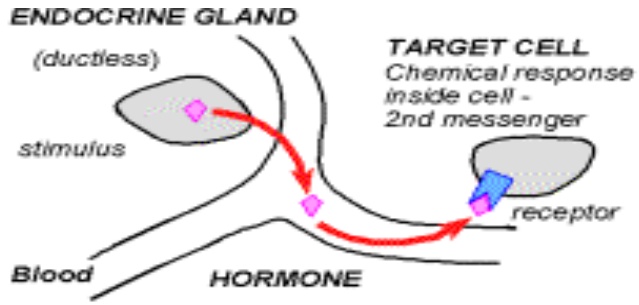
Biochemistry of Hormones

Hormones

- A hormone is chemical **regulatory** substance ,secreted by **ductless** glands (endocrine gland).
- It pass through **blood** stream to reach the tissues on which it acts.
- These tissues are called **target tissues**



Hormone Binding to a Receptor

- Hormones - biologically active substances, They regulate metabolism and physiological processes. Hormones, as universal regulators of the body functioning, play an important role in the maintenance of homeostasis.

Relationships between endocrine and neural regulation

- Hormonal regulation is closely related to that exerted by the **nervous system**, and the two processes have generally been distinguished by :
- 1-The rate at which each causes effects,
- 2- The duration of these effects, and their extent; i.e., the effects of **endocrine regulation** may be **slow** to develop but prolonged in influence and widely distributed through the body, whereas nervous regulation is typically concerned with **quick** responses that are of brief duration and localized in their effects.

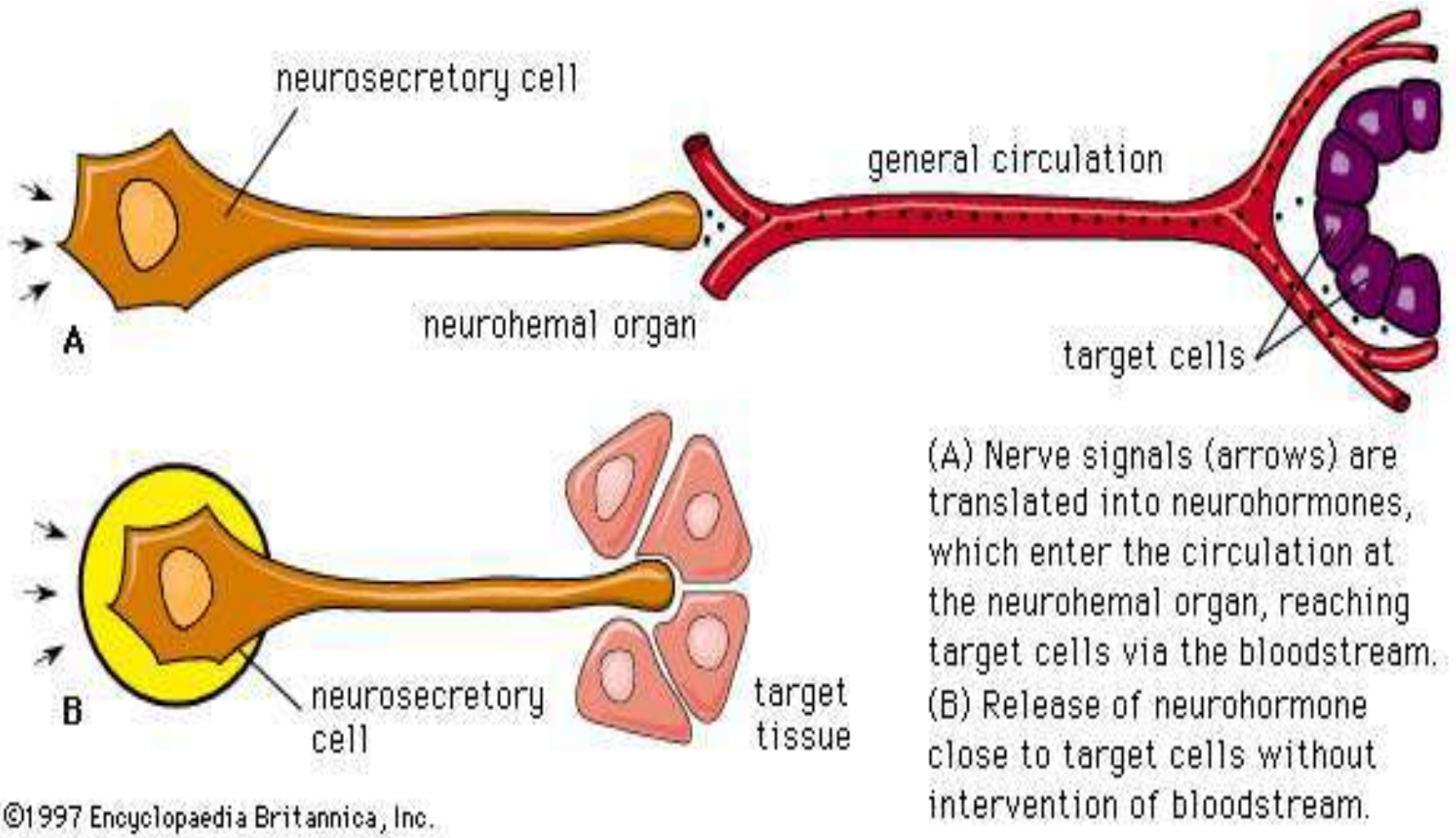
Relationships between endocrine and neural regulation

- Nerve cells are secretory, for responses to the nerve impulses that they propagate depend upon the production of chemical transmitter substances, or neurotransmitters,
- such as acetylcholine and norepinephrine (noradrenaline), which are liberated at nerve endings in minute amounts and have only a momentary action. It has been established, however, that certain specialized nerve cells, called neurosecretory cells, can translate neural signals into chemical stimuli by producing secretions called neurohormones.

Relationships between endocrine and neural regulation

- These secretions, which are often polypeptides (compounds similar to proteins but composed of fewer amino acids), pass along nerve-cell extensions, or axons, and are typically released into the bloodstream at special regions called neurohemal organs, where the axon endings are in close contact with blood capillaries. Once released in this way, neurohormones function in principle similar to hormones that are transmitted in the bloodstream and are synthesized in the endocrine glands

Relationships between endocrine and neural regulation



(A) Nerve signals (arrows) are translated into neurohormones, which enter the circulation at the neurohemal organ, reaching target cells via the bloodstream. (B) Release of neurohormone close to target cells without intervention of bloodstream.

Functions of hormones

- The hormones conduct a wide variety of functions:They influence on all essential life processes, such as:
- **Growth**
- M**etabolism of carbohydrates, proteins and fats, development**
- **Immune defense**
- **Reproduction**
- **Behavior**
- A**daptation to the conditions of existence**.

- Hormones, as universal regulators of the body functioning, play an important role in the maintenance of homeostasis

Principal functions of the endocrine system

- **Regulation** of sodium and water balance and control of blood volume and pressure
- **Regulation** of calcium and phosphate balance to preserve extracellular fluid concentrations required for cell membrane integrity and intracellular signaling
- **Regulation** of energy balance and control of fuel mobilization, utilization, and storage to ensure that cellular metabolic demands are met
- **Coordination** of the host hemodynamic and metabolic counter regulatory responses to stress
- **Regulation** of reproduction, development, growth, and senescence

General characteristics of hormones

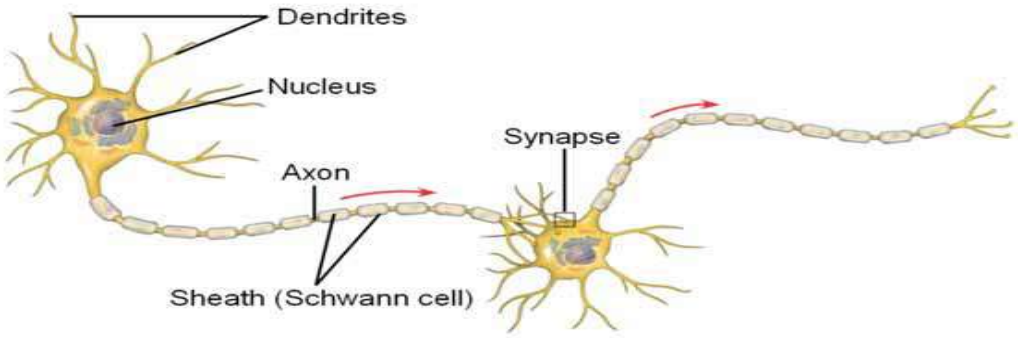
- Hormones are molecules synthesized by *specific* tissue. Classically these tissue were called **glands**.
- Hormones are secreted directly into the blood which **carries** them to their sites of action.
- Hormones are present at very **low** levels in the circulatory system.
- Hormones specifically affect or alter the activities of the responsive tissue (**target** tissue).
- Hormones act specifically via **receptors** located on, or in, **target** tissue.

