Introduction to Endocrinology

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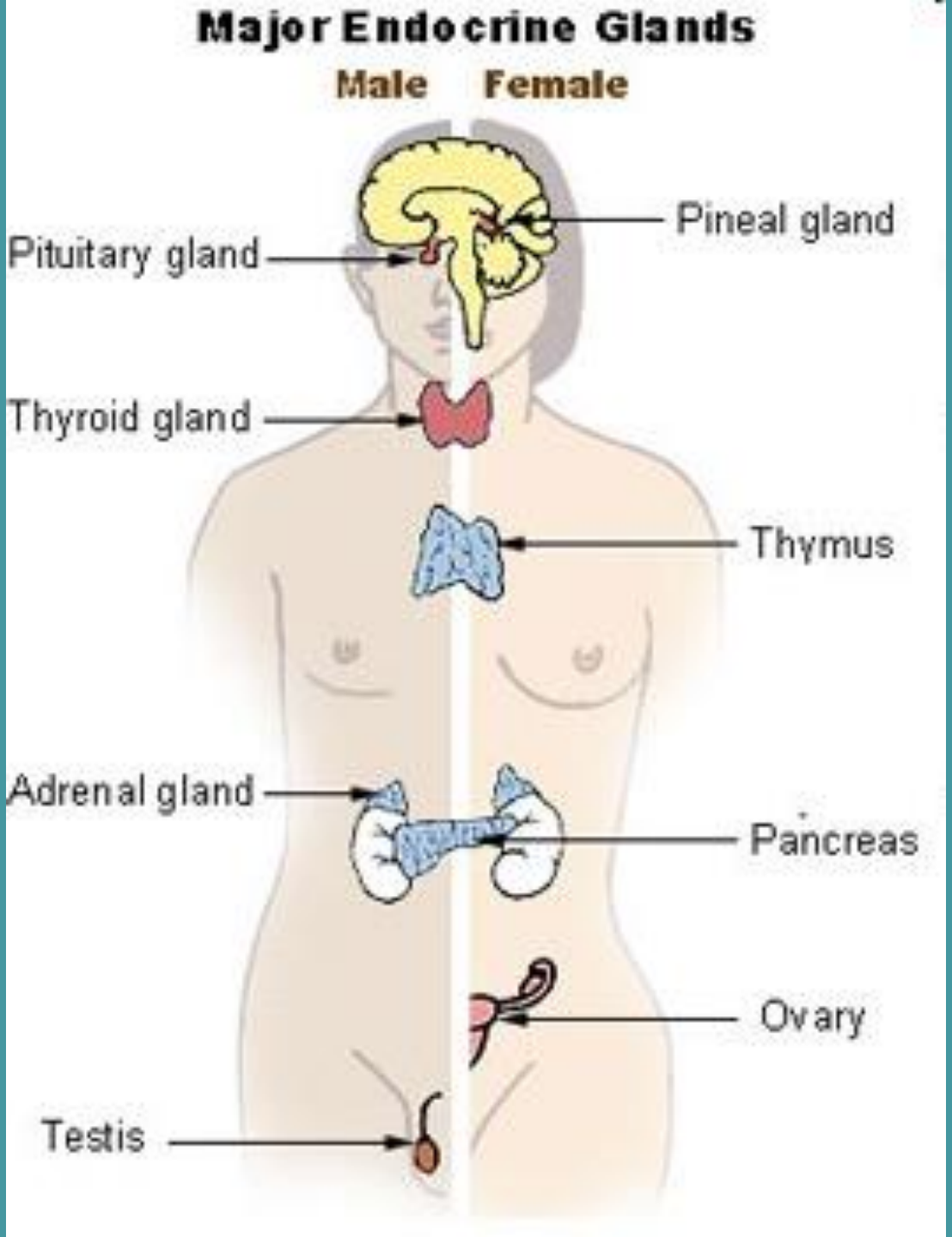
Endocrinology is the study of hormones, their receptors and the intracellular signaling pathways they initiate.

- **Endocrine glands** are ductless and secret hormones to bloodstream
- **Hormones** are chemical messengers secreted into blood or extracellular fluid by one cell that affect the functioning of other cells.
- The major glands of the endocrine system are the pituitary, pancreas, thyroid, parathyroids, adrenals, pineal, and the reproductive organs (ovaries and testes).

Endocrinology is about communications between cells

- **Hormone functions**: reproduction and sexual differentiation; development and growth; maintenance of the internal environment; and regulation of metabolism and nutrient supply.
- A single hormone may affect more than one of these functions and each function may be controlled by several hormones.


