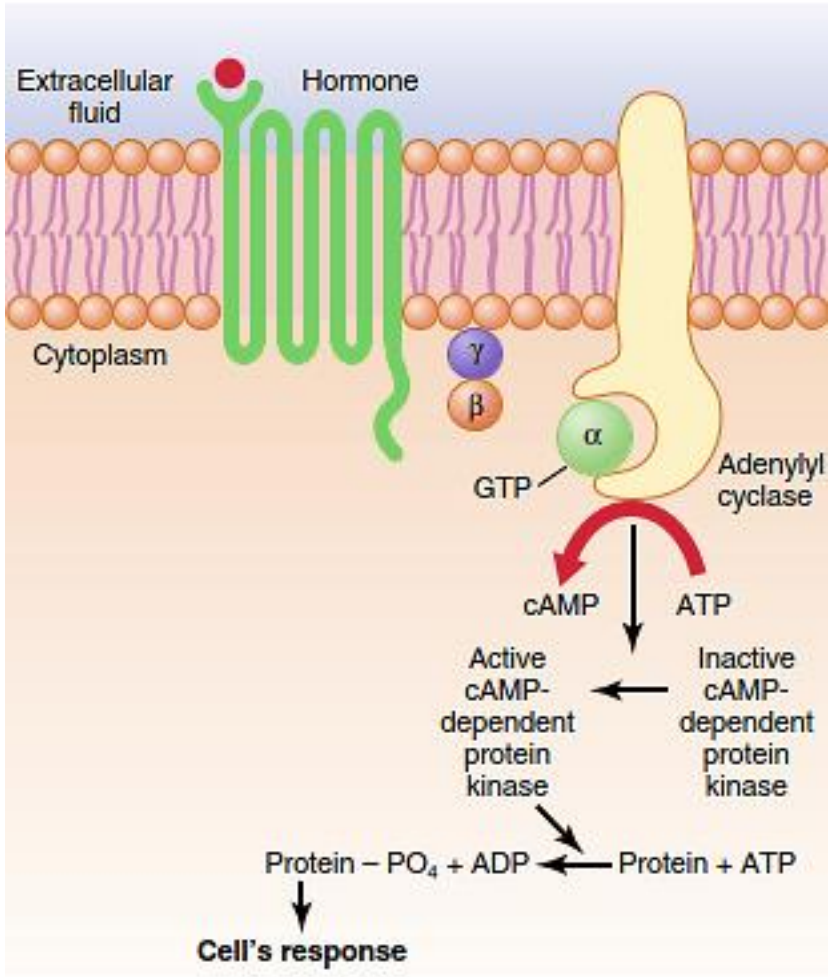
Protein/peptide hormones and the catecholamines are water-soluble substances and, accordingly, are unable to cross the plasma membrane to enter the cell. Therefore, these hormones must bind to their specific receptors on the cell surface. This receptor binding causes a response within the cell by way of signal transduction or by the production of intracellular second messenger molecules. The original, extracellular hormone is considered the first messenger because it carried the signal to the target tissue.

The most common second messenger activated by protein/peptide hormones and catecholamines is *cyclic adenosine monophosphate* (*cAMP*). The pathway by which cAMP is formed and alters cellular function is illustrated in Figure.

The process begins when the hormone binds to its receptor. These receptors are quite large and span the plasma membrane. On the cytoplasmic surface of the membrane, the receptor is associated with a *G protein* that serves as the transducer molecule. In other words, the G protein acts as an intermediary between the receptor and the second messengers that will alter cellular activity. These proteins are referred to as G proteins because they bind with guanosine nucleotides. In an unstimulated cell, the inactive G protein binds guanosine diphosphate (GDP). When the hormone binds to its G protein-associated receptor, the G protein releases GDP and binds with *guanosine triphosphate* (*GTP*) taken up from the cytoplasm. Upon binding with the GTP, the now activated G protein loses its affinity for the receptor and increases its affinity for the plasma membrane-embedded enzyme, *adenylyl cyclase*. In turn, the adenylyl cyclase becomes activated and splits adenosine triphosphate (ATP) to form cAMP. The cAMP molecule serves as the second messenger, which carries out the effects of the hormone inside the cell.