Two systems act individually and together in regulating an animal's physiology

.Two systems control all physiologic processes:

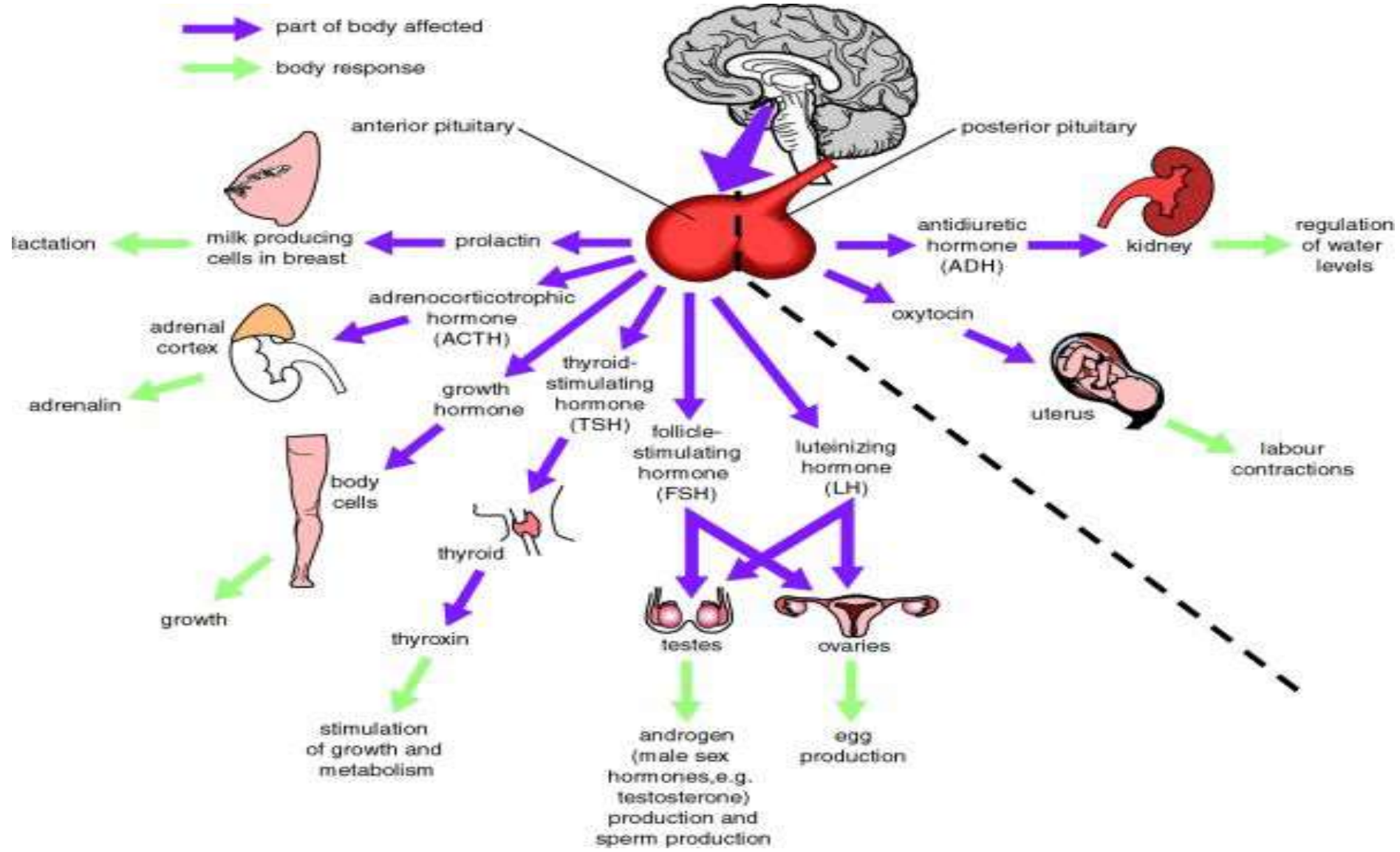
1- Nervous system

2-Endocrine system



The endocrine system is one of the two coordinating and integrating systems of the body. It acts through chemical messengers - *hormones –carried in the circulation.*

Neural control



Similarities of Hormone and Enzyme

- The hormones have several characteristics in common with enzymes:
- They act as body catalysts resembling enzymes in some aspect.
- They are required only in small quantities.
- They are not used up during the reaction.

Dissimilarities of Hormone and Enzyme

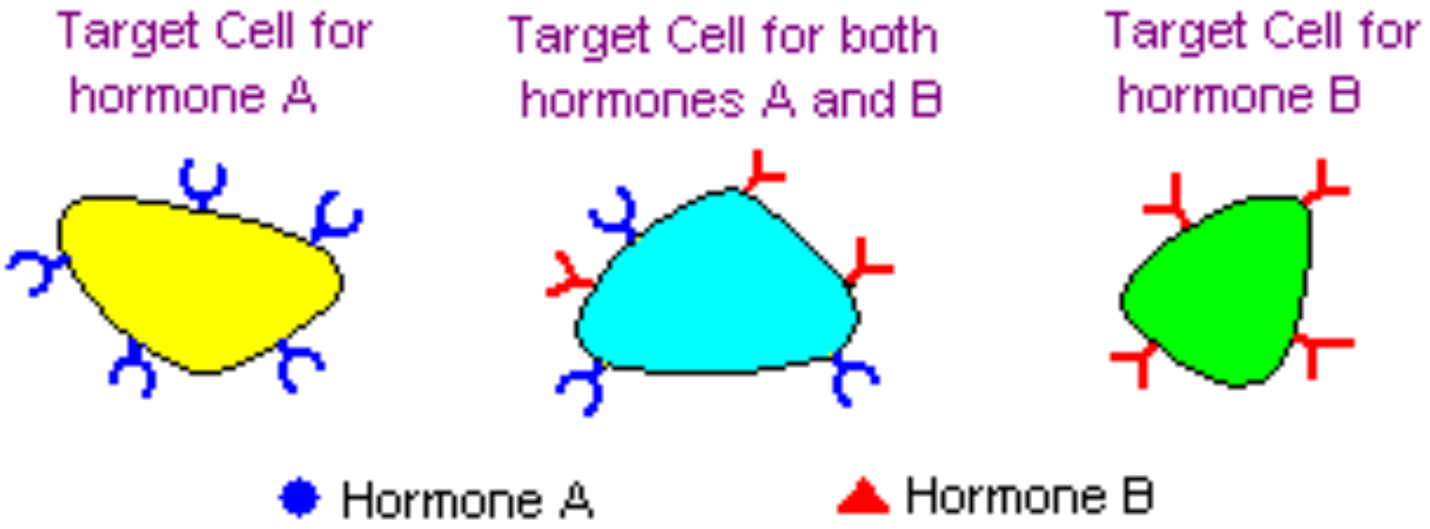
- They differ from enzymes in the following ways:
- • They are produced in an organ other than that in which they ultimately perform their action.
- • They are secreted in blood prior to use.
- • Thus the circulating levels of hormones can give some indication of endocrine gland activity and target organ exposure. Because of the small amounts of the hormones required, blood levels of the hormones are extremely low. In many cases it is ng/µg or mIU, etc.
- • Structurally they are not always proteins. Few hormones
- are protein in nature, few are small peptides. Some hormones are derived from amino acids while some are steroid in nature.

Target tissues

- Target tissues of certain hormone is the tissue ,Which contains the specific receptor of that hormone

Receptors and Target Cells

- A given hormone usually affects only a limited number of cells, which are called target cells. A target cell responds to a hormone because it bears receptors for the hormone. Hormone receptors are found either exposed on the **surface of the cell** or **within the cell**, depending on the type of hormone. In very basic terms, binding of hormone to receptor triggers a cascade of reactions within the cell that affects function



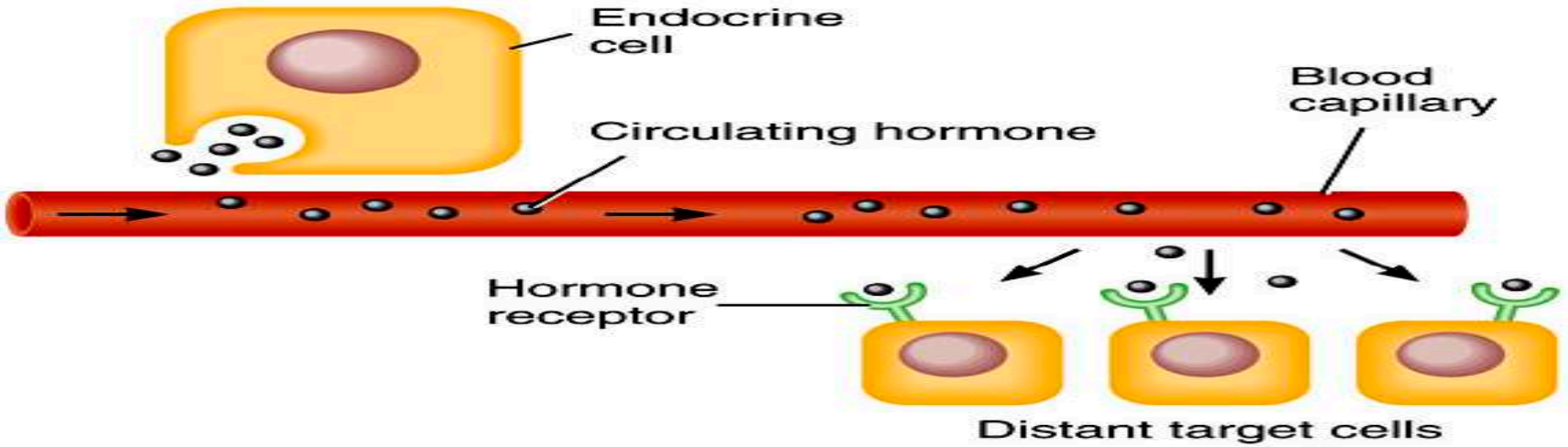
Receptors and Target Cells

- Hormone receptors have two essential qualities:

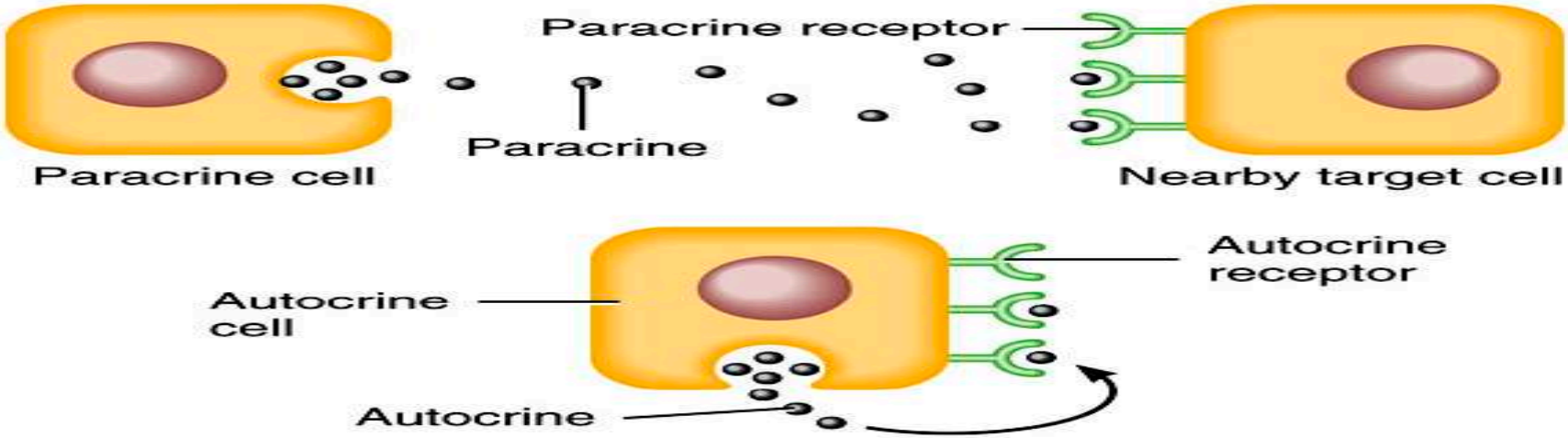
- **1**. The receptor must be able to recognize a unique binding site within the hormone in order to discriminate between the hormone and all other
- proteins.
- **2.** The receptor must be able to transmit the information gained from binding to the hormone into a cellular response.

