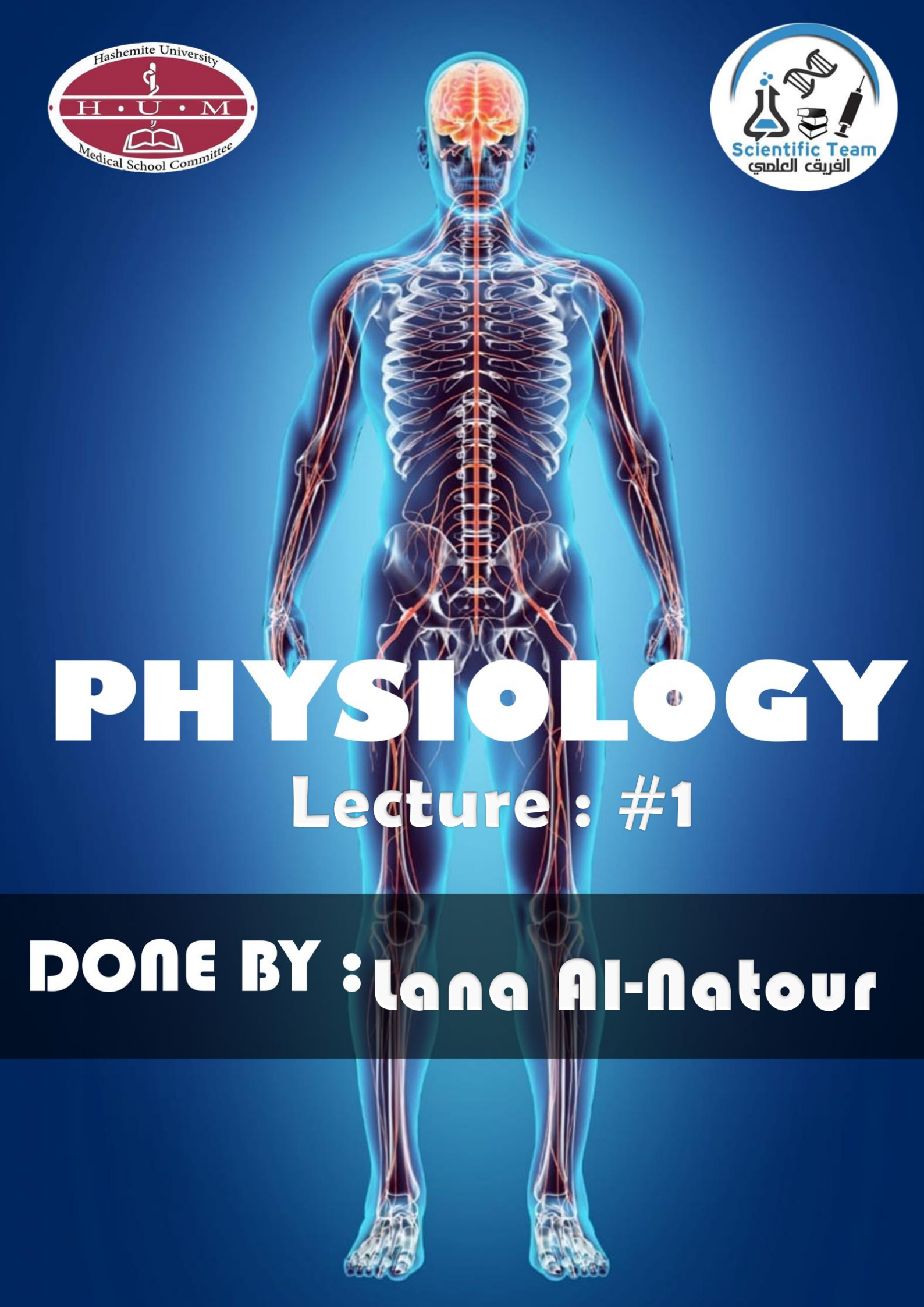


PHYSIOLOGY

Lecture : #1

DONE BY : Lana Al-Natour

General Principles of Endocrine Physiology

سلايدات الدكتور باللون الاسود وحكي الدكتور باللون الازرق وشرح خارجي باللون الاخضر

Control Systems of The Body's Nervous and Endocrine Systems

((differences between endocrine system and nervous system))

• The nervous and endocrine systems act together to coordinate all systems of the body.

• The nervous system releases neurotransmitters; the endocrine system releases hormones.

• Most hormones circulate through the blood some binds to plasma proteins and bind to receptors on "target cells." when released

• The action of nervous are rapid whereas the actions of the endocrine system are slower

• The hypothalamus and the pituitary gland coordinates the activity of both systems**(through hypothalomo-hypophyseal axis)**

Overview of the endocrine system functions

• Maintenance of internal environment

• Regulation of sodium and water balance and control of blood volume and pressure;

• Regulation of calcium and phosphate balance required for cell membrane integrity and intracellular signaling

• sexual and CNS differentiation in the fetus

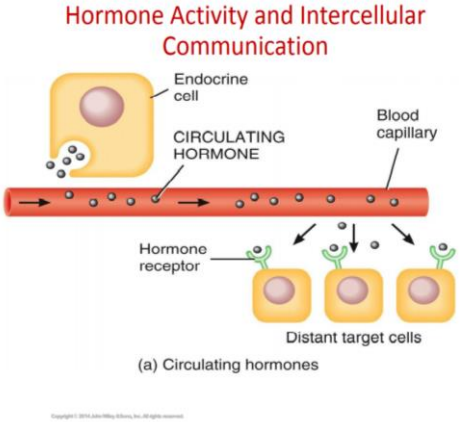
• Regulation of reproduction functions

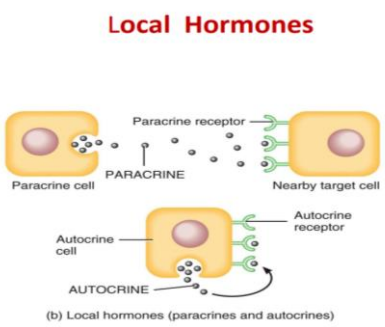
• Development and growth

• Adaptation to emergency and stress

• Regulation of energy balance and control of fuel mobilization, utilization

As we know hormones are chemicals which are released from endocrine glands to the blood ,and they are carried from the blood to the target cells and interact with specific receptors ..this type of hormones are called circulating hormomes





شرح د.ناجي:

Paracrine : when the hormone is released from the cell and affect the same tissue

Autocrine: when the hormone is released from the cell and affect the same cell

COORDINATION OF BODY FUNCTIONS BY CHEMICAL MESSENGERS

• Endocrine hormone hormones

• Neuroendocrine hormones.