Major Endocrine Glands
Male
Female
Pineal gland
Pituitary gland
Thyroid gland
Thymus
Adrenal gland
Pancreas
Ovary
Testis

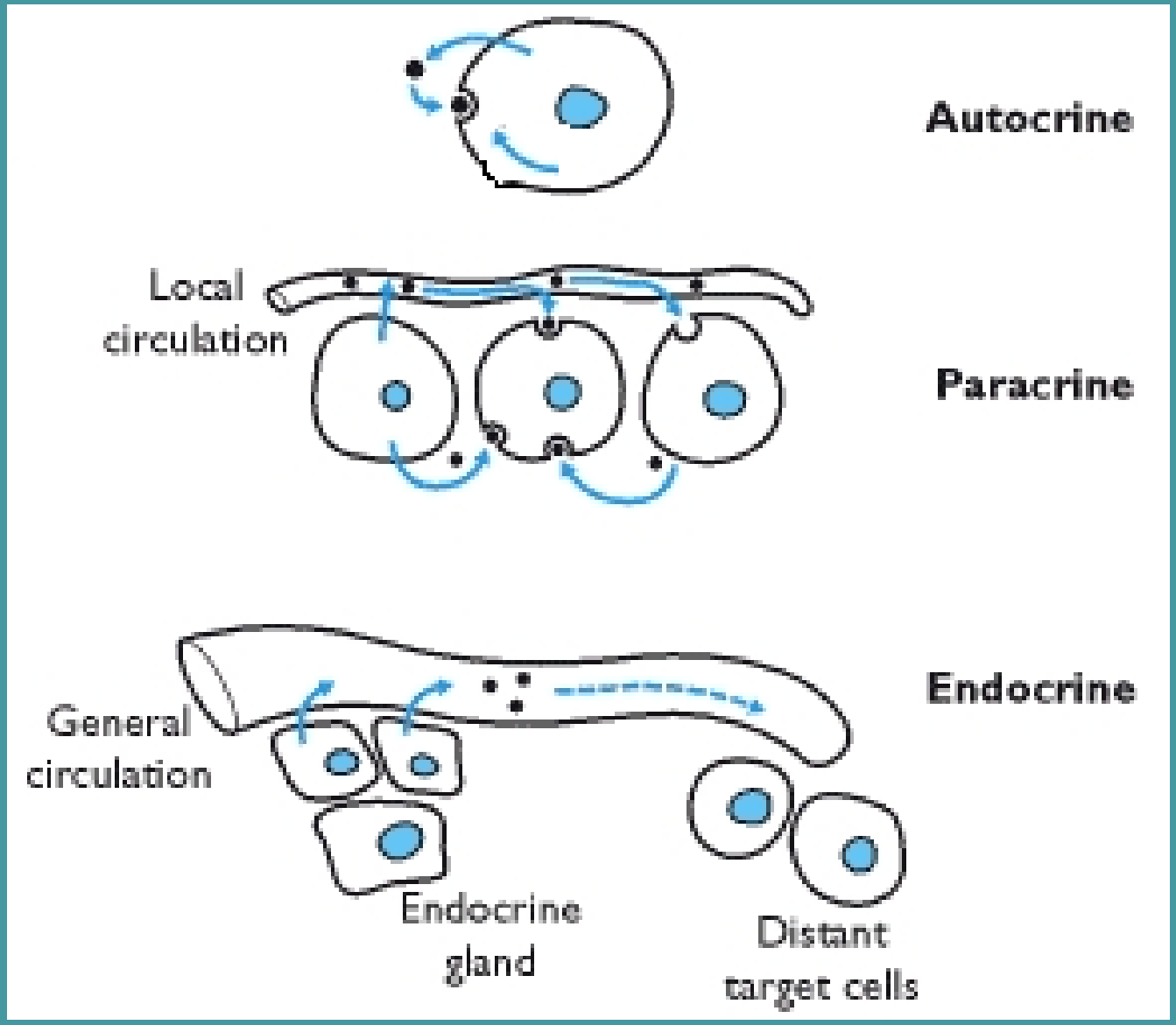
Chemical signaling

Depending on the distance between the secreting and target cells, hormones can be classified as

1- **Endocrine action**: the hormone is distributed in blood and binds to distant target cells. (neuroendocrine: neurons produce both neurotransmitter and hormone (eg. epinephrine))

2- **Paracrine action**: (Para: near) the hormone acts locally by diffusing from its source to target cells in the neighboring cells within a tissue or organ without entering blood.

3- **Autocrine action**: the hormone acts on the same cell that produced it.


Autocrine
Local
circulation
Paracrine
Endocrine
General
circulation
Endocrine
gland
Distant
target cells