- **Hormones** may be secreted into blood and affect cells at distant sites. Some hormones known to act and affect neighboring cells or even have effects on the same cells that secreted the hormone.
- **Three actions are defined:**
- 1· **Endocrine action: the hormone is distributed in blood and binds to distant** target cells.
- 2· **Paracrine action: the hormone acts locally by diffusing from its source to** target cells in the neighborhood.
- **3· Autocrine action: the hormone acts on the same cell that produced** it.

Hormones action



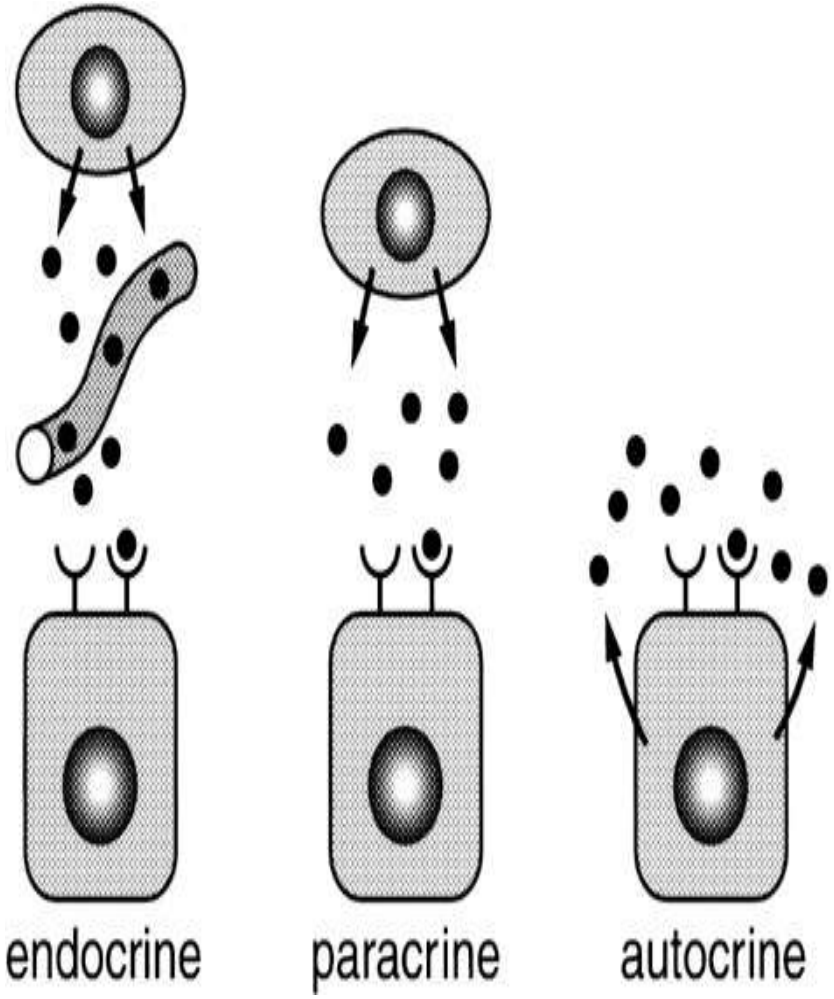
(a) Circulating hormones

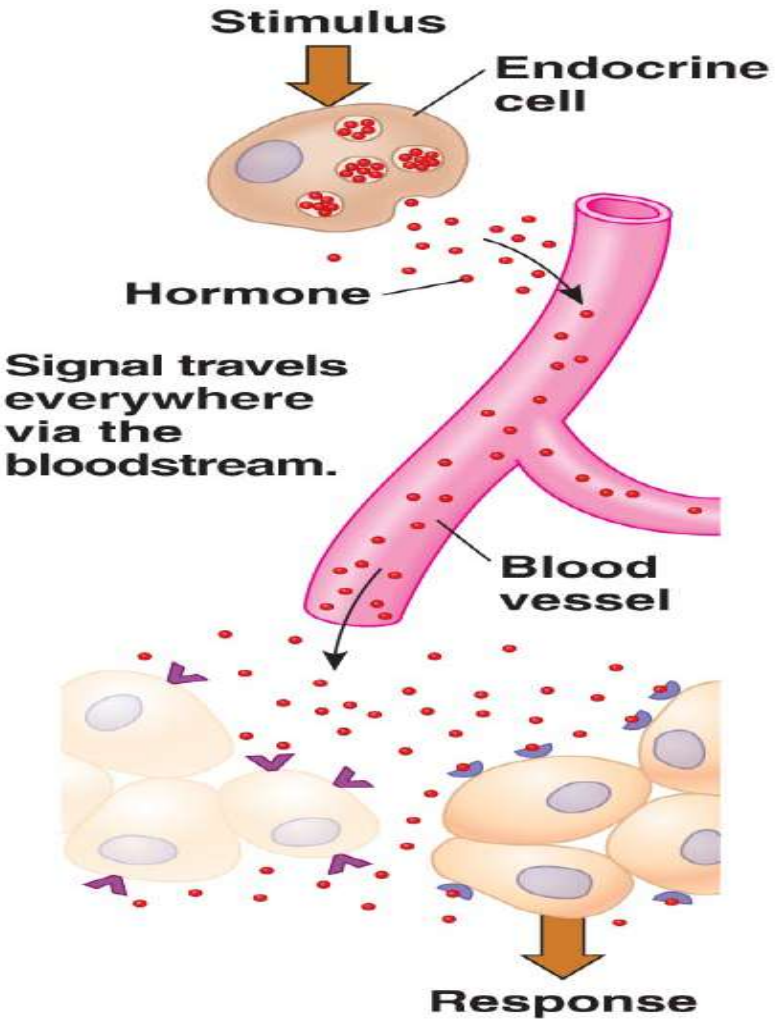


(b) Local hormones (paracrines and autocrines)

Figure 18.02 Tortora - PAP 12/e

Hormone signaling





(a) Signaling by hormones

Hormone receptors

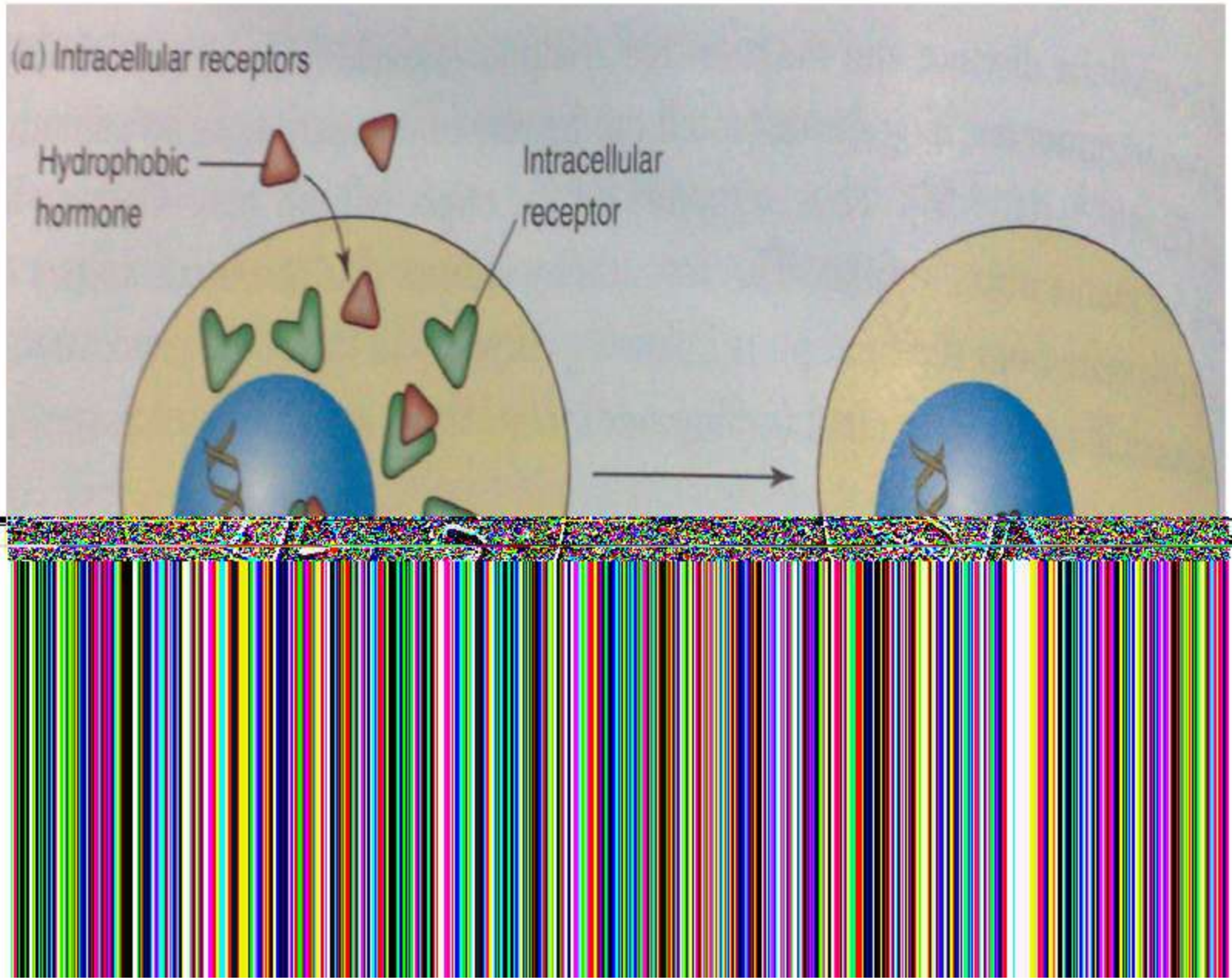
- **Definition:**
- Cell-associated **recognition** molecules which are **protein** in nature
- **Functional sites:**
- Two functional sites
- **Recognition site: It** binds the hormone specifically.
- **Signaling site** :It couples hormone binding to intracellular effect

