

Hormones, Receptors and Receptor-Hormone Interactions

- Classification of Hormones
- Synthesis of Protein Hormones and Amine Hormones
- Hormone Activity
- Locations of Receptors
- Mechanisms of Hormone Action
- Types of Membrane Receptors (to be continued in the next lecture)

- **Classification of Hormones:**

Criteria: (Chemical Structure, site of action, solubility, polarity)

Criterion1) Chemical structure: (4types)

Proteins/ peptides: (Water-soluble)

What is the difference between proteins and peptides?

Polypeptides: the chain has less than 100 amino acids

Proteins: have more than 100 amino acids

2) Steroids: (Lipid-soluble)

Derivatives of cholesterol (cholesterol is the backbone of steroids)

Cholesterol goes under reactions like methylation, hydroxylation and oxygenation → then gives a certain steroid.

Eg) estrogen, progesterone, cortisol, aldostiron

3) Amines: (they could either be water-soluble or lipid-soluble)

Derivatives of a single amino acid which is Tyrosine

a) Thyroxines/(thyroid hormones): lipid-Soluble

Eg) T3: triiodothyronine has 3 iodine atom

T4: tetraiodothyronine has 4 iodine atom

They are both amines but they are not the same in terms of solubility

b) Catecholamines: water-soluble

Eg: dopamine, norepinephrine and epinephrine.

4) Gases: (Highly lipid-soluble)

Eg: Nitric Oxide NO

Criterion2; Site of Action: (2types)

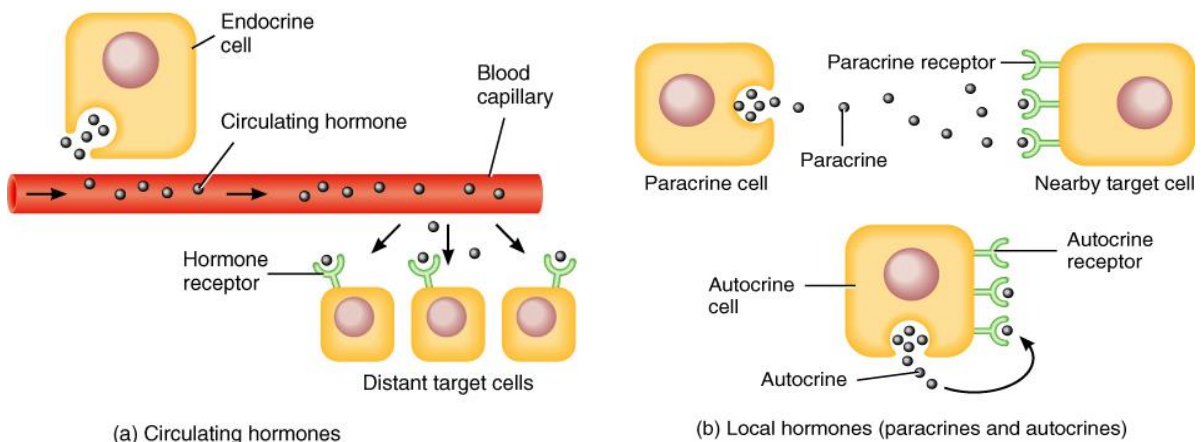
1) Circulating hormones:

In endocrine systems, hormones are secreted into the blood, then they travel to their distant target cells to perform their actions.

2) Local Hormones:

a) Paracrine: (act on nearby cells)

b) Autocrine: (act on the same cell that secreted them)



Criterion 3; Solubility: (2 types)**1) Lipid-Soluble: (lipophilic)**

Eg; gas hormones NO, steroids, sex hormones, thyroid hormones (T3 & T4)

These need transporters because they don't dissolve in blood plasma (since it's mostly composed of water)

2) Water-soluble: (hydrophilic)

They don't pass through the membrane they need receptors

These don't need transporters; they directly dissolve in the blood plasma.