• Paracrine are secreted by cells into the extracellular fluid and affect neighboring target cells of different types.

• Example :

• cytokine interleukin-1 in monocytes

• Neurotransmitters across synapses

• Estrogens produced in the ovaries are crucial for the maturation of ovarian follicles before

• Ovulation

• Testosterone in the testis

• Autocrine are secreted by cells into the extracellular fluid and affect the

function of the same cells that produced them.

• Cytokines are peptides secreted by cells into the extracellular fluid and can function as autocrine, paracrine, or endocrine hormones.

• Cytokines include the interleukins and other lymphokines that are secreted by T helper cells and act on other cells of the immune system

• Cytokine hormones (e.g., leptin) produced by adipocytes are sometimes

called adipokines

ملاحظة:هاد سلايد الدكتور ما قرأه بس هو عبارة عن معلومات عامة ومراجعة

class of hormones:

• Peptide & Protein Hormones

• Steroid Hormones

• Amine Hormones

• Eicosanoids

Chemical Nature of Hormones

• Amino acid derivatives such as dopamine, catecholamine, and thyroid hormones

• Small neuropeptides GnRH), (TRH), somatostatin, and vasopressin

• large proteins such as insulin, LH, and PTH produced by classic endocrine glands

• Steroid hormones such as cortisol and estrogen vitamin D that are synthesized from cholesterol-based precursors

• Eicosanoids such as leukotriene, lymphokines, prostaglandins and adipokines like leptin

Classification of hormones

Lipid-soluble Hormone

• steroid hormones, thyroid hormones.

• Lipid-soluble hormones circulate bound to transport proteins

Because they are lipid soluble ,they can't move freely in the plasma so that plasma protiens have high affinity for such types of hormones

• Receptors are Inside the cell, usually in nucleus

• Intracellular action stimulates synthesis of specific new proteins synthesized as needed

• Long half life Long (hours, days) due to affinity for protein carrier**(low rate of metabolic clearance)**

this type of hormones can easily penetrate the cell membrane so there receptors are located inside the cells so once the hormone binds with its specific receptor, a new proteins will be synthesized in order to give a response

Water-soluble hormones

• amine hormones, peptide and protein hormones, eicosanoid hormones).

• Act on membrane bound receptors **(because they can't cross the cell membrane)**

• stored in vesicle along with an enzyme that splits off the active hormone**(released by exocytosis)**

But the lipid soluble are excreted by fusion not by exocytosis

• Mostly dissolved in plasma (free, unbound)

• Short half life (**fast degradation**)

Peptide & Protein Hormones

Gland/Tissue	Hormones	Gland/Tissue	Hormones
Hypothalamus	• TRH, GnRH, CRH GHRH, Somatostatin,	Placenta	• HCG, HCS or HPL
Anterior pituitary	• ACTH, TSH, FSH, LH, PRL, GH	Kidney	• Renin
Posterior pituitary	• Oxytocin, ADH	Heart	• ANP
Thyroid	• Calcitonin	G.I. tract	• Gastrin, CCK, Secretin, GIP, Somatostatin, GLP-1
Pancreas	• Insulin,Glucagon, Somatostatin		
Liver	• Somatomedin C (IGF-1)	Adipocyte	• Leptin
Parathyroid	• PTH		

Peptide hormones are also classified into families as shown in the figure :

Peptide Hormone Families

Insulin Family	Glycoprotein Family	POMC Family
Insulin Insulinlike growth factor I (IGF-1, somatomedin C) Insulinlike growth factor II Relaxin	Lutenizing hormone (LH) Follicle-stimulating hormone (FSH) Thyroid-stimulating hormone (TSH) Chorionic gonadotropin (HCG)	Adrenocorticotropic hormone (ACTH) Melanocyte-stimulating hormone (MSH)

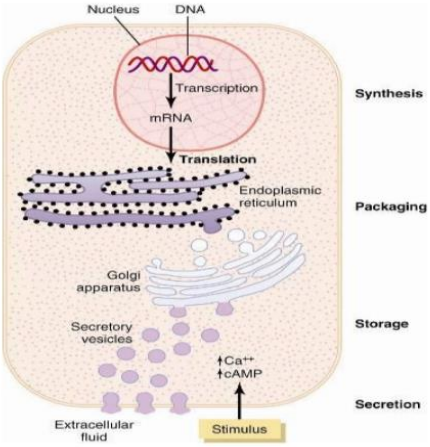
Secretin-Glucagon Family	Growth Hormone Family	Neurohypophyseal Family
Secretin Glucagon Gastrointestinal polypeptide Glicentin Gastric inhibitory polypeptide (GIP) Glucagon-like peptide 1 (GLP-1)	Growth hormone (GH) Prolactin (PRL) Chorionic somatomammotrophin (HCS) or Human placental lactogen (HPL)	Antidiuretic hormone (ADH) Oxytocin

This classification depends mainly on the site of the origin of each hormone for example: insulin like hormones because they have the same effect of insulin, neurohypophyseal hormones because they are released from neurohypophysis ,glycoprotein hormones because of their structure

((not important to memorize such classification but read it ☺))

Synthesis & Secretion of Peptide Hormones

The stimulus for hormone secretion often involves changes in intracellular calcium or changes in cyclic adenosine monophosphate (cAMP) in the cell



So let's say that this a pituitary gland that release thyroid stimulating hormone ..the hypothalamus will release TRH(thyroid releasing hormone),this hormone will bind to a specific receptor on the gland and induces transcription so that new proteins will be synthesized

(by MRNA → ribosomes → new proteins)

so these proteins (hormones)will be stored in vesicles inside the cells ,so that once the stimulus come the CAMP will be increased inside the cell and the calcium permeability increase in order to stimulate the release of such vesicles by exocytosis.