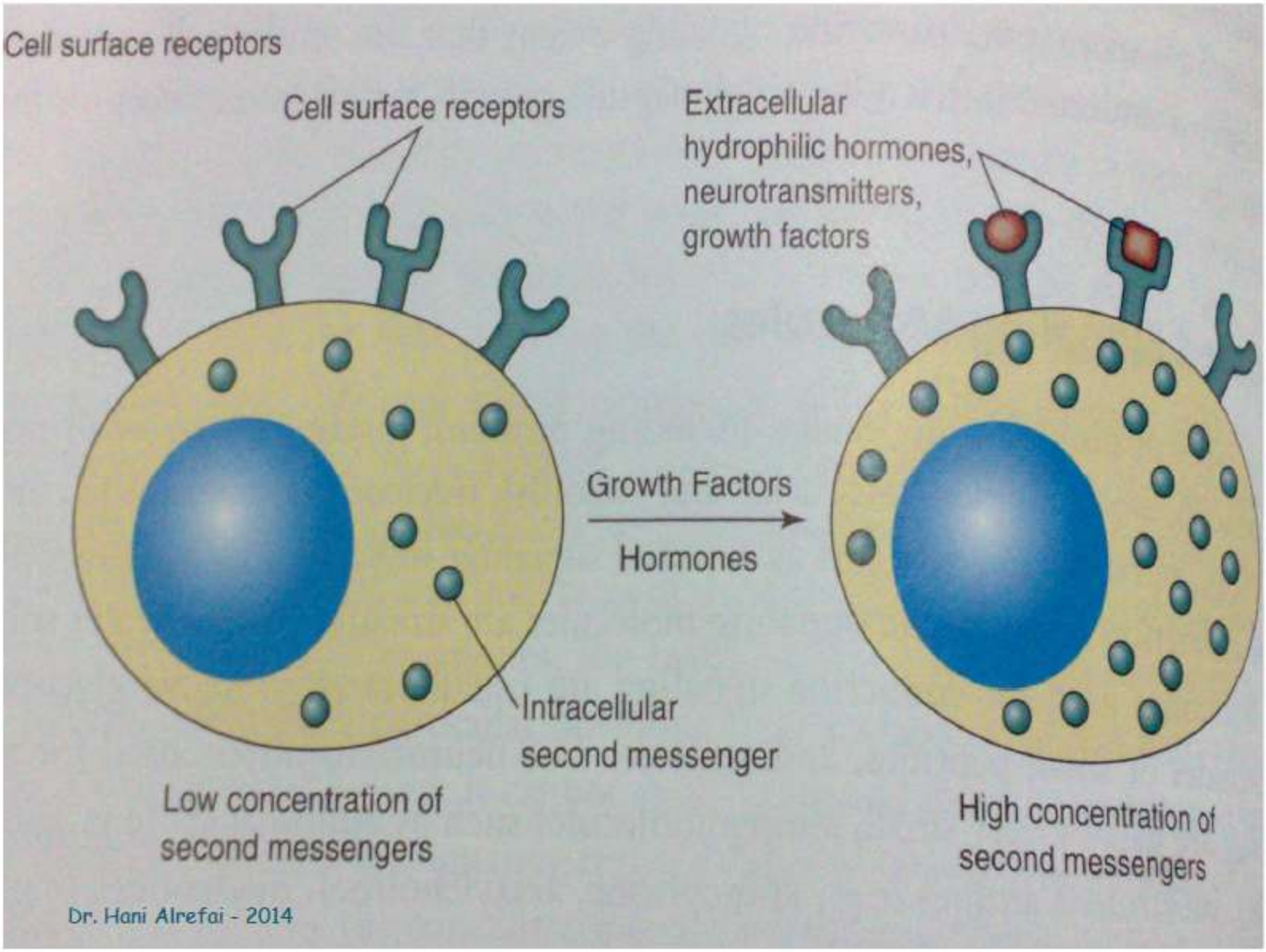
Hormone receptors

- **Location:**
- **Receptors may be :**

- **Intracellular receptor: (in the cytosol or in the nucleus)**

- **Cell-membrane receptor: (in the plasma membrane)**


(a) Intracellular receptors
Hydrophobic hormone
Intracellular receptor


Cell surface receptors
Cell surface receptors
Extracellular
hydrophilic hormones,
neurotransmitters,
growth factors
Growth Factors
Hormones
Intracellular
second messenger
Low concentration of
second messengers
High concentration of
second messengers
Dr. Hani Alrefai - 2014

How are hormones classified?

Hormones are classified by various criteria:

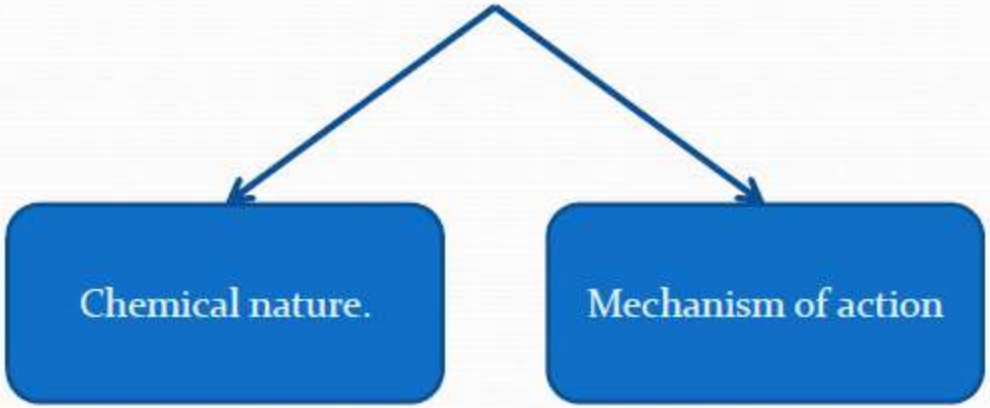
- By Proximity of their site of synthesis to their site of action,
- By their chemical structure,
- By their degree of solubility in aqueous medium

How are hormones classified by proximity of site of synthesis to site of action?

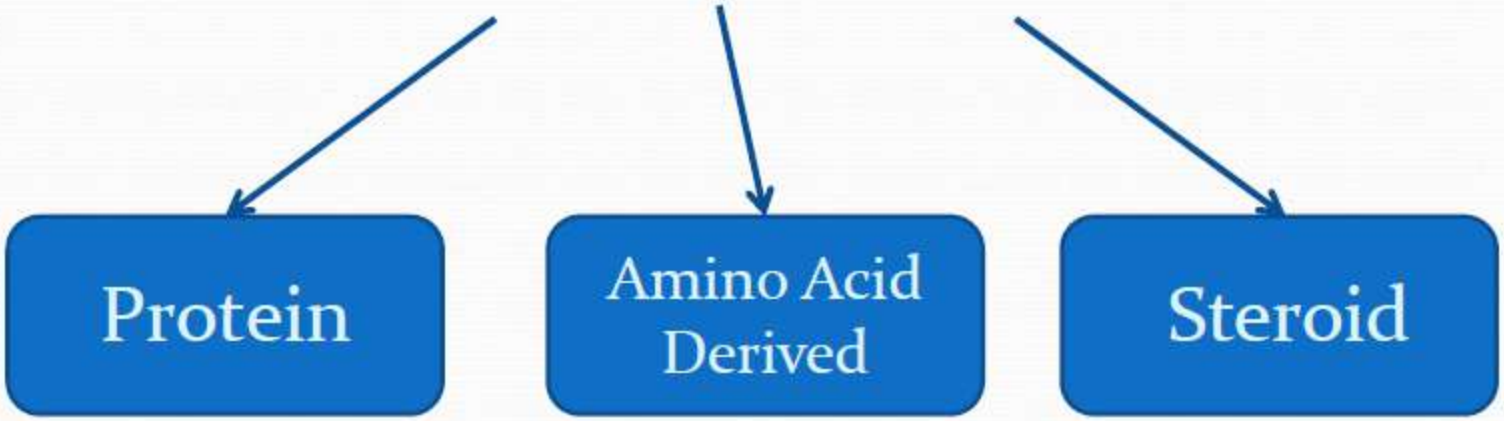
- **3 classes of hormones** based on proximity of site of Synthesis to Site of Action: (**Fig. 1**)
  - **Autocrine Hormones**: those that act on the same cells that synthesize them;
  - **Paracrine Hormones**: those that are synthesized very close to their site of action;
  - **Endocrine Hormones**: those that are synthesized by endocrine glands and transported in the blood to target cells that contain the appropriate receptors;

Classification of Hormones

Hormones can be classified according to:



Classification according to chemical nature



Classification of Hormones according to chemical nature

- Hormones can be classified chemically into **three major groups:**
- 1. ***Steroid hormones: These are steroid in nature derived from cholesterol such*** as adrenocorticosteroid hormones, androgens,estrogens and progesterone.
- 2. ***Amino acid derivatives: These are derived from*** amino acid tyrosine, e.g. epinephrine, norepinephrine and thyroid hormones.
- 3. ***Peptide/Protein hormones: These are either large*** proteins or small or medium size peptides, e.g. Insulin, glucagon, parathormone, calcitonin, pituitary hormones, etc.

Classification according to mechanism of action

- Hormones, which bind to intracellular receptors.
- Hormones, which bind to membrane receptors.

Hormones bind to intracellular RCs	Hormones bind to cell membrane RCs
•Lipophylic	•Hydrophilic
•Need transport proteins to reach target tissues	•Do not need transport protein
•Long plasma half-life (hours to days).	•Short plasma half-life (minutes).
•Action is mediated by forming hormone-receptor complex.	•Action is mediated by Second Messenger.
•Include: Steroid hs, Thyroid hs, Calcitriol, Retinoids	•All other hormones.