The cell membrane phospholipid second messenger system by which some hormones exert their control of cell function. DAG, Diacylglycerol; IP_3, inositol triphosphate; PIP_2, phosphatidylino- sitol biphosphate.

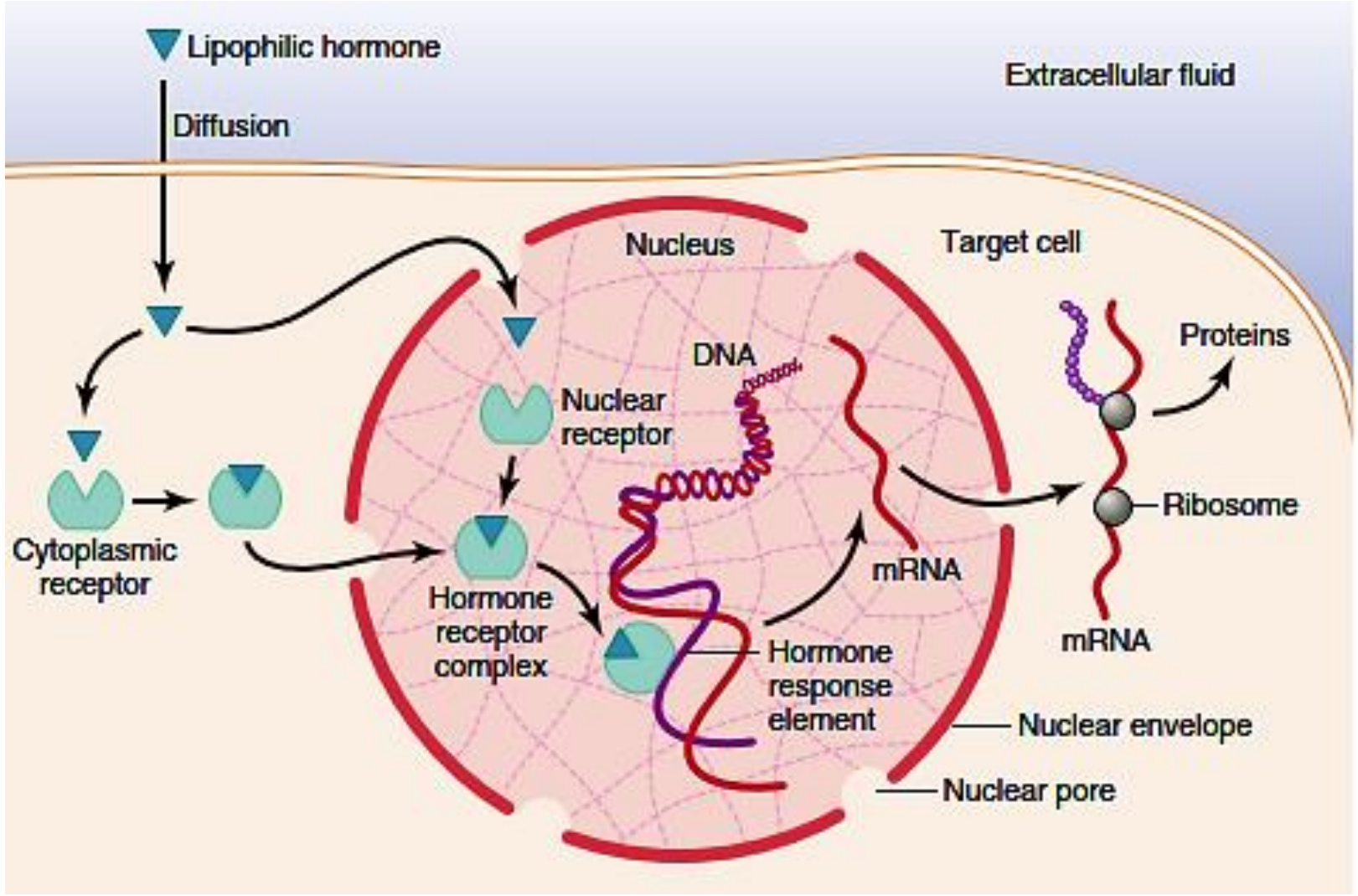


The cyclic adenosine monophosphate *(cAMP)* mechanism by which many hormones exert their control of cell function. ADP, Adenosine diphosphate; ATP, adenosine triphosphate; GTP, guanosine triphosphate.