• They are usually synthesized first as larger proteins that are not biologically active (preprohormones)

• and are cleaved to form smaller prohormones in the endoplasmic reticulum.

• These prohormones are then transferred to the Golgi apparatus for packaging into secretory vesicles. In this process, enzymes in the vesicles cleave the prohormones to produce smaller, biologically active hormones and inactive fragments.

• The vesicles are stored within the cytoplasm, and many are bound to the cell membrane until their secretion is needed.

• Secretion of the hormones and the inactive fragments by exocytosis.

**Amine hormones (thyroid hormones, epinephrine, norepinephrine) are

derivatives of tyrosine

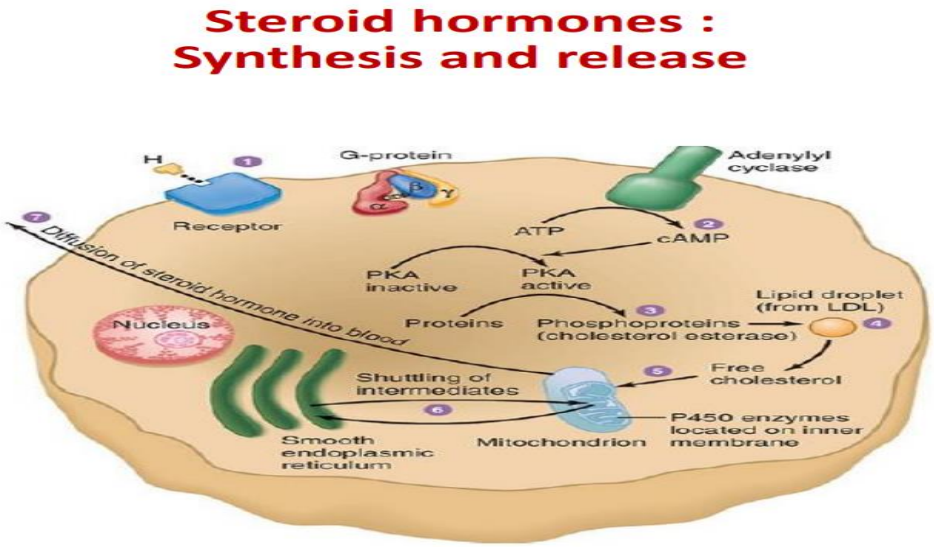
• NE and Epi are released by exocytosis

• Thyroid hormones are released by diffusion when the split from

Thyroglobulin **(thyroglobulin: is the other major component needed for synthesis of the thyroid hormones)**

Gland/Tissue	Hormones
Hypothalamus	• Dopamine
Thyroid	• T_3, T_4
Adrenal medulla	• NE, EPI

Synthesis and secretion of Steroid



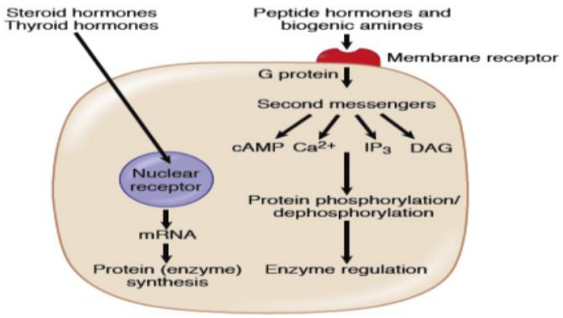
So let's say that this is a gland releases glucocorticoids ,this cell is usually stimulated by releasing ACTH (adrenocorticotropic hormone)so because ACTH is a peptide hormone it binds to G-protein coupled receptor ,this binding will lead to activate adenyl cyclase → ATP will be converted to CAMP → so the protein kinase will be activated and it will phosphorylate the cholesterol esterase → the cholesterol esterase will be activated and it will split the LDL to free cholesterol inside the cytoplasm → the cholesterol will enter to the mitochondria by P450 enzymes and there will be shuttling with the smooth endoplasmic reticulum → leading to synthesize cortisol and it will be released by diffusion.

Summary for steroid synthesis:

- Are Usually Synthesized From Cholesterol and are not stored.
- The chemical structure of steroid hormones is similar to that of cholesterol, and in most instances
- Although there is usually very little hormone storage in steroid producing endocrine cells
- large stores of cholesterol esters in cytoplasm vacuoles can be rapidly mobilized for steroid synthesis after a stimulus.
- Much of the cholesterol in steroid-producing cells comes from the plasma, but there is also de novo synthesis of cholesterol in steroid producing cells.
- Because the steroids are highly lipid soluble, once they are synthesized, they can simply diffuse across the cell membrane and enter the interstitial fluid and then the blood.

Hormonal signal transduction

so how hormones produce their effect and cause a change of the activity in the cell



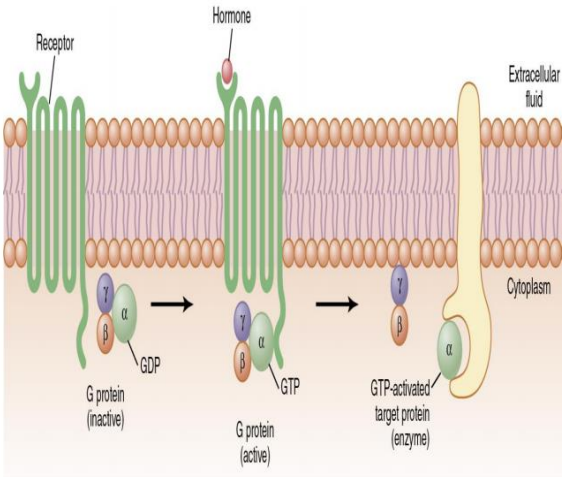
we have steroid hormones they can pass easily through the cell membrane and bind either to cytoplasmic receptor or nuclear receptor ,so they will eventually will change gene expression and lead to transcription (mRNA) ..this will synthesize new enzymes and proteins that will change the activity of these cell to induce a response.