Chemical classification of hormones

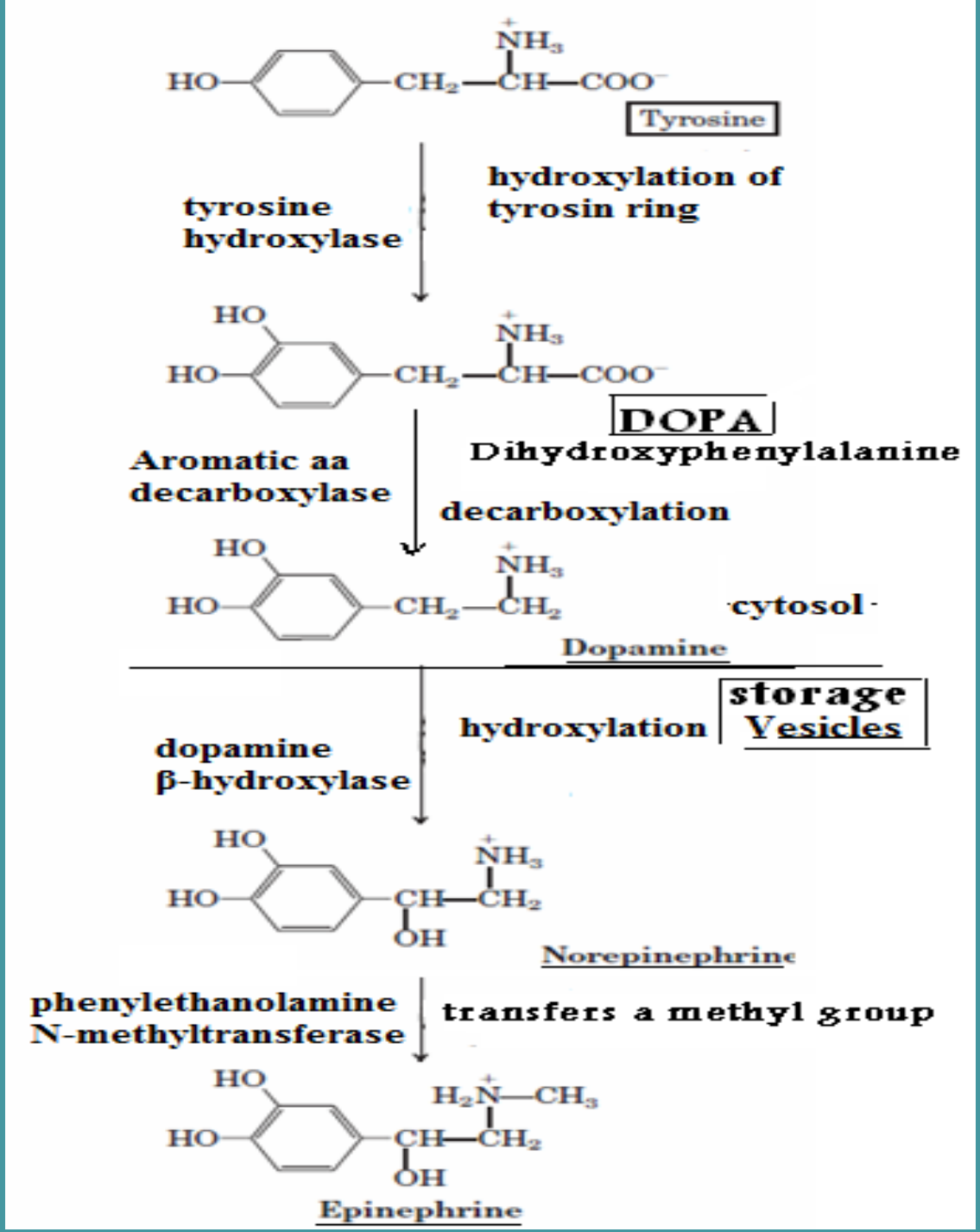
Chemically hormones are grouped into three classes:

1-Steroid hormones: are hydrophobic and synthesized from cholesterol and are categorized in the human into six different classes or families that include:

Progestins (C-21) (Progesterone), Gluco-corticoids (C-21) (Cortisol), Mineralo-corticoids (C-21) (Aldosterone), Androgens (C-19) (Testosterone), Estrogens (C-18) (Estradiol), and vitamin D.

Steroid hormones affect carbohydrate metabolism salt and water balance, and reproductive function.