Steroid hormones and thyroid hormone carry out their effects by way of *gene activation*. In contrast to the protein/peptide hormones, which alter existing enzyme activity, these hormones induce the synthesis of new enzymes that then influence cellular metabolism.
Hormones in this category are lipophilic and easily enter the cells of the target tissue by diffusing through the plasma membrane. The hormone continues into the cell nucleus where it binds to its receptor forming a *hormone–receptor complex*, resulting in the formation of *mRNA molecules*. The mRNA then diffuses into the cytoplasm and binds to a ribosome where protein synthesis takes place. These new proteins serve as enzymes that regulate cellular reactions and processes.

Measurement of Hormone Concentrations in the Blood

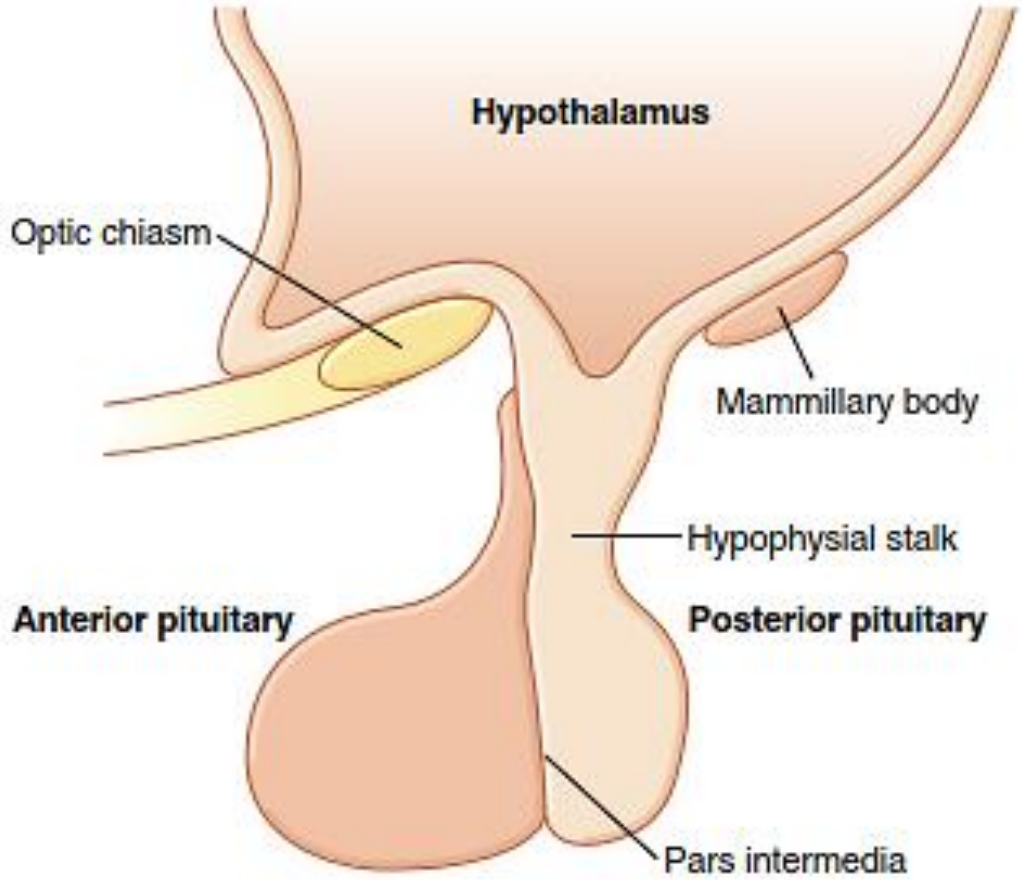
Most hormones are present in the blood in extremely minute quantities; some concentrations are as low as one billionth of a milligram (1 picogram) per milliliter. Therefore, it was difficult to measure these concentrations by the usual chemical means. ***radioimmunoassay,*** was developed in 1959 and revolutionized the measurement of hormones.
More recently, additional methods, such as ***enzyme- linked immunosorbent assays***, have been developed for accurate measurements of hormones.