- **Hydrophilic Hormones** (Lipophobic Hormones):
  - Hormones that are soluble in aqueous medium;
  - They cannot cross the cell membrane,
  - Thus, they bind to **receptor molecules on the outer surface** of target cells, initiating reactions within the cell that ultimately modifies the functions of the cells;
  - Examples: Insulin, Glucagon, Epinephrine,

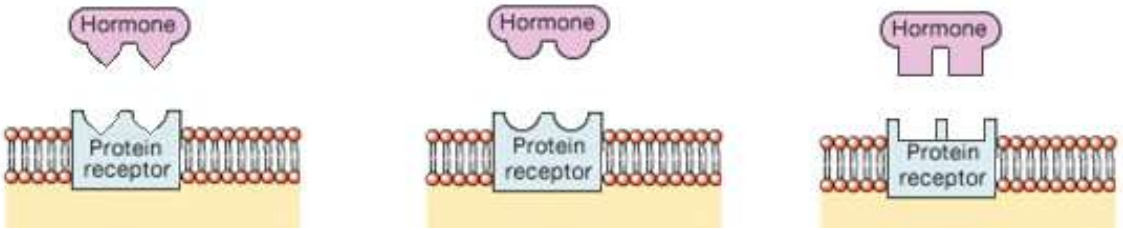
- **Lipophilic Hormones** (Hydrophobic Hormones):
  - Hormones that are not soluble in aqueous medium, but soluble in lipid;
  - They can easily cross the cell membrane,
  - Thus, they can enter target cells and bind to **intracellular receptors** to carryout their action;
  - Examples: Thyroid hormones, Steroid hormones;

Hormones:
Mechanisms of action

- The hormonal effects on metabolic processes of target cells are realized through interaction with specific receptors.
- Depending on the localization of these receptors different mechanisms of action of hormones are presented.

Mechanisms of hormone action

- Each hormone's shape is specific and can be recognized by the corresponding target cells



- The binding sites on the target cells are called hormone receptors.
  - Receptors for peptide hormones, are located on the surface of cell membranes because they can not cross the membrane to enter the cell
  - Thyroid and steroid hormones can cross the membrane and bind to receptors in the cytoplasm or nucleus

Mechanism of Action of Hormone:

There are two fundamental mechanisms by which a hormone can change its target cell. These mechanisms are:

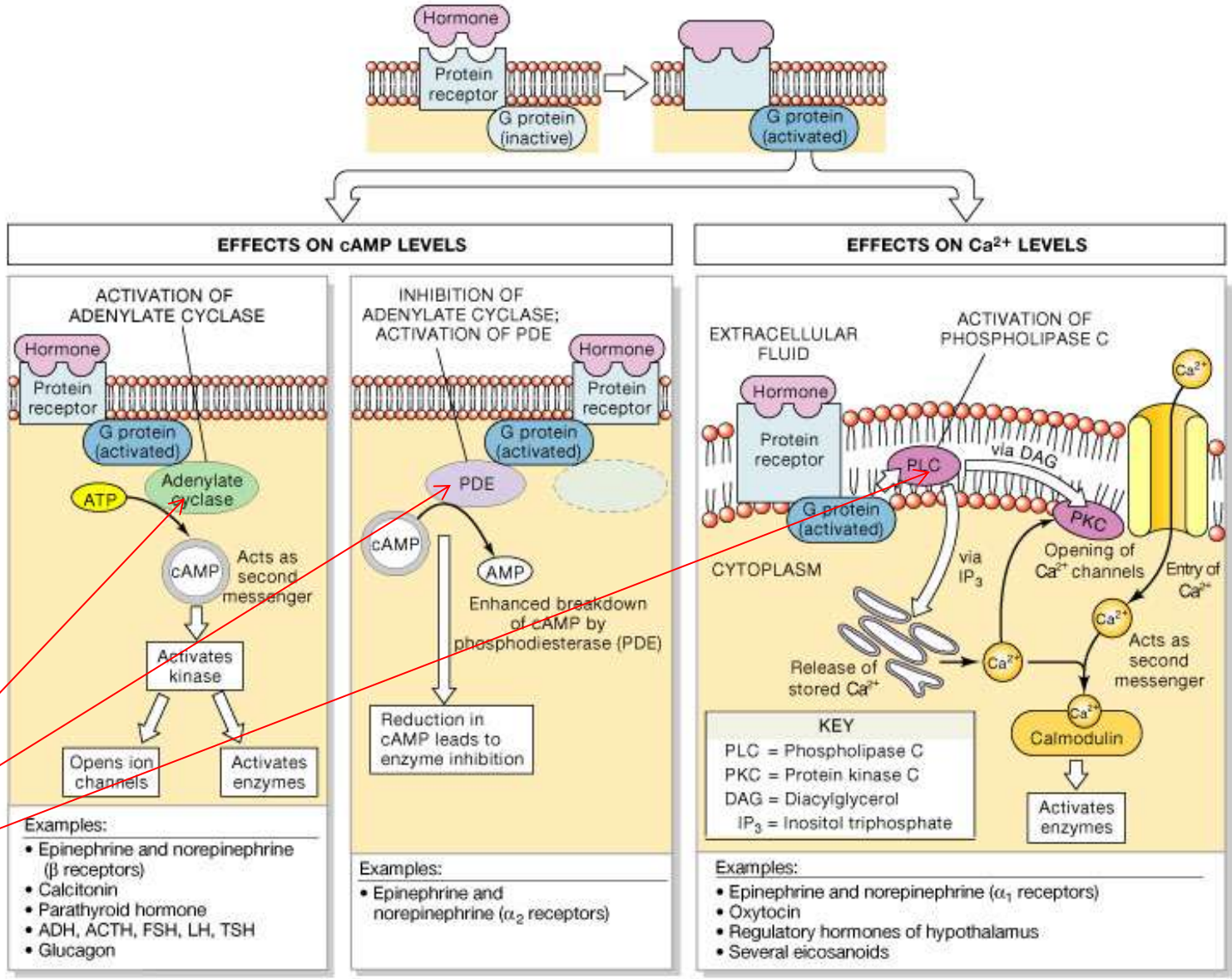
1-Activation of enzymes

2-Modulation of gene expression

1-Activation of enzymes

- **Hormones that can not cross the membrane (e.g. Peptide hormones) bind to the receptor on the surface of the cell**
- **Binding of hormones to the receptor activate secondary messenger (in this figure binding of hormone activates G protein, and activated G protein activates adenylcyclase**

or activate PDE or activates PLC



Outline the mechanism of action of Lipophilic hormones with receptors in target cells (Fig. 3)

- Lipophilic hormone crosses cell membranes to bind with Intracellular Receptor, forming **Hormone-Receptor Complex**;
- Hormone-Receptor Complex then bind to Specific Sequence of Nucleotide Bases in DNA called **Hormone Response Element (HRE);**
- Binding of Hormone-Receptor Complex to HRE results in synthesis of **Messenger-RNA** required for biosynthesis of specific protein;
- Lipophilic hormones are slower to act and have longer duration of action than Hydrophilic hormones;
- Duration of action may range from hours to days;