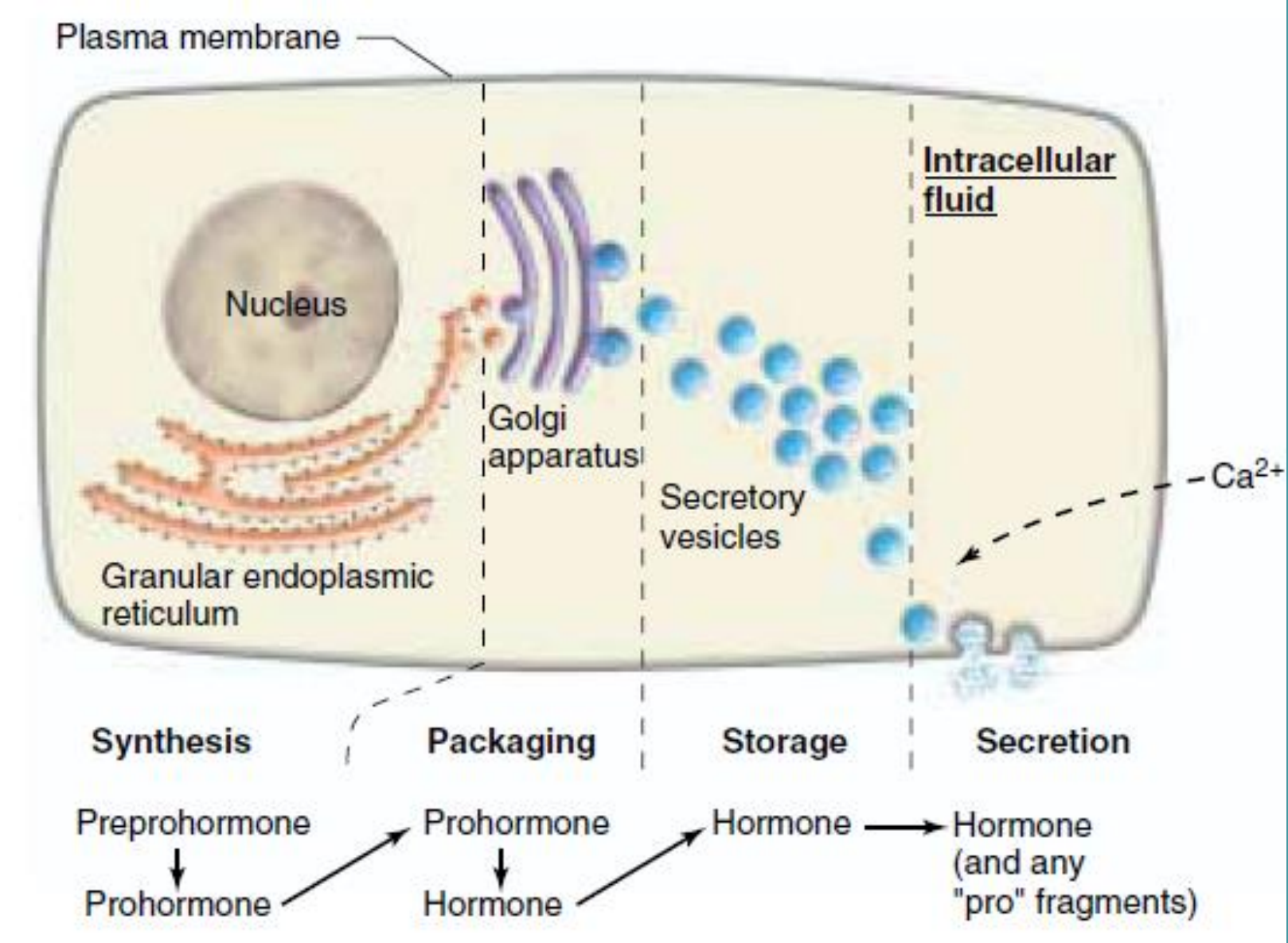
2-Tyrosine derivatives hormones including: A. catecholamine hormones (hydrophilic) and B. thyroid hormones (hydrophobic). Catecholamine hormones include epinephrine, norepinephrine and dopamine. Dopamine is a neurotransmitter that can act as hormone is released from median eminence and suppress the secretion of prolactin from anterior pituitary. The thyroid hormones-thyroxin and triiodothyronine-each have two fused molecule of tyrosine. Thyroxin has four iodine atoms attached to the amino rings while triiodothyronine has three iodine atoms.


Tyrosine
tyrosine hydroxylase
hydroxylation of tyrosin ring
DOPA
Dihydroxyphenylalanine
Aromatic aa decarboxylase
decarboxylation
cytosol
Dopamine
storage Vesicles
hydroxylation
dopamine β-hydroxylase
Norepinephrine
phenylethanolamine N-methyltransferase
transfers a methyl group
Epinephrine

3-Peptides and proteins hormones: are hydrophilic and the most numerous hormones, they range in size from just three to over 200 amino acids.

- Some hormones, such as insulin which is regarded as a small protein, are made up of two sub-units joined by disulfide bonds between two cysteine molecules whilst the glycoprotein hormones of the anterior pituitary gland are not only made up of two protein sub-units but also have complex sugar moieties attached. Most peptide hormones are water-soluble.

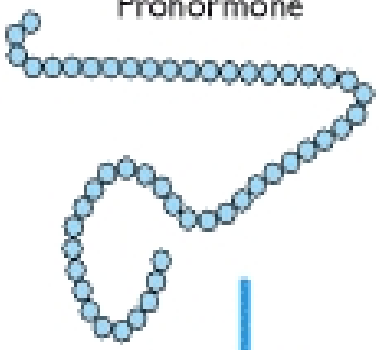
- In peptides and proteins hormones they are synthesized on the ribosomes of the endocrine cells as larger proteins known as preprohormones, which are then cleaved to prohormones by proteolytic enzymes in the granular endoplasmic reticulum. The prohormone is then packaged into secretory vesicles by the Golgi apparatus which is cleaved to active hormone.



Typical synthesis and secretion of peptide hormones. In some cells, the calcium that causes exocytosis is released from the endoplasmic reticulum by action of a second messenger rather than entering from the extracellular fluid