E.g;

a) Catecholamines: (norepinephrine, epinephrine, dopamine)

b) Polypeptides: (*ADH Anti-diuretic hormone, Oxytocin*) (both from the pituitary gland)

Note: these 2 are octa-peptides (they have 8 amino acids in their chains), they only differ in one amino acid.

Note: not all amines have the same solubility

c) Proteins (Growth hormone, eicosanoid (prostaglandins))

*** Prostaglandins and Aspirin ***

Prostaglandin is derived from the fatty acid arachidonic acid (20 carbons 4 double bonds).

An enzyme found on membranes called Cyclooxygenase converts arachidonic acid to prostaglandins.

Prostaglandin increases the sensitivity of pain receptors due to lowering the threshold.

Cyclooxygenase is the site where Aspirin (pain killer) binds, Aspirin inhibits Cyclooxygenase, and so it will decrease the levels of prostaglandins and thus relieve pain.

d) Glycoproteins: (proteins + carbohydrates)

* sub-type of proteins in chemical structure classification *

They usually have 2 subunits an alpha and a beta.

The alpha is common and it's the same in all glycoproteins in the body, while the beta is different, beta subunits are specific.

If we want to measure the amount of the glycoprotein hormone, we measure the activity of the beta subunits.

E.G;

FSH follicle stimulating hormone, LH luteinizing hormone, TSH thyroid stimulating hormone, hCG *human chorionic gonadotropin* (This is released from the placenta during pregnancy, it indicates pregnancy)

Criterion 4; Polarity: (2types)

- 1) **Polar:** water-soluble (charged)
 - 2) **Non-polar:** lipid-soluble (lipophilic)
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- **Synthesis of Amines:**

Refer to slide 24

Two totally different pathways for forming 1)thyroid hormones/ thyroxines
2)catecholamines

Amino acid Tyrosine → hydroxylation by tyrosine hydroxylase → L-Dopa → decarboxylation by dopa decarboxylase → Dopamine → hydroxylation at the beta side → norepinephrine → methylation by N-methyl transferase → epinephrine.

The difference between epinephrine and norepinephrine is the presence of a methyl group; epinephrine has a methyl group while norepinephrine doesn't.

- **Synthesis of Hormones: (Protein hormones)**

- 1) Very long polypeptide chains (prohormones) are formed in the RER rough endoplasmic reticulum.

- 2) These long chains go to **Golgi apparatus** for **post translational modification** and cleavage of some parts.
- 3) In **Golgi Apparatus** as well, hormones are packed into vesicles.
- 4) Then they are transported and released to the outside by exocytosis

a certain stimulus causes exocytosis to occur

Prohormones are the precursors for hormones. Eg) Proinsulin gives insulin(the active is insulin)

Pre-pro-hormone: is the precursor protein to one or more prohormones, which are in turn precursors to hormones.

Prehormone: is a substance secreted by glandular tissue and has minimal or no significant biological activity, but it is converted in peripheral tissues into an active hormone.

Prehormones and prohormones → inactive

Hormones → active

Sometimes we have some hormones that are secreted to the blood but they are not in the needed active form, but when they converted to a certain hormone they become more active (the needed form)

Example; (T3&T4)

T4 is not as active as T3, T3 is 4-5 times more active than T4

In order to convert T4 to T3 we must remove one iodine molecule through deiodination (this happens in the tissue not in the circulation). T4 circulates in blood, goes to tissue, where conversion to T3 takes place to increase its activity.