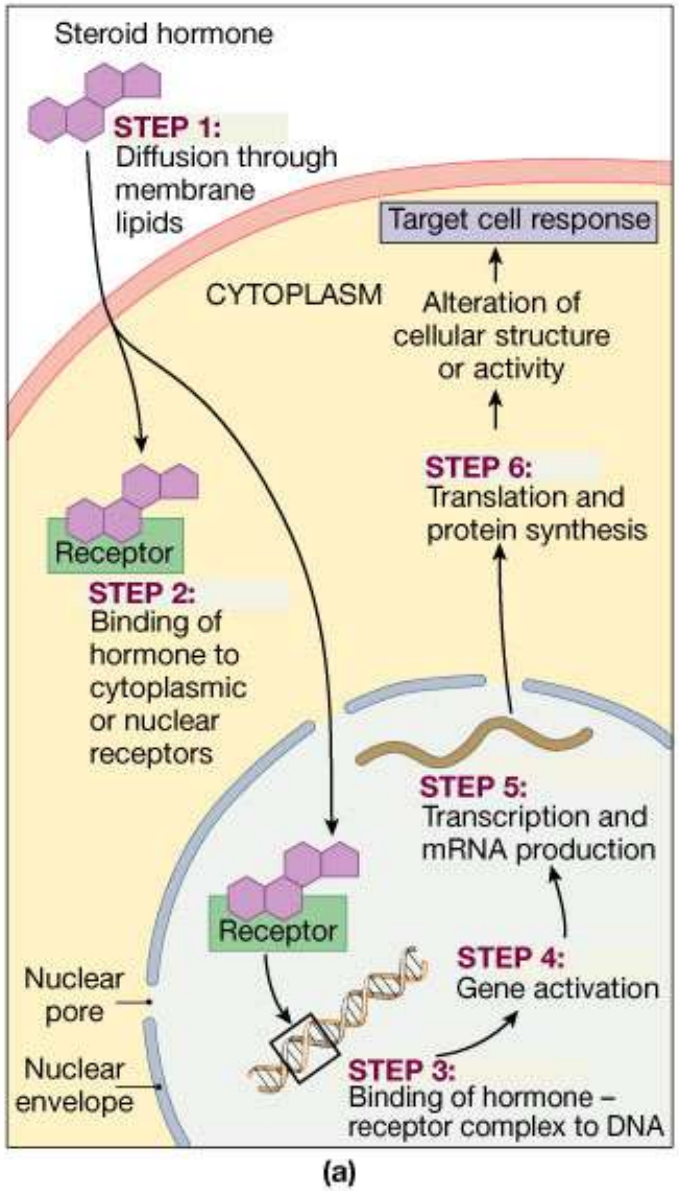
The Second Messenger

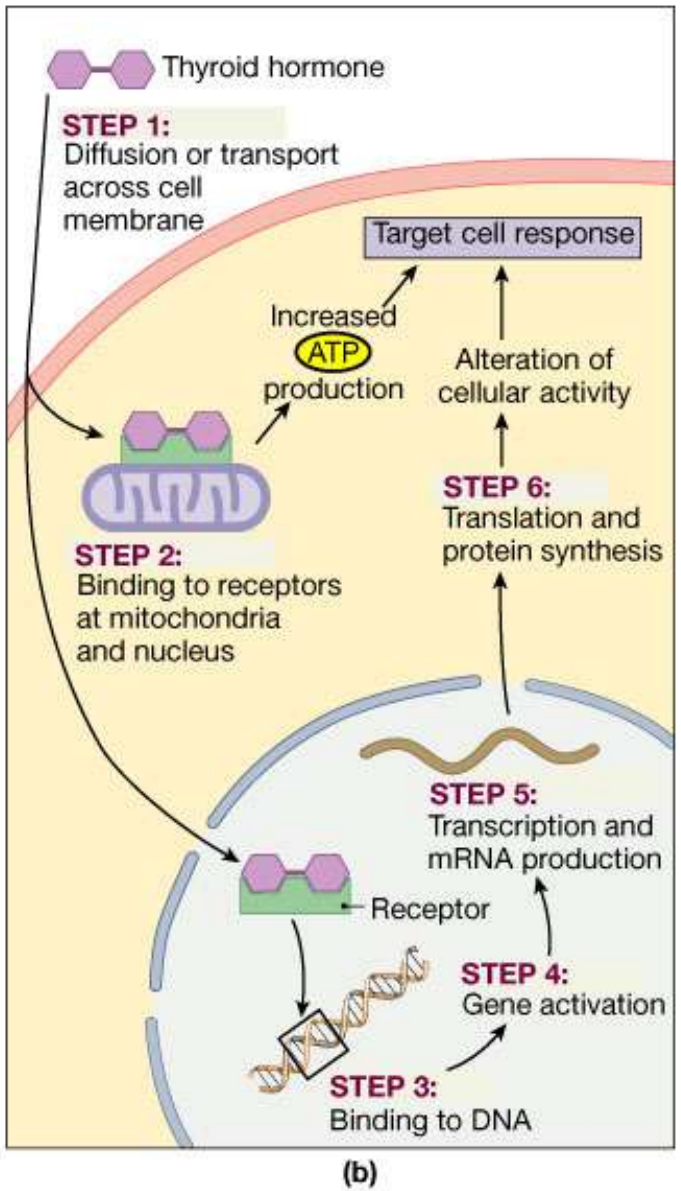
- Is the signal produced as a result of hormone binding to its cell membrane receptor.
- It mediates the effects of the hormone.
- The second messenger may be:
  - Cyclic Adenosine Monophosphate (cAMP).
  - Cyclic Guanosine Monophosphate (cGMP).
  - Calcium or phosphatidyl inositol or both.
  - Protein kinase cascade.

N.B. The hormone is considered to be the first messenger

2-Modulation of gene expression

- Hormones that can cross the membrane (e.g. steroid hormones) bind to the receptor inside the cell, at the cytoplasm, or they will enter the nucleus and bind to the receptor at the nucleus and initiate transcription)





Acronyms of some hormones

Hormones	Acronym
AdrenoCorticoTrophic Hormone (Corticotrophin)	ACTH
Arginine Vasopressin (Anti-Diuretic Hormone)	AVP (ADH)
Corticotrophin Releasing Hormone	CRH
Follicular Stimulating Hormone	FSH
Gonadotrophin Releasing Hormone	GnRH
Growth Hormone	GH (HGH)
Growth Hormone Releasing Hormone	GHRH
Luteinizing Hormone	LH
Parathyroid Hormone	PTH
Thyroid Stimulating Hormone	TSH
Thyrotrophin Releasing Hormone	TRH
Tri-iodothyronine	T_3
Thyroxine	T4

How do hormones exit in blood plasma?

- Hormones are normally present in blood plasma at very low concentrations;
- In blood, hormone binds to **Specific Plasma Carrier Protein**, forming a complex, which is then transported in the plasma to distant target cells;
- Plasma carrier proteins exist for all classes of endocrine hormones;

What are the functions of carrier proteins for hormones?

Carrier proteins for:

- **Peptide Hormones** prevent destruction of peptide hormones by Protease enzymes in plasma;
- **Steroid Hormones and Thyroid Hormones** significantly increase the solubility of these very hydrophobic compounds in plasma;
- **Small, Hydrophilic Amino Acids – derived hormones** prevent their filtration by the kidneys, thus greatly prolonging their circulating half-life;

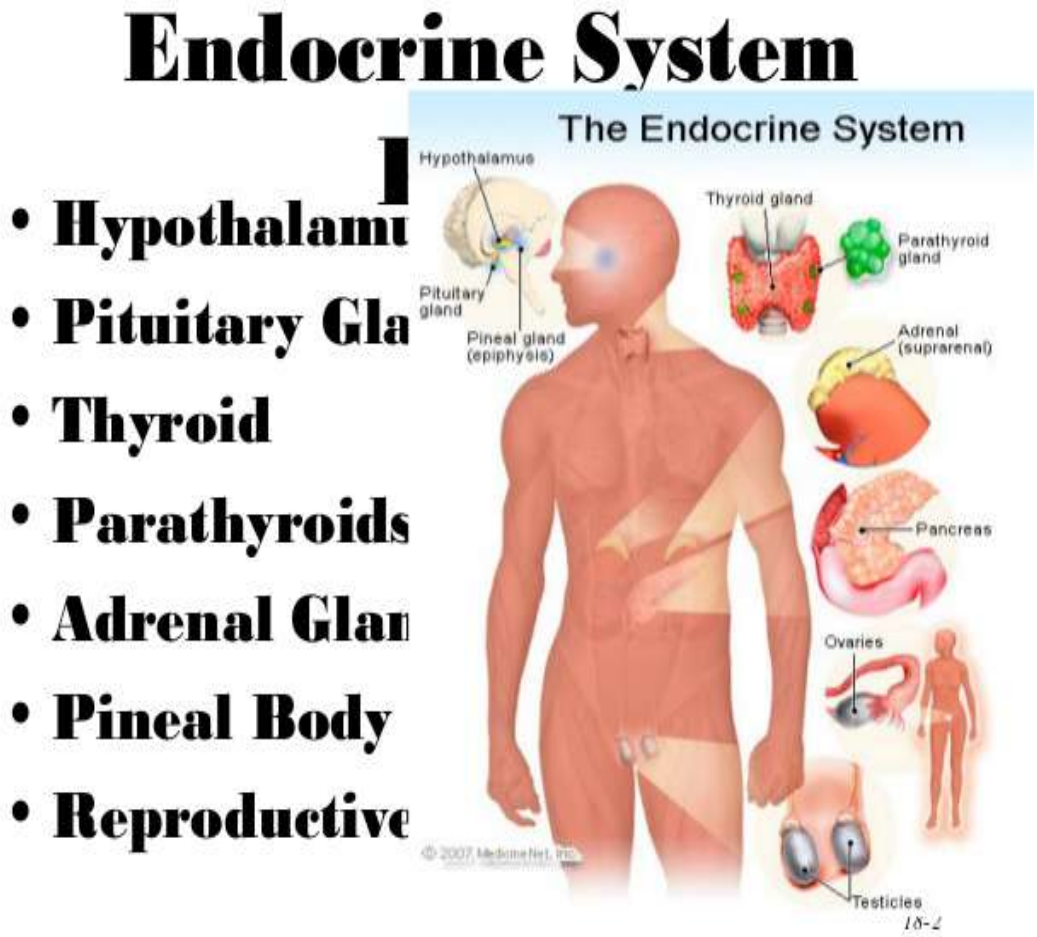
What are some of the factors controlling hormone secretion?

- Hormone secretion is influenced by variety of factors:
  - Stimulatory and Inhibitory agents, such as: Hypothalamic Peptides or Neurotransmitters;
  - Other hormones: Gonadotrophin Releasing Hormone (GnRH), are released in a pulsatile fashion;
  - Some hormones exhibit Circadian Rhythm:
    - Adreno-Cortico-Trophic Hormone (ACTH),
    - Cortisol;
    - Prolactin, TSH, GH and PTH have peak secretion at different times during the day or night;

- Stress can increase hormone synthesis and release (e.g., ACTH, GH and Prolactin);
- Hormones synthesized by target cells may regulate release by Negative Feed Back control;
- Changes in metabolic products caused by hormone action may exert feedback control;
- Other hormones or drugs may modulate normal endocrine responses;

The major hormone secreting glands are:

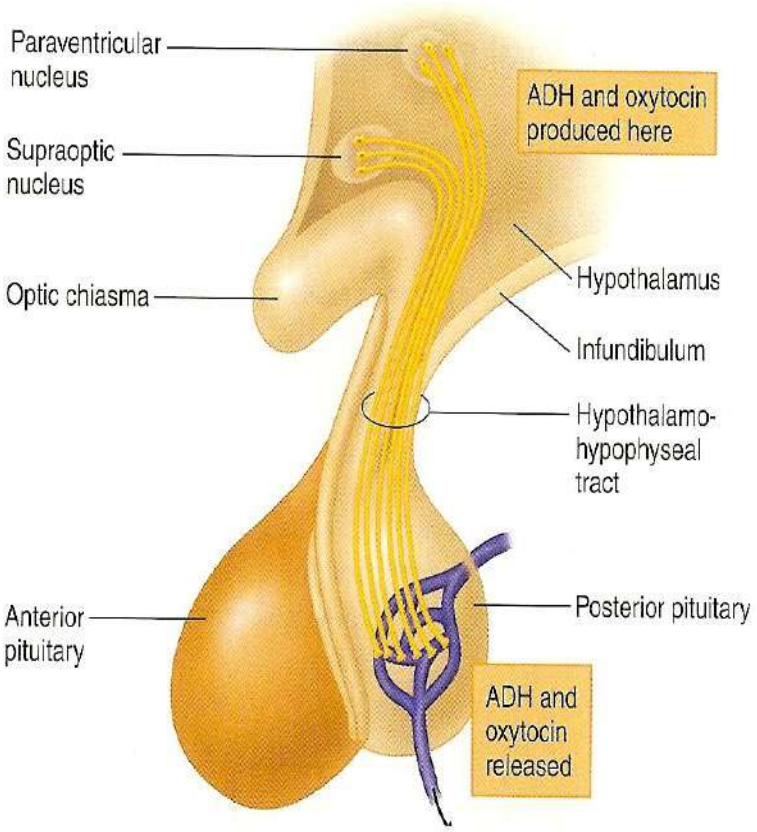
- • Pituitary
- • Thyroid
- • Parathyroid
- • Adrenal
- • Pancreas
- • Ovaries
- • Testes.