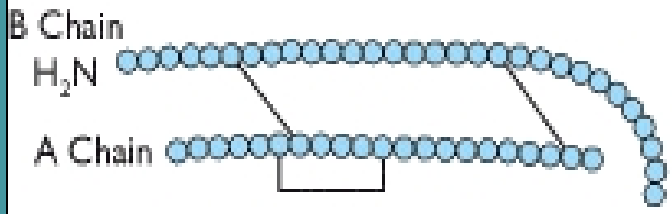
Protein and Peptide Hormones

Prohormone



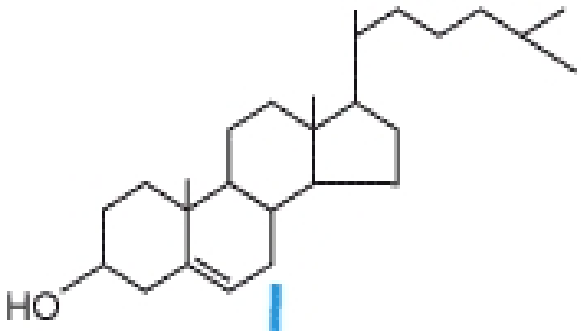
Endothelin

Insulin

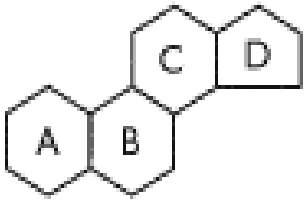


Steroid Hormones

Cholesterol

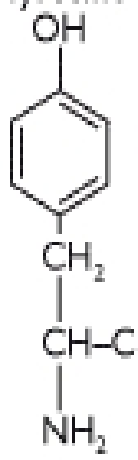


Steroid Nucleus

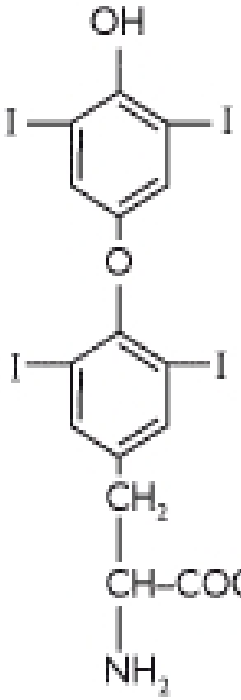


Tyrosine Derivatives

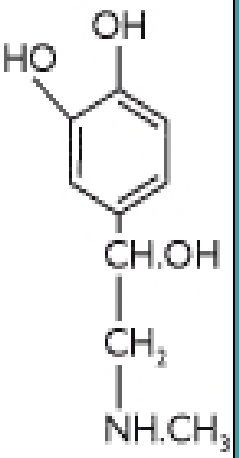
Tyrosine



Thyroxine



Epinephrine



Control of Hormone Secretion

1. Neural

The adrenal medulla (the inner part of an **adrenal** gland, it releases the hormones that initiate the flight or fight response it secret epinephrine and norepinephrine hormones) is directly stimulated by the sympathetic nervous system.

2. Hormonal

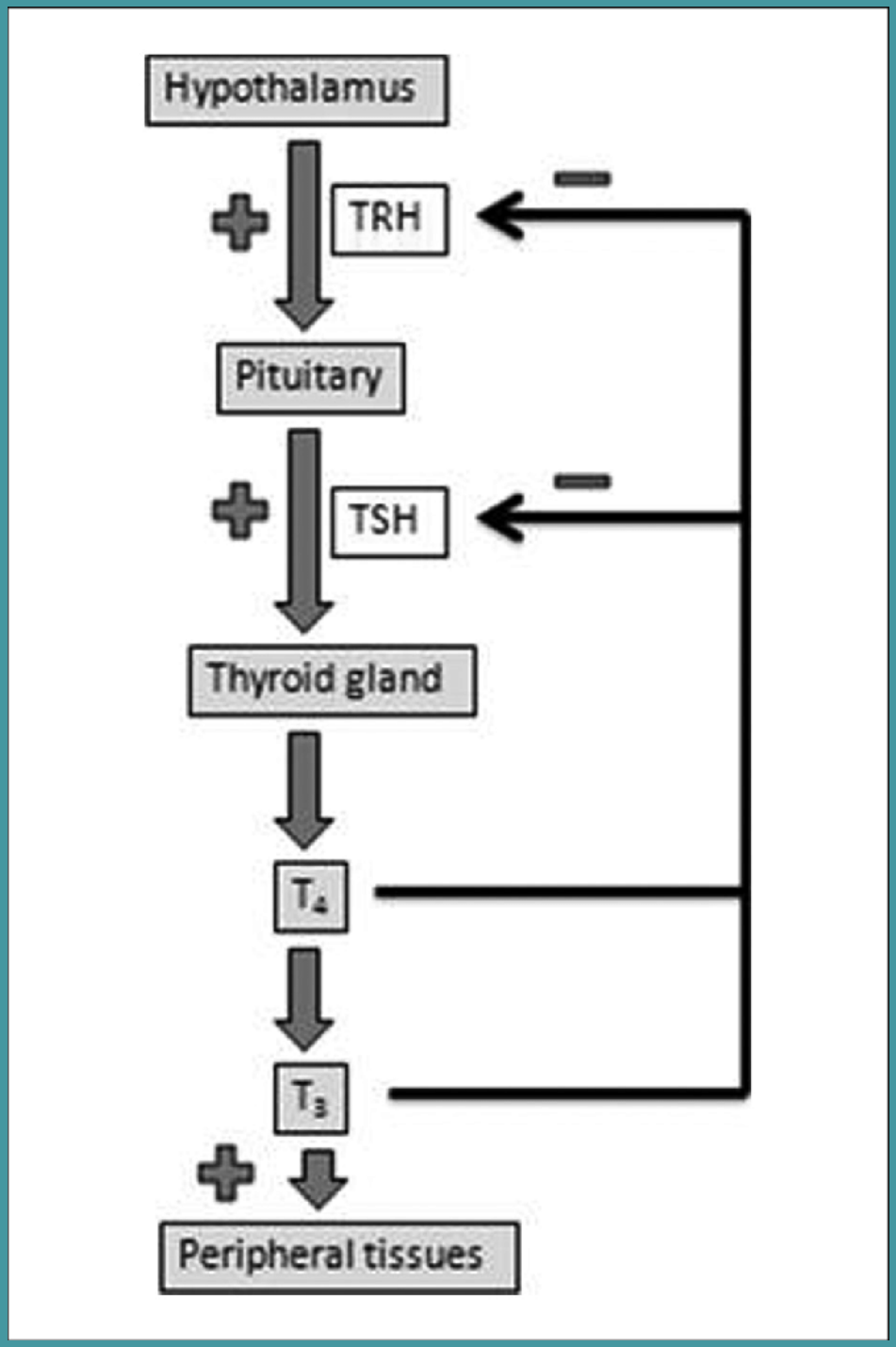
Occurs when hormones from one endocrine gland stimulate the secretion of hormones from another endocrine gland. These routes of secretion are usually controlled in a negative feedback manner.