But the other types of hormones (water - soulabe) they will bind to G-protein coupled receptor, so they don't act directly on protein synthesis ..at the time of binding may be the adynel cyclase will be activated converting ATP to CAMP(second messenger)this will eventually lead to phosphorylation for specific enzymes ..also maybe at the time of binding the phospholipase C will be activated leading to formation of 2 second messengers (IP3/DAG)..at the time of binding may be also lead to increase in entry of calcium then calcium will bind to calmodulin ,this complex will induce a change in the cell…

Mechanism of Hormone action

G Protein-Coupled Receptors

1.hormone activates the receptor.



Inactive α, β, and γ G protein

complex associates

(**when they are inactivated these subunits are bind to GDP)**

2.with the receptor and is activated, exchange of guanosine triphosphate

(GTP) for guanosine diphosphate (GDP).

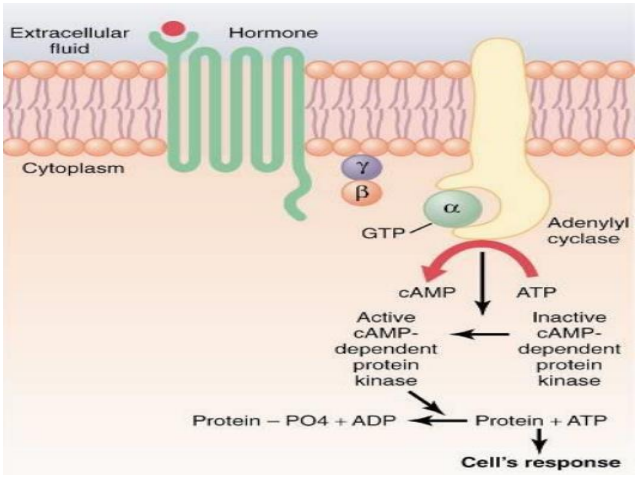
(so once the hormone is bound to G-protien receptor ,the receptor will be activated and GDP will be replace to GTP)

3. This process causes the α subunit (to which the GTP is bound) to dissociate from the β and γ subunits of the G protein and to interact with membrane bound target proteins (enzymes,

for example Adenyl cyclase) that initiate intracellular signals.**((by second messenger))**

cyclic adenosine monophosphate (CAMP) second messenger

Then adenyl cyclase will be activated converting ATP to CAMP this will activate CAMP dependent protein kinase which will phosphorylate specific enzymes and protiens to have the cell response ((by opening new channels /activation of other enzymes which might be necessary for such hormonal action)



intrinsic GTPase activity in the G protein converts GTP back to GDP, and the αs subunit returns to its inactive state.

So then alpha subunit will go back to other subunits in order to reunion to put the receptor back where it was,, all of the subunits will be together and inactivated.

Intracellular cAMP is degraded to an inactive metabolite, 5′ AMP, by the enzyme phosphodiesterase**(in order to get rid from CAMP)**

A QUICK VIDEO FOR REVISION ((ADYENYL CYCLASE PATHWAY)):

https://www.youtube.com/watch?v=dfUIhhTJhdY

Summary

G proteins coupled receptors properties

• Are guanosine triphosphate (GTP)-binding proteins that couple hormone receptors to adjacent effector molecules.

• For example, in the cyclic adenosine monophosphate (cAMP) second messenger system G proteins couple the hormone receptor to adenylate cyclase.

• The G protein couples the hormone to inositol 1,4,5-triphosphate (IP3) second messenger systems

• have intrinsic GTPase activity.

• have three subunits: α, β, and γ.

• The α subunit can bind either guanosine diphosphate (GDP) or GTP.

• When GDP is bound to the α subunit, the G protein is inactive. When GTP is bound, the G protein is active.

• G proteins can be either stimulatory (Gs) or inhibitory (Gi). **((depend on the action))**

Effects cAMP

• The specific action that occurs in response to increases or decreases of cAMP in each type of target cell depends on the nature of the intracellular machinery some cells

• Therefore, different functions are elicited in different target cells, such as

initiating synthesis of specific intracellular chemicals, causing

➢ muscle contraction or relaxation

➢ initiating secretion by the cells,

➢ altering cell permeability to ions

➢ Synthesis and secretion of hormones example thyroid

➢ increases water channels epithelial cells of the distal and collecting tubules of the kidney leading to permeability to water.**((ACTH))**

Hormones That Use the Adenylyl Cyclase–cAMP Second Messenger System

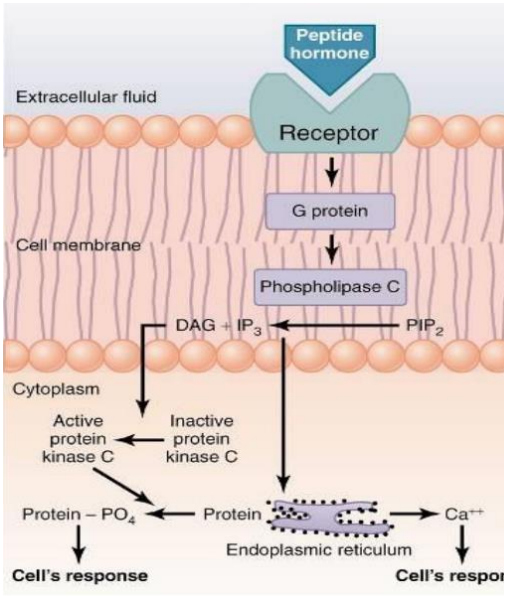
- **Adrenocorticotropic hormone (ACTH)**
- **Angiotensin II (epithelial cells)**
- **Calcitonin**
- **Catecholamines (β receptors)**
- **Corticotropin-releasing hormone (CRH)**
- **Follicle-stimulating hormone (FSH)**
- **Glucagon**
- **Growth hormone–releasing hormone (GHRH)**
- **Human chorionic gonadotropin (hCG)**
- **Luteinizing hormone (LH)**
- **Parathyroid hormone (PTH)**
- **Secretin**
- **Somatostatin**
- **Thyroid-stimulating hormone (TSH)**
- **Vasopressin (V2 receptor, epithelial cells in collecting duct of neoprene**

You don't have to memorize them now we will learn them through their specific mechanism ☺