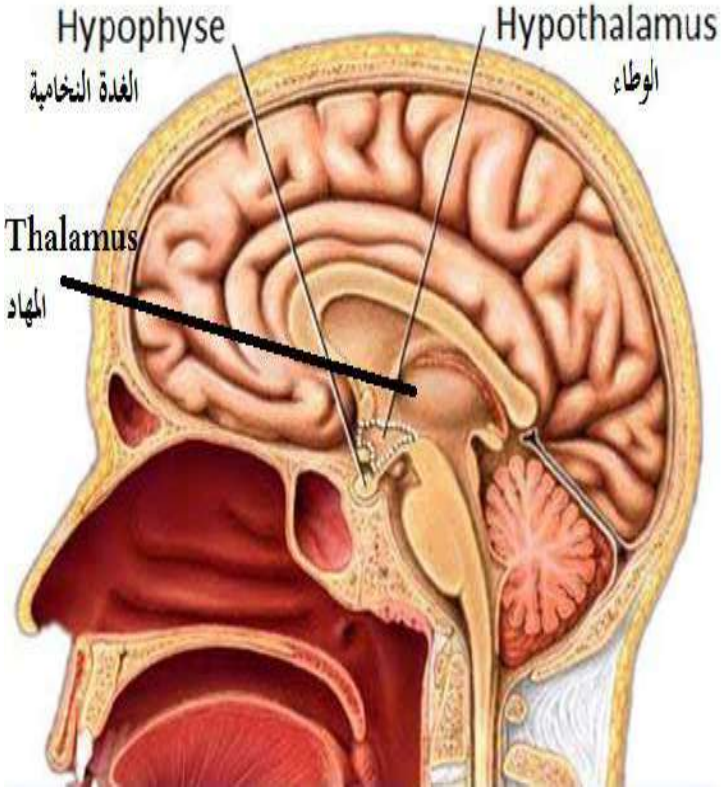


Hypothalamus and Pituitary Gland

- Hypothalamus is a major link between nervous and endocrine system
- Pituitary attached to hypothalamus by infundibulum
  - Anterior pituitary or adenohypophysis
  - Posterior pituitary or neurohypophysis

Hypothalamus and Pituitary Gland





Endocrine Glands

- *1. The pituitary gland : it is composed of :*
- ***A. The Anterior pituitary secretes:***
- • Luteinizing hormone **(LH) and follicular stimulating hormone (FSH), which act on the gonads.**
- • Prolactin **(PRL) which acts on the mammary gland**
- • Adrenocortiotrpic hormone **(ACTH), which acts on the adrenal cortex to regulate the secretion of glucocorticoids.**
- • Growth hormone **(GH), which acts on bone, muscle and liver.**
- • Thyroid stimulating hormone or thyrotropin **(TSH) which stimulates the release of thyroxine (T4) and triiodothyronine (T3) from thyroid gland**

Pituitary Gland

The anterior pituitary hormones

Hormone	Function
(GH) Growth hormone	Promotes growth of the entire body
(ACTH) Adrenocorticotropin	Controls secretion off adrenocortical hormones
Thyroid-stimulating hormone **(TSH)**	Controls rate of secretion of thyroxine and trrodothyronin
(PRL) Prolactin	Promotes mammary gland development and milk production
Follicle-stimulating hormone)**(FSH)**	Control growth of ovaries and testes
(LH) Luteinizing hormone	Control growth of ovaries and testes

Endocrine Glands

- *1. The pituitary gland : it is composed of :*
- *B. The posterior pituitary secretes:*
- • Antidiuretic hormone **(ADH) also called vasopressin which controls excreted water from kidney.**
- • Oxytocin which controls labour

Pituitary Gland

The posterior pituitary hormone

Hormone	Function
Oxytocin (OT)	Helps with the delivery of a baby during pregnancy and let down of milk after suckling
Anti-diuretic hormone (ADH) (Vasopressin)	Regulates water reabsorption in the kidneys at low levels. At higher levels, effects the arteriole pressure.

Endocrine Glands

- *2. The hypothalamus secretes:*
- • Corticotropin-releasing hormone **(CRH) which stimulates the release of ACTH from anterior pituitary.**
- • Gonadotropin-releasing hormone **(GnRH) which stimulates the release of FSH and LH from anterior pituitary.**
- • Growth hormone-releasing hormone **(GHRH) which stimulates the release GH from anterior pituitary.**
- • Prolactin releasing hormone **(PRH) which stimulates the release of prolactin from anterior pituitary**
- • Thyrotropin-releasing hormone **(TRH) which stimulates the release thyroid-stimulating hormone (primarily), also stimulate prolactin release.**

1. Hormones of the hypothalamus

Hormone	
Thyrotropin-releasing hormone **(TRH)**	Stimulates secretion of thyroid stimulating hormone
Gonadotropin-releasing hormone **(GnRH)**	Stimulates secretion of follicle &stimulating hormone luteinizing stimulating hormone
Corticotropin-releasing hormone **(CRH)**	Stimulates secretion of ACTH
Growth hormone-releasing hormone **(GHRH)**	Stimulates secretion of growth hormone
Growth hormone inhibitory hormone (somatostatin) **(GHIH)**	Inhibits secretion of growth hormone
Prolactin-inhibiting hormone (PIH)	Inhibits synthesis and secretion of prolactin

1. Hormones which are lipophilic and/or are transported in plasma by special proteins:

- They have relatively long half-life, their action is prolonged.
- They enter the cells of the target organ and bind to receptor protein in the cytoplasm or the nucleus.
- They exert their action by altering the function of a portion of DNA.
- Steroid hormones of the adrenal cortex, testis and ovary belong to this group.
- Thyroid hormones which are water soluble and easily transportable also act in this manner

2. Hormones which are hydrophilic (water soluble)and easily transported in plasma in a free state:

- Their half-life is very short and their action is also for a very short time.
- They bind to receptors on the cell membrane and their further action is mediated through a **second messenger**, the hormone itself being the **first messenger**.
- Most peptide hormones like insulin, glucagon, and hormones of the pituitary gland belong to this group.

Factors Regulating Hormone Action

- Action of a hormone at a target organ is regulated by four factors:
- **1**. ***Rate of synthesis and secretion: The hormone is stored*** in the endocrine gland.
- **2**. In some cases, ***specific transport systems in plasma.***
- **3.** ***Hormone-specific receptors in target cell membranes*** which differ from tissue to tissue, and
- **4.** ***Ultimate degradation of the hormone usually by the*** liver or kidneys

Factors Regulating Hormone Action

- Action of a hormone at a target organ is regulated by four factors:
- **1**. ***Rate of synthesis and secretion: The hormone is stored*** in the endocrine gland.
- **2**. In some cases, ***specific transport systems in plasma.***
- **3.** ***Hormone-specific receptors in target cell membranes*** which differ from tissue to tissue,
- **4.** ***Ultimate degradation of the hormone usually by the*** liver or kidneys

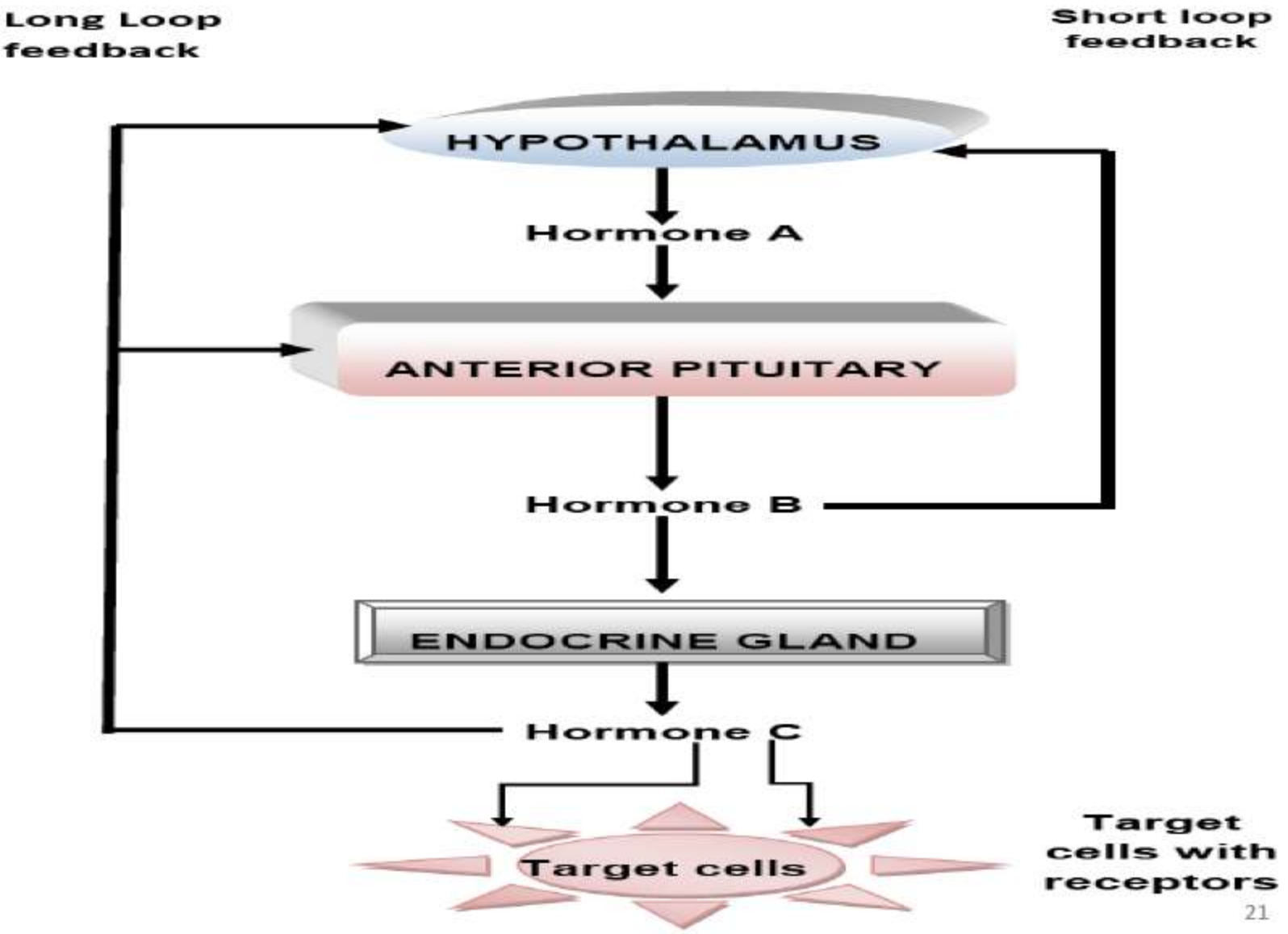
Control of Endocrine Activity

- The physiologic effects of hormones depend largely on their concentration in blood and extracellular fluid. The concentration of hormone as seen by target cells is determined by three factors:
- 1. ***Rate of production: Synthesis and secretion of hormones are the most highly*** regulated aspect of endocrine control. Such control is mediated by positive and negative feedback circuits.
- 2. ***Rate of delivery: An example of this effect is blood flow to a target organ or group*** of target cells:
- 3. ***Rate of degradation and elimination: Hormones, like all biomolecules, have*** characteristic rates of decay, and are metabolized and excreted from the body through several routes.