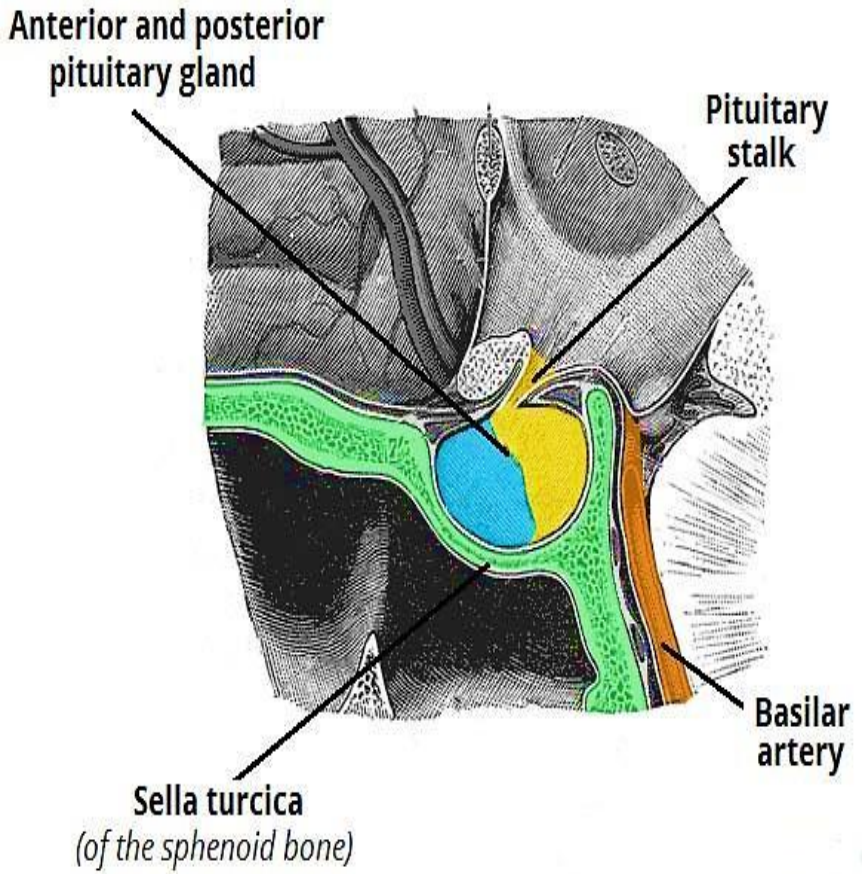


Mechanisms of interaction of **lipophilic hormones**, such as steroids, with intracellular receptors in target cells. After the hormone binds to the receptor in the cytoplasm or in the nucleus, the hormone- receptor complex binds to the hormone response element (promoter) on the DNA. This action either activates or inhibits gene transcription, formation of messenger RNA *(mRNA)*, and protein synthesis.

Pituitary gland

The *pituitary gland*, or *hypophysis*, is located at the base of the brain just below the hypothalamus. It is composed of two functionally and anatomically distinct lobes (see Figure):





Neurohypophysis (posterior pituitary)
Adenohypophysis (anterior pituitary)

As its name implies, the *neurohypophysis* is derived embryonically from nervous tissue. It is essentially an outgrowth of the hypothalamus and is composed of bundles of axons, or neural tracts, of neurosecretory cells originating in two hypothalamic nuclei. These neurons are referred to as *neuro-secretory cells* because they generate action potentials as well as synthesize hormones. The cell bodies of the neurosecretory cells in the supraoptic nuclei produce primarily antidiuretic hormone (ADH) and the cell bodies of the paraventricular nuclei produce primarily oxytocin. These hormones are then transported down the axons to the neurohypophysis and stored in membrane-bound vesicles in the neuron terminals.

The *adenohypophysis* is derived embryonically from glandular tissue, specifically, *Rathke's pouch*. Unlike the neurohypophysis, which releases hormones originally synthesized in the hypothalamus, the adenohypophysis synthesizes its own hormones in specialized groups of cells. Similar to the neurohypophysis, however, the release of these hormones into the blood is regulated by the hypothalamus.