Doctor Comments on Slide #21

Peptide & Protein Hormones

Gland/Tissue	Hormones	Gland/Tissue	Hormones
Hypothalamus	<ul style="list-style-type: none"> ■ TRH, GnRH, CRH ■ GHRH, Somatostatin, 	Placenta	<ul style="list-style-type: none"> ■ HCG, HCS or HPL
Anterior pituitary	<ul style="list-style-type: none"> ■ ACTH, TSH, FSH, LH, ■ PRL, GH 	Kidney	<ul style="list-style-type: none"> ■ Renin
Posterior pituitary	<ul style="list-style-type: none"> ■ Oxytocin, ADH 	Heart	<ul style="list-style-type: none"> ■ ANP
Thyroid	<ul style="list-style-type: none"> ■ Calcitonin 	G.I. tract	<ul style="list-style-type: none"> ■ Gastrin, CCK, ■ Secretin, GIP, ■ Somatostatin
Pancreas	<ul style="list-style-type: none"> ■ Insulin, Glucagon, ■ Somatostatin 	Adipocyte	<ul style="list-style-type: none"> ■ Leptin
Liver	<ul style="list-style-type: none"> ■ Somatomedin C (IGF-1) 	Adrenal medulla	<ul style="list-style-type: none"> ■ Norepinephrine, ■ epinephrine
Parathyroid	<ul style="list-style-type: none"> ■ PTH 		

- Examples **not for memorization**
- TSH, FSH, LH examples of glycoproteins.
- Oxytocin, ADH differ in only one amino acid, both are octapeptides.
- Calcitonin comes from the thyroid but is a protein not an amine (like thyroxins T3&T4)
- Insulin and glucagon (both peptides) are antagonists meaning they work against each other. Both are secreted from the pancreas.
- Insulin decreases blood glucose, glucagon increases blood glucose.

Doctor Comments on slide #25

Steroid Hormones

Gland/Tissue	Hormone
Adrenal Cortex	■ Cortisol, Aldosterone, Androgens
Testes	■ Testosterone
Ovaries	■ Estrogens, Progesterone
Corpus <u>Luteum</u>	■ Estrogens, Progesterone
Placenta	■ Estrogens, Progesterone
Kidney	■ 1,25-Dihydroxycholecalciferol (calcitriol)

- Placenta secretes steroids like Estrogen and progesterone, plus the glycoprotein hCG mentioned before.
- 1,25-Dihydroxycholecalciferol or (calcitriol) are the active forms of VitaminD. VitaminD precursor comes from the skin through light, circulates in the blood and goes to the liver where hydroxylation occurs at position 25, then it goes to the kidney for more hydroxylation at position 1. (Activation of VitaminD takes place in the kidney and not the secretion.)
- Vitamin D increases the reabsorption of *calcium* in the GI tract.

Remember

* at the preganglionic neurons, neurotransmitters are acetylcholine in both types of the autonomic nervous system whether sympathetic or parasympathetic

* at the postganglionic neurons they differ, sympathetic postganglionic neurons release epinephrine and norepinephrine. Parasympathetic postganglionic neurons release acetylcholine.

- **Hormone Activity:**

- 1) Hormones act only on specific target tissue when they bind to their specific receptors.
- 2) The receptors are not static but dynamic; which means that the number of receptors might decrease or increase.

- **Down-Regulation:**

Extensive stimulation for the sympathetic nervous system raises the levels of Epinephrine and Norepinephrine to an extent our body can't sustain, so the body decreases the number of receptors by internalization (openings of receptors are directed inwards). With the receptors no longer exposed to hormones, hormones won't perform their actions and so we get a less sensitive and a less responsive system.

This is called desensitization (decreasing sensitivity) or down-regulation.

*Internalization: happens by phosphorylation which is adding phosphate to the proteins by protein kinases *

- **Up-Regulation:**

If we have a dormant/ relaxed system that needs stimulation, the body increases the number of receptors by forming new ones.

Increasing receptors on target cells causes greater response by target cells and so the system is more responsive and more sensitive.

This is called up-regulation or up-sensitization

- **Pulsatile Secretion and Down-Regulation:**

High levels of glucose and high levels of insulin at the same time mean the number of insulin receptors is decreased and we have (insulin resistance), this is due to down-regulation and occurs in adipose cells (lipid cells).

Our system removes the effect of down-regulation by Pulsatile Secretion (secretion in pulses) and not continuous secretion.

Pulsatile Secretion of hormones affects our biological clock

If someone came back from the states, they would feel sleepy in the morning and alert at night. That's because their biological clocks are still not adapted to the new routine.

The hormone that is very important for alertness is Cortisol which is secreted in the morning and decreased at night, that's why we feel alert in the morning and we prefer taking lectures during day time.