3. Humoral

Occurs when substances other than hormones control the secretion of endocrine glands.

E.g. Insulin secretion by the pancreas is determined by several factors. Rise in glucose and amino acids after a meal triggers insulin secretion.

- **Feedback control**
- For the hormones that are regulated by the pituitary gland, a signal is sent from the hypothalamus to the pituitary gland in the form of a "releasing hormone," which stimulates the pituitary to secrete a "stimulating hormone" into the circulation. The stimulating hormone then signals the target gland to secrete its hormone. As the level of this hormone rises in the circulation, the hypothalamus and the pituitary gland shut down secretion of the releasing hormone and the stimulating hormone, which in turn slows the secretion by the target gland.
- Example: Thyrotropin releasing hormone (TRH) produced by the hypothalamus stimulate the release of thyrotropin-stimulating hormone (TSH produced by anterior pituitary gland) which stimulate the release of thyroid hormones. In turn, high level of thyroid hormones inhibit production and secretion of both TRH and TSH. Decreased production of thyroid hormone results in increased TRH secretion and thus increased thyroid hormone secretion.



Feedback control Example: Thyrotropin -Releasing Hormone (TRH) produced by hypothalamus stimulate pituitary gland to secrete Thyrotropin -stimulating hormone (TSH). That stimulate the thyroid gland to release T4 and T3

When T4 and T3 levels are high they block the release of TRH and TSH

- **Hormone synthesis, storage, secretion and transport**

1- Synthesis

A-Most protein and peptide hormones require the transcription of a single gene and then translation on ribosome in the rough endoplasmic reticulum.

B-The synthesis of steroid hormones occurs in the mitochondria and endoplasmic reticulum requires the presence of specific enzymes that convert cholesterol into the appropriate steroid.

- Mitochondria contain the cholesterol side-chain cleavage enzyme, P450scc, and its two electron-transfer partners: ferredoxin reductase and ferredoxin. This enzyme system converts cholesterol to pregnenolone (21 carbon atoms

2- Storage

- Protein or peptide hormone-secreting cells store the newly synthesized hormone in small vesicles or secretory granules inside the cell membrane. On the other hand steroid producing hormone cells do not store steroid hormone but synthesis hormone for secretion as required.