Relationship between hypothalamus and pituitary gland

The hypothalamus plays a very important role in the maintenance of homeostasis. It carries out this function, in large part, by regulating the activities of the neurohypophysis and the adenohypophysis.

For example, the hypothalamus processes signals from other regions of the nervous system including information regarding pain and emotional states such as depression, anger, and excitement. In other words, it is an important processing center for information concerning the internal environment. This information is then used to control the release of hormones from the pituitary. Due to their embryonic origins, the neurohypophysis and the adenohypophysis are regulated by the hypothalamus, using two very different mechanisms:

Neuronal signals **Hormonal signals**

The hypothalamus regulates the release of hormones from the neurohypophysis by way of *neuronal signals*.

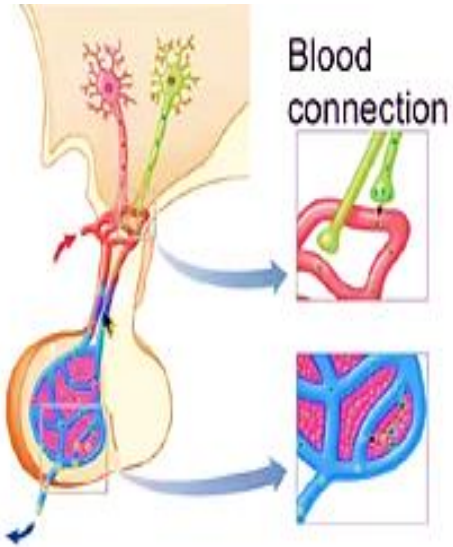
The secretion of hormones from the adenohypophysis is regulated by *hormonal signals* from the hypothalamus. The blood flows to the adenohypophysis through the *hypothalamic–hypophyseal portal veins*.

Pituitary Gland

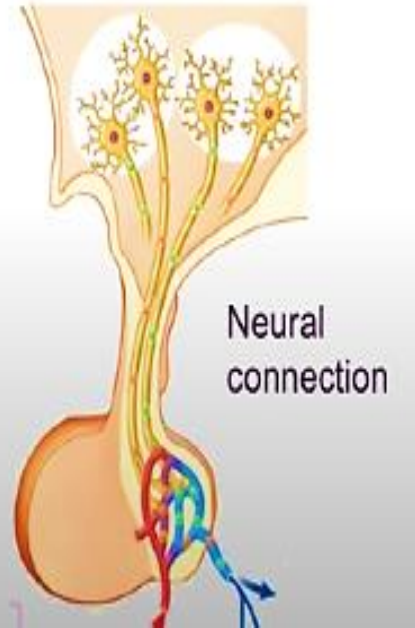
- The Pituitary Gland has 2 lobes, anterior and posterior that are related only by location
- Anterior Pituitary (adenohypophysis):
  - glandular tissue
  - produces and secretes 6 hormones
- Posterior Pituitary (neurohypophysis):
  - neural tissue
  - NO hormone production
  - stores and secretes 2 hormones

Hypothalamus – Pituitary: Anatomical Connections

- **Hypothalamus → Anterior Pituitary**
  - Hypothalamic-Hypophyseal Portal System
  - ***Blood connection***: The Hypothalamus is connected to the anterior pituitary by a network of capillaries called the Hypothalamic-Hypophyseal Portal System



- **Hypothalamus→ Posterior Pituitary**
  - ***Neural connection***: a direct neural connection, cell bodies of neurons are located in hypothalamus, axons and axon terminals in posterior pituitary



Negative feedback control of hormone release

In many cases, hormones released from the adenohypophysis are part of a three-hormone axis that includes the:

Hypothalamic hormone Adenohypophyseal hormone Endocrine gland hormone

The hypothalamic hormone stimulates or inhibits the secretion of the adenohypophyseal hormone. The trophic hormone from the adenohypophysis then stimulates the release of a hormone from another endocrine gland. This final endocrine gland hormone not only carries out its effects on its target tissues, it may also exert a *negative feedback* effect on the release of the hypothalamic and/or adenohypophyseal hormones.