Cell Membrane Phospholipid Second Messenger System

Phospholipase C attached to the inside projections of the receptors

This enzyme catalyzes the breakdown of phospholipids PIP2 phosphatidylinositol 4,5-Diphosphate



So once the hormone bind to it's specific receptor (coupled with G-protien) it will activate phospholipase C ((this enzyme will break down PIP2 and this will cause the formation of triphosphate IP3 and Diacyglecrol DAG))

IP3 will cause release of calcium from endoplasmic reticulum

Also IP3 and DAG will activate the protien kinase C and cause phosphorylation of protein

Summary IP3 mechanism

• Hormone binds to a receptor in the cell membrane and, via a G protein activates phospholipase C

• Phospholipase C liberates diacylglycerol and IP3 from membrane lipids

• IP3 mobilizes Ca2+ from the endoplasmic reticulum

• Together, Ca2+ and diacylglycerol activate protein kinase , which phosphorylates proteins and causes specific physiologic actions

• Lipid portion of DAG is arachidonic acid, which is the precursor for the prostaglandins and other local hormones that cause multiple effects in tissues throughout the body.

A QUICK VIDEO REVION ((IP3 PATHWAY)):

https://www.youtube.com/watch?v=2bbBrpgeheY

Hormones That Use the Phospholipase C Second Messenger System

- **Angiotensin II (vascular smooth muscle)**
- **Catecholamines (α receptors)**
- **Gonadotropin-releasing hormone (GnRH)**
- **Parathyroid hormone (PTH)**
- **Oxytocin**
- **Thyrotropin-releasing hormone (TRH)**
- **Vasopressin (V1 receptor, vascular smooth muscle)**

Hormones That Use the guanylate cyclase

Second Messenger System cGMP

• Atrial natriuretic peptide (ANP) **(lowering blood pressure)**

• Nitric oxide **(vasodilator)**

Some hormones acted through cGMP instead of CAMP ,so the second messenger is fomed by conversion of GTP

Brs :

Atrial natriuretic peptide (ANP) acts through receptor guanylyl cyclase, Activation of guanylyl cyclase converts GTP to cyclic GMP, which is the second messenger

Nitric oxide (NO) acts through cytosolic guanylyl cyclase. Activation of guanylyl cyclase converts GTP to cyclic GMP, which is the second messenger.

Ca calmodulin system

It's other type of second messenger

• Intracellular calcium ion (Ca++) concentration increases by :

So the hormone binds to it's receptor and increase the intercellular calcium concentrations with 2 ways:

• when Ca++ enters the cell through calcium channels in the cell membrane

• released from the sarcoplasmic reticulum.

• **The Ca++ binds to (CaM) to form a Ca++-CaM complex, which then activates myosin light chain kinase (MLCK).CaM:calmodulin**

• **The active MLCK phosphorylates the myosin light chain leading to attachment of the myosin head with the actin filament and contraction of the smooth muscle.**

A QUICK VIDEO REVESION ((CA-CALMODULIN)):

https://www.youtube.com/watch?v=VMVdVnDX5jM

**احضروا الفيديو لعند دقيقة 1:17باقي الفيديو تفاصيل contraction مش مهمة حاليا

(Receptor Tyrosine Kinase Signaling)

Tyrosine Kinases receptors **with2 types:**

• **Receptor tyrosine kinases have intrinsic tyrosine kinase** activity within the receptor molecule.

So when hormone binds to the receptor ,the tyrosine kinase will phosphorylate …

• **Tyrosine kinase associated receptors do not have intrinsic tyrosine kinase activity but associate noncovalently with proteins** known as associated Janus kinase (JAK) which have tyrosine kinase activity

When the hormone binds to this receptor, JAK will be activated and have the tyrosine kinase,the tyrosine kinase will be activated

Receptor tyrosine kinases

We have different structures with different shapes of tyrosine kinase

• One type of receptor tyrosine kinase is a monomer(e.g., nerve growth factor [NGF] and epidermal growth factor receptors,).

• In this monomeric type, binding of ligand to the extracellular domain results in dimerization of the receptor,

• activation of intrinsic tyrosine kinase, and phosphorylation of tyrosine moieties on itself and other proteins, leading to its physiologic actions.

• Another type of receptor tyrosine kinase is already a dimer (e.g., insulin and insulin-like growth factor [IGF] receptors binding of the ligand (e.g., insulin) activates intrinsic tyrosine kinase and leads to phosphorylation of itself and other proteins and ultimately the hormone's physiologic actions.

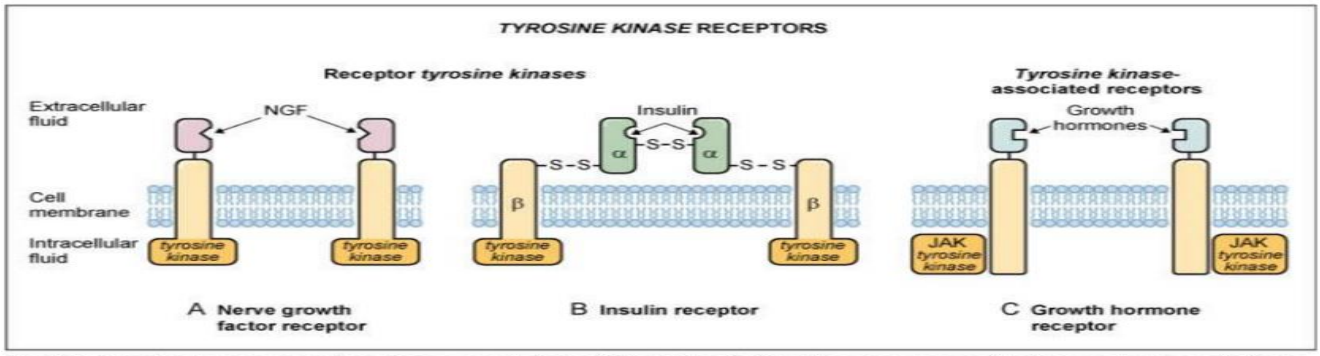


Fig. 9-6. **Tyrosine kinase receptors.** Nerve growth factor **(A)** and insulin **(B)** utilize receptor tyrosine kinases that have intrinsic tyrosine kinase activity. Growth hormone **(C)** utilizes a tyrosine kinase–associated receptor. NGF, nerve growth factor; JAK, Janus family of receptor-associated tyrosine kinase.