3- Secretion

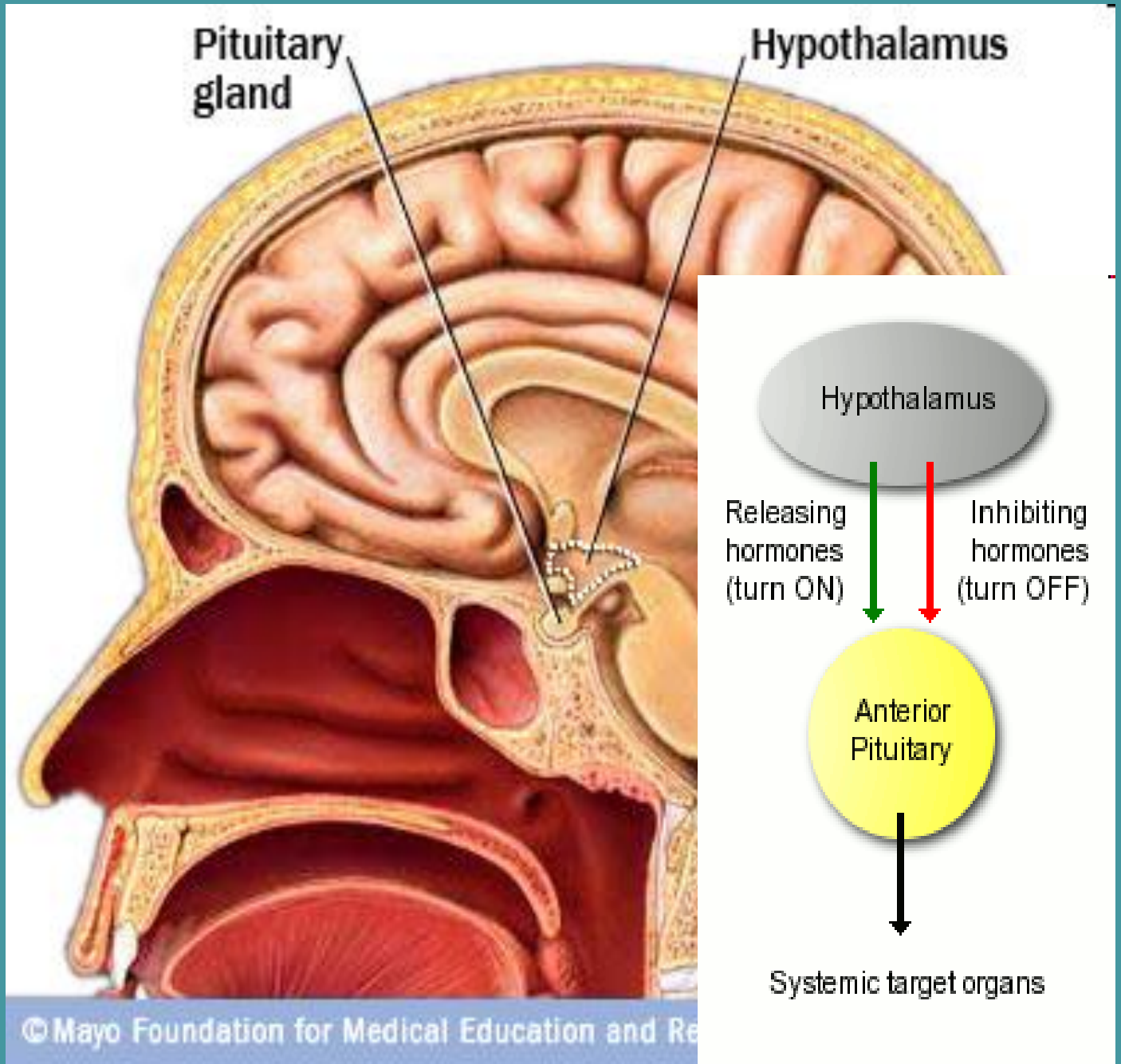
- The cell requires some stimulus before the stored prohormone is activated and released. The stimulation may be hormonal and usually involve a change in permeability of the cell to Ca^{2+} ions. The metal ions are required for interaction between the vesicle and plasma membranes and for the activation of enzymes, microfilaments and microtubules. Specific endopeptidases present together with the prohormone in the storage vesicle are activated during the secretory process and produce the active form of the hormone for release from the cell. The mode of secretion from the cell is called exocytosis.

4- Transport of hormones in the circulation

- Steroid and thyroid hormones are less soluble in aqueous solution (hydrophobic) than catecholamine hormones and protein and peptide hormones (hydrophilic) and over 90% circulate in blood as complexes bound to specific plasma globulins or albumin and a more specific transport protein, such as steroid hormone binding globulin (SHBG) and thyroid hormone-binding globulin (TBG).
- Free hormone (unbound) is the biologically active and not the bound hormone. Bound hormones are not available for diffusion in to cells and thus can't affect the target organ or tissue.
- Bound and free hormones are in equilibrium.
- Therefore, bound hormone act as a storage of free hormone and it regulates the amount of free hormones available for diffusion into tissues.
- it has been suggested that the specific binding globulins may interact with membrane receptors and that hormone binding to the globulins initiates a signal transduction pathway.
- The rates of metabolism of hormones in the circulation vary but generally speaking the half life ($t_{1/2}$) of catecholamines from the adrenal medulla is in the order of seconds, minutes for protein and peptide hormones and hours for steroid and thyroid hormones.

Neuroendocrine interactions

- How the endocrine and nervous system linked?
- Hypothalamus connects these two important communication systems. The hypothalamus is a group of tiny nuclei that lie along the base of the brain near the pituitary gland. The hypothalamus controls the pituitary gland by secreting hormones which control the secretion of many endocrine glands, and this gives the hypothalamus a great deal of control over many body functions.
- Moreover, all endocrine glands are innervated by autonomic nerves and these may directly control their endocrine function and/or regulate blood flow (and hence function) within the gland. Hormones, in turn, may affect central nervous system functions such as mood, anxiety and behavior.


Pituitary gland
Hypothalamus
Hypothalamus
Releasing hormones (turn ON)
Inhibiting hormones (turn OFF)
Anterior Pituitary
Systemic target organs
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Hormones effects

The physiologic effects of hormones depend largely on their concentration in blood and extracellular fluid.

The concentration of hormone is determined by three factors:

1- Rate of production: regulated by positive and negative feedback circuits.