What is Negative-Feedback Mechanism for Regulation of Hormone secretion? (Fig. 4)

- Regulation of secretion of some hormones from endocrine glands is controlled via "**Negative-Feedback**" Mechanism, (Long-Loop, Short-Loop negative Feedback):
- Hormone released from one gland regulates the release of another hormone from a second gland, which then controls hormone production from the endocrine gland;
- Plasma level of the hormone itself or of a substance produced by the target tissue in response to the hormone may inhibit further release of the hormone;
  - Example: **Negative-Feedback control of Thyroid hormones**;

Feedback hormonal control
(Hypothalamic-Pituitary-Endocrine gland)



Hormone Regulation: Feedback Mechanisms

- Hormones control many cell activities, so they are very important for homeostasis. Most hormones are regulated by feedback mechanisms. A **feedback mechanism** is a loop in which a product feeds back to control its own production. Most hormone feedback mechanisms involve **negative feedback loops**. Negative feedback keeps the concentration of a hormone within a narrow range.

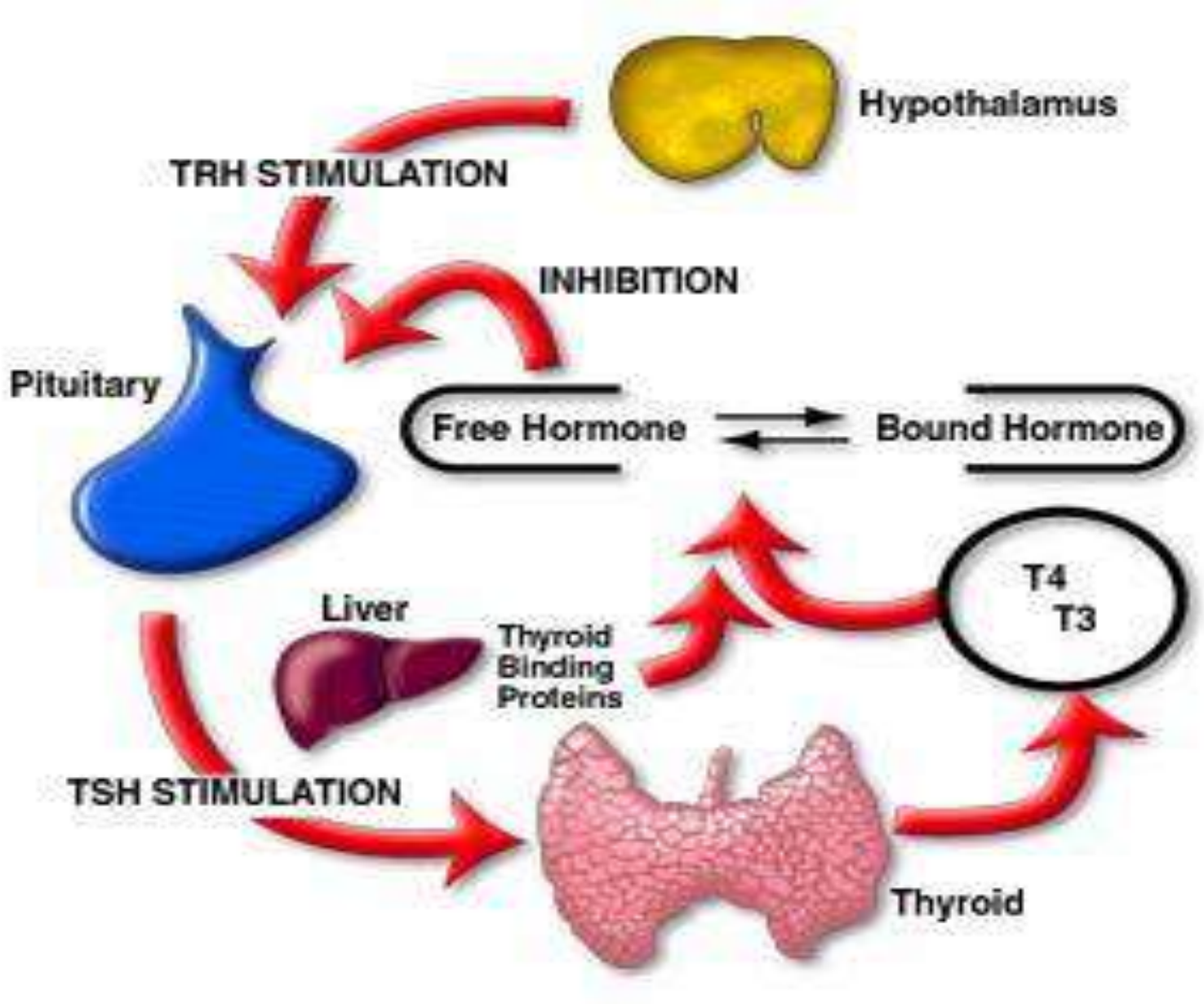
Feedback Control of Hormone Production

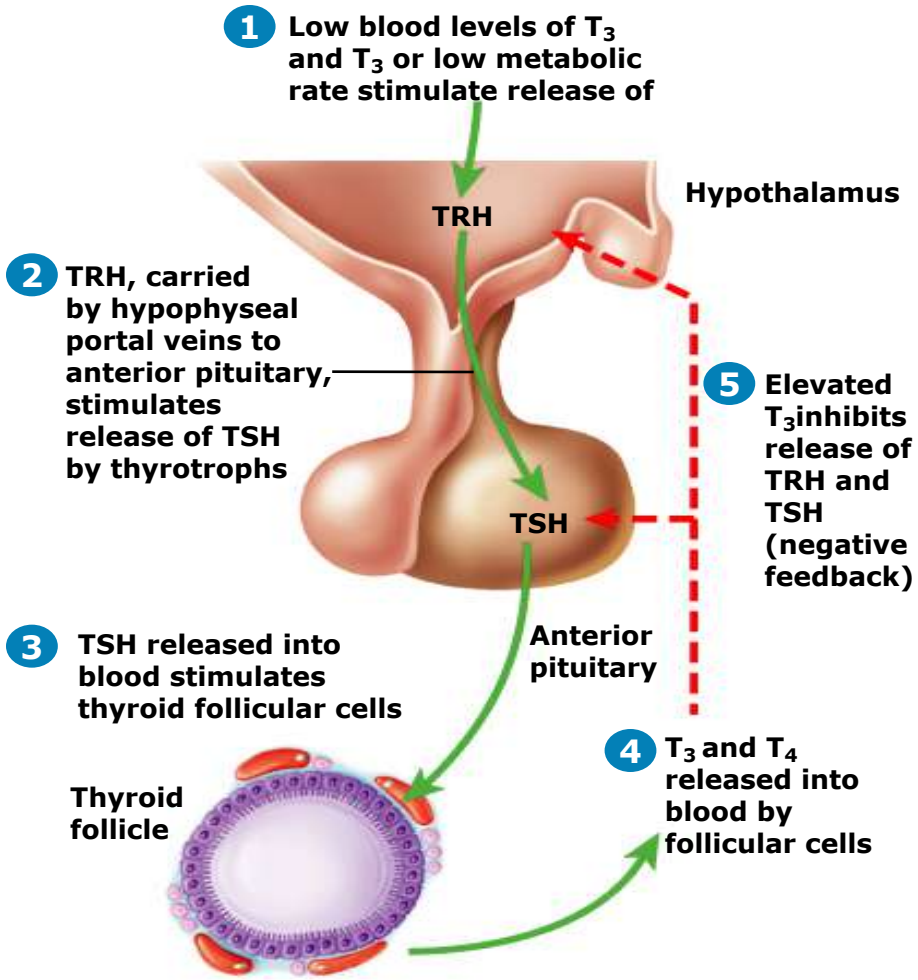
- Instances of positive feedback certainly occur, but negative feedback is much more common. Feedback loops are used extensively to regulate secretion of hormones in the hypothalamic-pituitary axis. An important example of a negative feedback loop is seen in control of thyroid hormone secretion. The thyroid hormones thyroxine and triiodothyronine("T4 and T3") are synthesized and secreted by thyroid glands and affect metabolism throughout the body.

Feedback Control of Hormone Production

- The basic mechanisms for control in this system are:
- •Neurons in the hypothalamus secrete thyroid releasing hormone (TRH), which stimulates cells in the anterior pituitary to secrete thyroid-stimulating hormone (TSH).
- • TSH binds to receptors on epithelial cells in the thyroid gland, stimulating synthesis and secretion of thyroid hormones, which affect probably all cells in the body.
- • When blood concentrations of thyroid hormones increase above a certain threshold,TRH-secreting neurons in the hypothalamus are inhibited and stop secreting TRH.
- ***This is an example of "negative feedback".***

"Negative feedback".





Actions of Thyroid Hormones:

Increase basal metabolic rate

Stimulate synthesis of Na^+/K^+ ATPase

Increase body temperature (calorigenic effect)

Stimulate protein synthesis

Increase the use of glucose and fatty acids for ATP production oduction

Stimulate lipolysis

Enhance some actions of catecholamines

Regulate development and growth of nervous tissue and bones and bones

Negative feedback".

- Inhibition of TRH secretion leads to shut-off of TSH secretion, which leads to shut-off of thyroid hormone secretion. As thyroid hormone levels decay below the threshold, negative feedback is relieved, TRH secretion starts again, leading to TSH secretion