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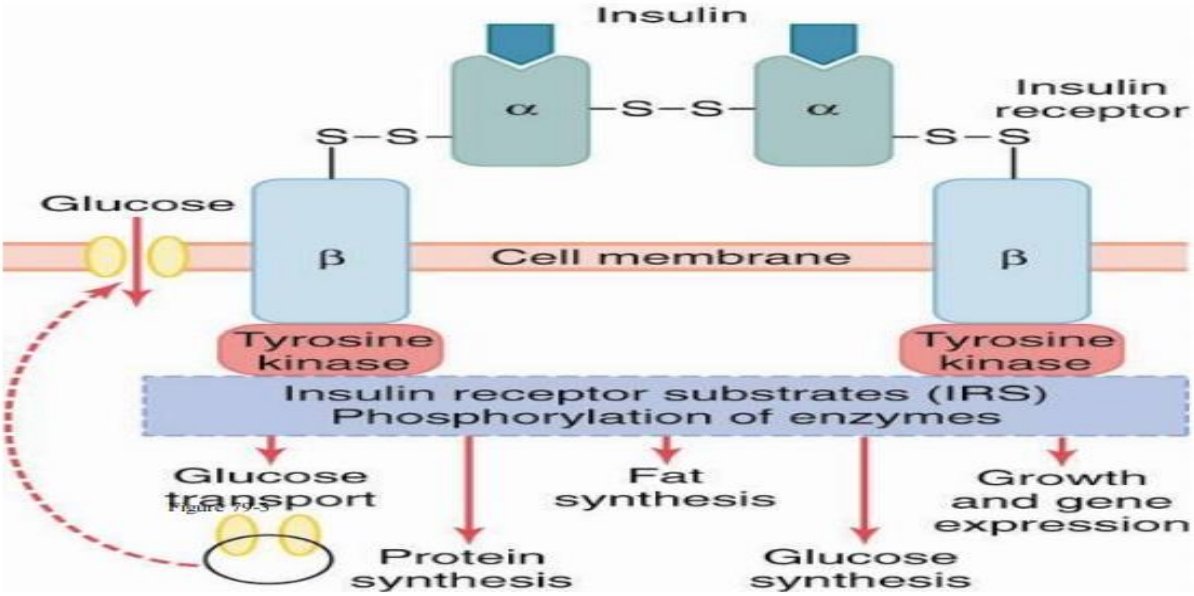
As shown in figure A :the receptor has it's tyrosine activity so when NGF binds this receptor will be activated, and it will activate the tyrosine activity

Figure B:the other type is dimer because 2 monomers connected together ,so once insulin binds it will lead to insulin action after phosphorylation of some enzymes

Figure c: in this receptor there is no enzymatic activity within the receptor, but it is non-covalently binding to JAK ,so when you have growth hormone this bind will activate JAK this will to phosphorylation of other proteins ((because of it's intrinsic tyrosine activity))

The Insulin Receptor & Mechanisms of Insulin



Insulin will bind to it's receptor which has tyrosine kinase activity within it ,so when the receptor is activated this will lead to phosphorylation of some enzymes ,this phosphorylation will induce fat synthesis /growth and gene expression..also it cause formation of glucose transporter which they are very important for the entry of glucose inside the cells

Tyrosine kinase-associated receptors (e.g., growth hormone receptors)

• The intracellular domain of the receptor domain does not have tyrosine kinase activity

• is noncovalently "associated" with tyrosine kinase such as those in the Janus kinase family (JAK Janus family of receptor-associated tyrosine kinase, or "just another kinase").),

• Hormone binds to the extracellular domain, leading to receptor dimerization and activation of tyrosine kinase in the associated protein (e.g., JAK).

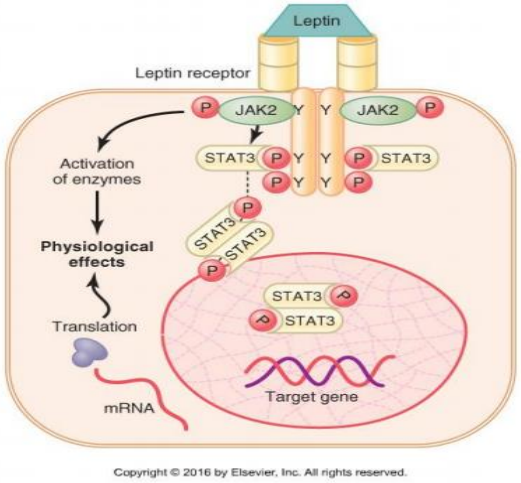
• The associated tyrosine kinase phosphorrylates tyrosine moieties on itself, the hormone receptor, and other proteins.

• Downstream targets of JAK include members of the STAT (signal transducers and activators of transcription) family, which cause transcription of mRNAs and ultimately new proteins involved in the hormone's physiologic actions.

An enzyme-linked receptor—the leptin receptor.

Google :

Leptin is a hormone released from fat cells in adipose tissue. Leptin does not affect food intake from meal to meal but, instead, acts to alter food intake and control energy expenditure over the long term.