Cortisol is secreted in pulses discontinuously.

This kind of secretion decreases down-regulation

The responsiveness to hormones depends on two things:

- 1) Concentration of the hormone
- 2) The number of receptors

Half-Life of hormone:

Half life: The time required for the concentration of the hormone to be halved.
Ranges from minutes to days.

Why is it important to know the half-life of hormones?

To know the frequency of drug dosages the patient needs.

Eg; the half-life for insulin is 20 minutes (short), so we must increase the dosage frequency (not once a day for example).

Eg; the half-life for thyroxins T₃ & T₄ is 7 days (long), we must decrease the dosage frequency (not once a day or 3 times a day but once a week would be enough).

Physiological action VS Pharmacological action:

Physiological Action: normal tissue responses are produced only when hormone concentrations are within physiological ranges.

Pharmacological Action: amounts of hormones needed to treat pathologies, amounts for treatment (not within physiological normal ranges).

- **Locations of Receptors:**

1) **On the membrane:** for water-soluble hormones, like peptides, growth hormone which is a protein, catecholamines (dopamine, epinephrine, norepinephrine)

They have second messenger mechanism

2) **In the cytoplasm or in the nucleus:** for lipid-soluble hormones

Eg) thyroxine receptors are found in the nucleus so the hormones act on the DNA to synthesize proteins like a) enzymes b) channels c) receptors (A,B,C are all proteins)

E.g; steroid receptors are found in the cytoplasm, the hormones bind to their receptors and then they are translocated to the nucleus to also work on the DNA for protein synthesis as well.

- ❖ The receptors for water-soluble (lipophobic) hormones are found on the membrane (the hormone cannot permeate the cell membrane).
- ❖ The receptors for lipid-soluble (lipophilic) hormones are found in the cytoplasm or in the nucleus (the hormone can permeate the cell membrane).

- **Mechanisms Of Hormone Action:**

Similarities in the structure give similarities in the receptors location and in the mechanisms of action. But not in the effect the hormones have on target cells/tissues.

Eg; the location of all water-soluble hormone receptors is on the cell membrane (second messenger mechanism)

Eg; the location of all lipid-soluble hormone receptors is either the cytoplasm or the nucleus (formation of proteins)

The limited number of receptors is responsible for saturation, and reaching the saturation is related to a matter of affinity, HOW COME?

AFFINITY AND SATURATION issues;

Affinity: (measure of sensitivity)

Affinity is K_m "the concentration of hormone at which the initial reaction rate is half max "

How sensitive the system is to the concentration of the hormone

(High affinity) when little amounts of the hormone stimulate the system

(Low affinity) when high levels of the hormone are needed to stimulate the system

Saturation: (measure of capacity)

When all the receptors are bound to hormones, and if the system is provided with more hormone molecules, they won't be used.

That means the affinity is responsible for reaching the saturation; high affinity means easily stimulated sys, faster binding to receptors then saturation is achieved faster.

RECEPTORS:

Specific membrane proteins which are able to recognize and bind to corresponding ligand molecules (signal molecules or hormones)

LIGAND:

A small molecule that binds specifically to a larger one. A substance that binds to its specific receptor.

- **Types Of Membrane Receptors:**

1) Ligand-gated ion channels:

Eg; acetylcholine

Ligand binds to its receptor which causes the permeability of ion channels to change either decrease or increase due to either opening or closing of these ion channels.

This type of receptor is called iono-tropic receptor. Iono-tropic is something different for contractility.

Ionotropic receptor is :ion channel coupled receptor

Action potential reaches the presynaptic neuron, the action potential opens slow voltage gated Ca^{++} channels, Ca^{++} enters the cell (down its electrochemical gradient), intracellular Ca^{++} causes fusion of the vesicles with the membrane and release of neurotransmitters, neurotransmitter (Acetylcholine) is released and binds to its receptors on the postsynaptic neuron, this binding leads to opening of Na^{+} voltage gated channels (changing the permeability of Na channels) then depolarization happens and action potential spreads.

Good Luck

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