In this way, this final hormone regulates its own release.This process is referred to as *long-loop negative feedback*. The adenohypophyseal hormone may also exert a negative feedback effect on the hypothalamic hormone and limit its own release. This process is referred to as *short-loop negative feedback*.

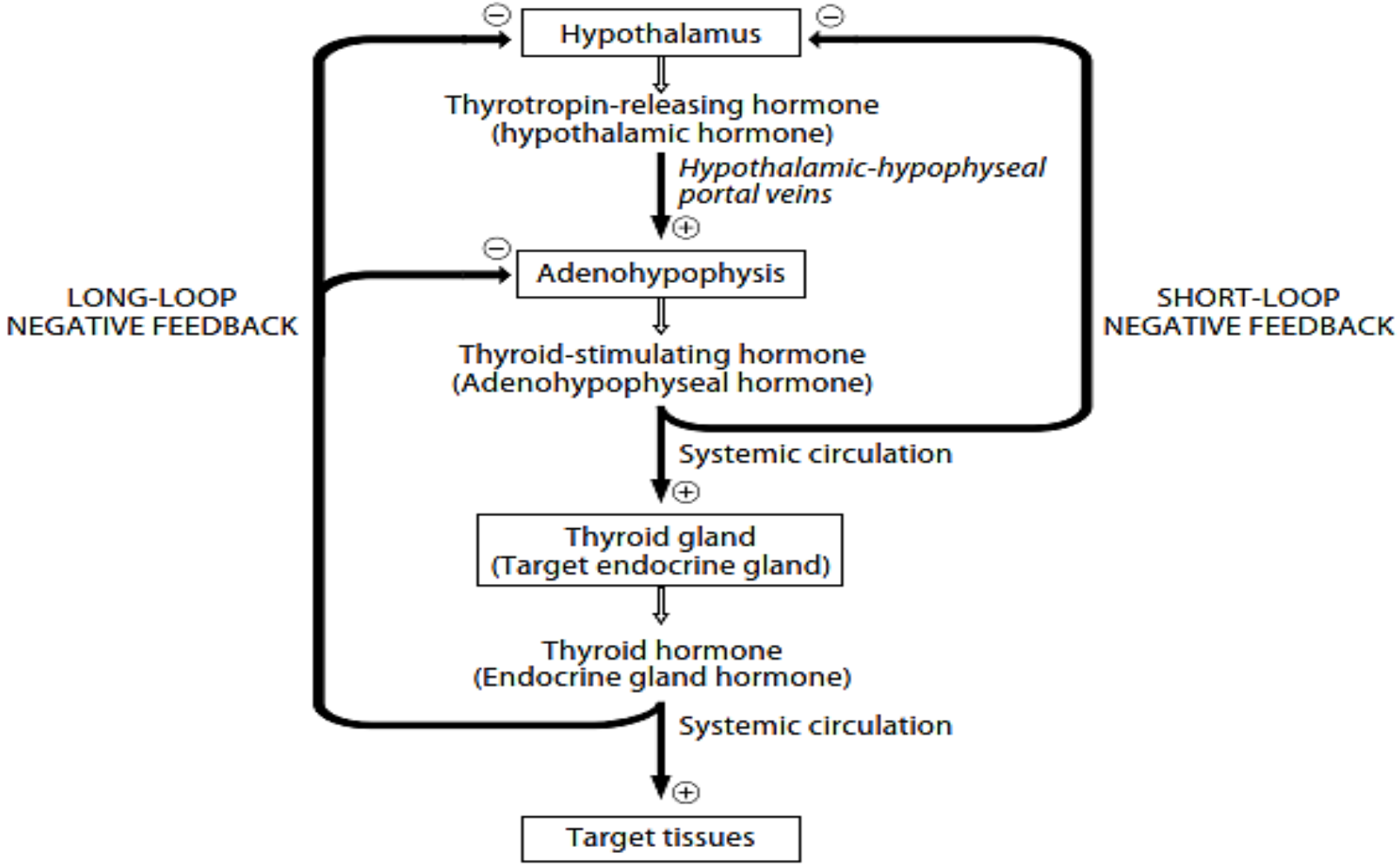


Figure Negative-feedback regulation of hormone release. Hormones released from the adenohypophysis are often part of a three-hormone axis that includes the hypothalamic hormone, the adenohypophyseal hormone, and the target endocrine gland hormone. Long-loop negative feedback occurs when the final hormone in the axis inhibits release of hypothalamic and/or adenohypophyseal hormones. Short-loop negative feedback occurs when the adenohypophyseal hormone inhibits release of the hypothalamic hormone. This figure illustrates the thyrotropin-releasing hormone–thyroid-stimulating hormone–thyroid hormone axis.

The major **hypothalamic releasing and inhibitory** hormones**,** are the following:

1. *Thyrotropin-releasing hormone* (TRH), which causes release of TSH

2. *Corticotropin-releasing hormone* (CRH), which causes release of ACTH

3. *Growth hormone–releasing hormone* (GHRH), which causes release of GH, and *growth hormone inhibitory hormone* (GHIH), also called *somatostain,* which inhibits release of GH

4. *Gonadotropin-releasing hormone* (GnRH), which causes release of the two gonadotropic hormones, LH and FSH

5. *Prolactin inhibitory hormone* (PIH), also known as *dopamine,* which causes inhibition of prolactin secretion.

Hormones of the neurohypophysis

Antidiuretic hormone (ADH), also referred to as *vasopressin*, has two major effects, both of which are reflected by its names:
(1) antidiuresis (decrease in urine formation by the kidney); and
(2) vasoconstriction of arterioles.
Antidiuretic hormone promotes the reabsorption of water from the tubules of the kidney, or *antidiuresis*. Specifically, it acts on the collecting ducts. This results in the body's conservation of water and the production of a low volume of concentrated urine.

The reabsorbed water affects plasma osmolarity and blood volume. This effect of ADH on the kidney occurs at relatively low concentrations. At higher concentrations, ADH causes *constriction of arterioles*, which serves to increase blood pressure.
Antidiuretic hormone secretion is regulated by several factors:
Plasma osmolarity
Blood volume
Blood pressure
Alcohol

The primary factor that influences ADH secretion is a change in *plasma osmolarity*. *Osmoreceptors* are present in the hypothalamus, stimulation of these osmoreceptors by an increase in plasma osmolarity results in stimulation of the neurosecretory cells; and the release of ADH from their axon terminals in the neurohypophysis. The water conserved due to the effect of ADH on the kidney helps to reduce plasma osmolarity or dilute the plasma back to normal.

Other factors regulating ADH secretion include blood volume and blood pressure.
A decrease in *blood volume* of 10% or more causes an increase in ADH secretion sufficient to cause vasoconstriction as well as antidiuresis.

A decrease in *mean arterial blood pressure* of 5% or more also causes an increase in ADH secretion. The resulting water conservation and vasoconstriction help increase blood volume and blood pressure back to normal.

Alcohol inhibits the secretion of ADH, thus allowing for loss of water from the kidney. Therefore, the consumption of alcoholic beverages may actually lead to excessive water loss and dehydration instead of volume expansion.

Oxytocin also exerts its major effects on two different target tissues. This hormone stimulates:

Contraction of uterine smooth muscle Contraction of myoepithelial cells

Oxytocin stimulates *contraction of the smooth muscle in the wall of the uterus*. During labor, this facilitates the delivery of the fetus.

Oxytocin also causes *contraction of the myoepithelial cells* surrounding the alveoli of the mammary glands. This results in "*milk letdown*" or the expulsion of milk from deep within the gland into the larger ducts from which the milk can be obtained more readily by the suckling infant.

In the lactating breast, suckling activates sensory neurons in the nipple to transmit signals to the hypothalamus to stimulate oxytocin release from the neuro-hypophysis and therefore milk letdown. Interestingly, this reflex may also be triggered through a conditioned response in which the sight or sound of the hungry infant is sufficient to enhance oxytocin secretion. In contrast, the release of oxytocin from the neurohypophysis may be inhibited by pain, fear, or stress.

The function of oxytocin in males is not clearly understood.


Thank you.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