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The receptor exists as a homodimer (two identical parts), and leptin binds to the extracellular part of the receptor, causing phosphorylation (P) and activation of the intracellular associated Janus kinase 2 (JAK2). This mechanism causes phosphorylation of signal transducer and activator of transcription (STAT) proteins, which then activates the transcription of target genes and the synthesis of proteins

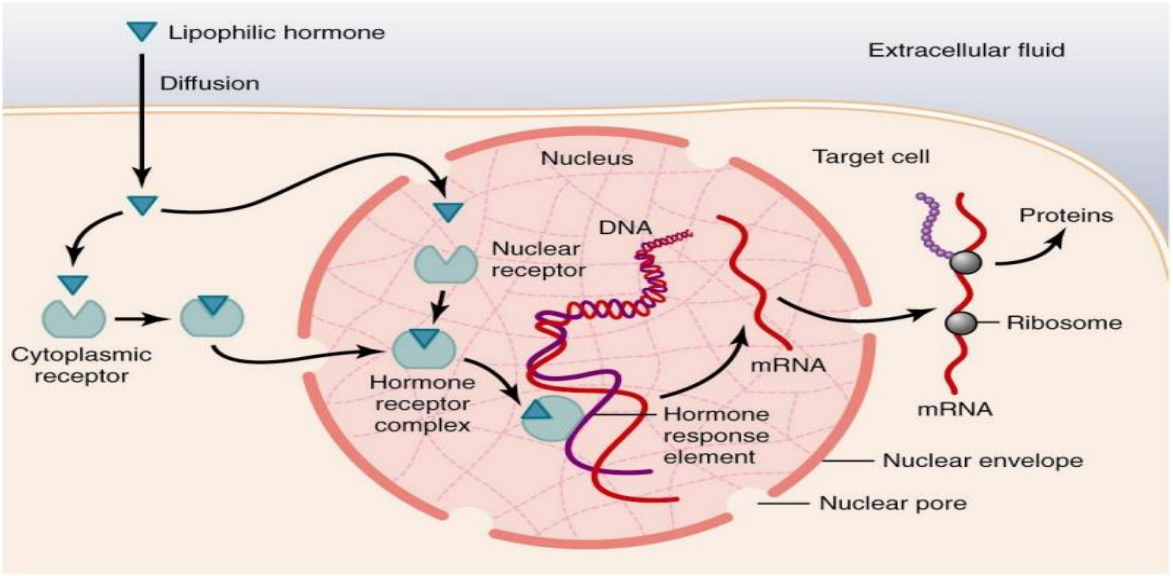
When the leptin binds to their specific receptors ,JAK will be activated (they have intrinsic tyrosine kinase activity) they will directly activate other enzymes needed for the action of leptin or the binding will activate STAT3(signal transducer and activator of transcription)this will lead to transcription and protien synthesis lead to a response

Summarization:we can see in the figure that this type of receptor doesn't have intrinsic tyrosine activity ,however it is linked non-covalently to JAK ,so when the hormone binds to the receptor JAK kinases will be activated

Hormones That Use Receptor Tyrosine Kinase Signaling

- **Growth hormone**
- **Insulin**
- **Insulin-like growth factor-1**
- **Leptin**
- **Prolactin**

Steroid & Thyroid Hormones - Mechanism of Action



Steroid hormones can cross steroid hormones easily by diffusion ,so when the hormone binds to cytoplasmic receptor ..this complex will penetrate the nuclear membrane and bind to the hormone response element on the DNA will respond to the complex action → mRNA will be formed → proteins → the metabolic changes will occur and enzyme activation for the action that is needed for the hormone

Intracellular Hormone Receptors and Activation of Genes.

Steroid hormone mechanism of action

• Steroid (or thyroid) hormone diffuses across the cell membrane and binds to its receptor

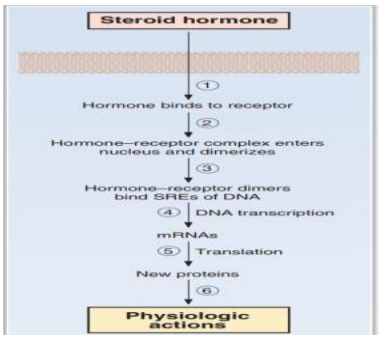
• The hormone–receptor complex enters the nucleus and dimerizes (step 2).

• The hormone–receptor dimers are transcription factors that bind to steroid-responsive elements (SREs) of DNA and initiate DNA transcription

• New messenger RNA is produced, leaves the nucleus, and is translated to synthesize new proteins

• The new proteins that are synthesized have specific physiologic actions.

• For example, Aldosterone**(steroidal hormone)** induces the synthesis of Na+ channels in the renal principal cells and thus increases Na reabsorption



A figure from BRS not from slides

(Summarization for steroid hormone action)

Control of hormone secretion

• Feedback Mechanisms**(regulate hypothalamus –pituitary gland axis)**

• Hormonal Rhythms**((circadian rhythms))((some hormones are high during night and other are high during the day))**

And this circadian rhythm is effected by suprachiasmatic nucleus

• Product mechanism

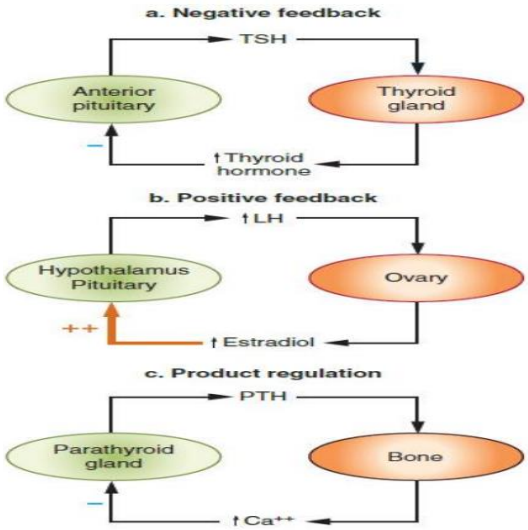
((the increase of the concentration of one substance will inhibit the hormone release))

Figure A: negative feedback ,let's see that anterior pituitary gland releases TSH ,TSH will activate thyroid hormone release so when thyroid hormone is elevated ,it inhibits the anterior pituitary gland to release TSH and thyroid hormone will decline.