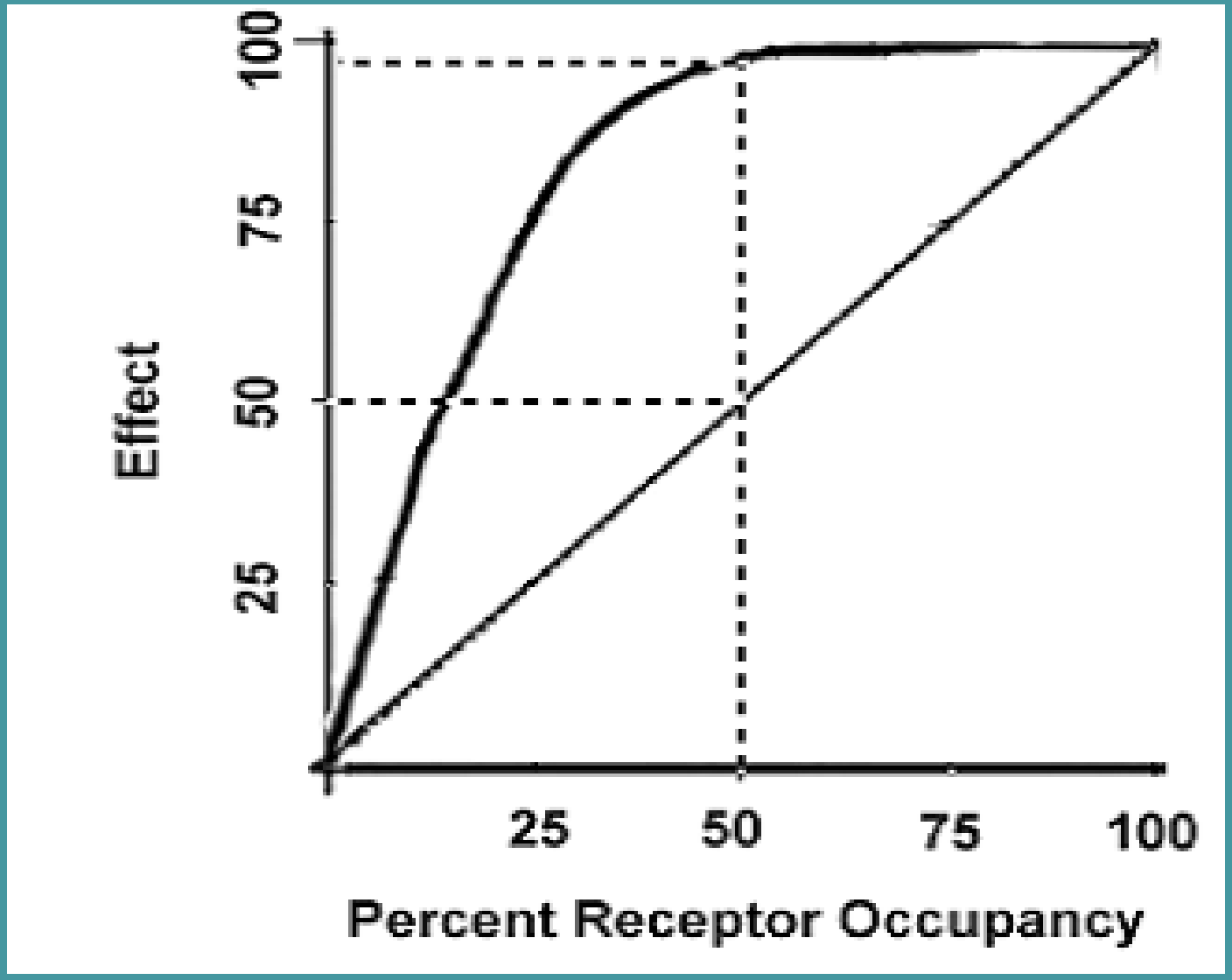
2- Rate of delivery: An example of this effect is blood flow to a target organ or group of target cells - high blood flow delivers more hormone than low blood flow.

3- Rate of degradation and elimination: most of hormone is cleared by liver and kidneys. Only a small fraction is removed by target tissue through enzymatic degradation.

Spare receptors

- Spare receptors are receptors which exist in excess of those required to produce a full effect therefore a maximum response can be reached with only 2-3% receptor bonded to hormones. The greater the proportion of spare receptors, the more sensitive the target cell to the hormone
- In most systems the maximum biological response is achieved at concentrations of hormone lower than required to occupy all of the receptors on the cell. For examples insulin stimulates maximum glucose oxidation in adipocytes with only 2-3% of receptors bound. Because hormones are normally present at very low concentrations only small receptors are occupied and it is enough to produce maximum effect. And when hormone is at high concentrations all receptors are occupied but without any extra effect.
- The effectors can be mobile, rapidly moving from one receptor molecule to another so the more receptors the more it can activate. Beside that the effecter has more opportunities to find and activate a receptor.

Spare receptors



- **Agonists** are molecules that bind the receptor and induce all the post-receptor events that lead to a biologic effect. In other words, they act like the "normal" hormone, although perhaps more or less potently
- **Antagonists** are molecules that bind the receptor but are unable to bring about receptor activation (fail to trigger intracellular signaling events) and block binding of the agonist.