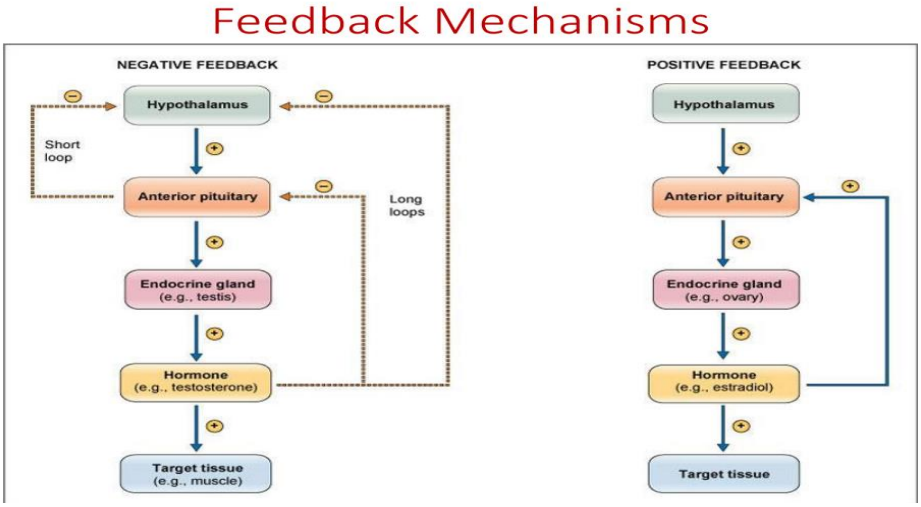
Figure B:positive feedback is not common, the release of one hormone will increase the activity of other hormone ..for example :when LH is released from pituitary ,it stimulates the ovary to release estradiol (estrogen) and increase the activity of pituitary to release LH ..

This type of feedback occurs during menstrual cycle prior to the day of ovulation because high estrogen is needed for the process of ovulation

Figure C : product mechanism, for example when the calcium ions are low, the parathyroid hormone will go to the bone and cause resorption of calcium ions (release of calcium ions from bones in order to increase calcium ions levels) so once the calcium ions is increased ,parathyroid gland activity of releasing PTH will be inhibited



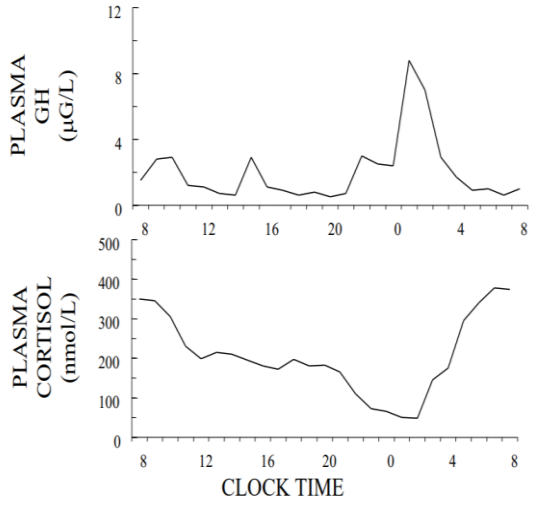
الفرق بين product feedback و negative feedback انه product feedback بكون عبارة عن(product (substance و negativefeedback بكون عبارة عن هرمون



So as we see in the negative feedback once the testosterone is increased it will inhibit the pituitary gland activity in releasing FSH and LH and possible that testosterone will inhibit the release of GNRH from the hypothalamus (long loops)//short loop:when FSH,LH inhibit the release of GNRH from hypothalamus

Menstrual cycle in the female before ovulation is a good example for positive feedback ,the hypothalamus will secrete GNRH and stimulate the pituitary gland to release FSH and LH to stimulate releasing of estradiol from the ovary so high levels of this hormone will increase the activity for anterior pituitary gland to release FSH and LH and we will have more estrogen levels ((in the middle of menstrual cycle))before one day of ovulation because it is important for the process of ovulation

The same positive feedback mechanism happens during labor so when the head of the baby get down ,dilatation of cervix send signals to the hypothalamus to release oxytocin for the process to be completed



Hormone rhythms

measuring different hormone levels at different times of the day

so GH when we go to sleep(at 12) hormone level starts to increase until it reaches it's peak at 3 or 4 o'clock and starts to decline

in cortisol release they start to be in high levels at 8 and start to decline and they are lowest at midnight and increase higher in early morning

Patterns of hormone release.(summary for the previous charts)

Plasma hormone concentrations fluctuate throughout the day.

• Plasma hormone measurements do not always reflect the function of a given endocrine system.

• Both cortisol and growth hormone show considerable variations in blood levels throughout the day.

• These levels can also be affected by sleep deprivation, light, stress, and disease, night work, sleep patterns

• Levels of hormones are dependent on their secretion rate, rates of metabolism and excretion, metabolic clearance rate, circadian pattern, fluctuating environmental stimuli

Regulation of hormones receptors and responsiveness of target tissue hormones

• Responsiveness **((how the response is after the hormone binds to it's target tissue))**

• is expressed in the dose-response relationship in which the magnitude of response is correlated with hormone concentration.

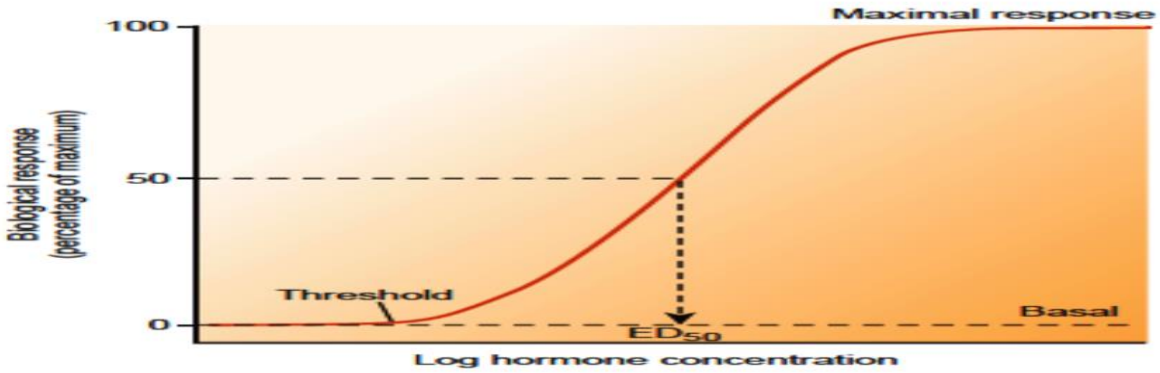
• As the hormone concentration increases, the response usually increases and then levels off.

• Sensitivity is defined as the hormone concentration that produces 50% of the maximal response.

• If more hormone is required to produce 50% of the maximal response, then there has been a decrease in sensitivity of the target tissue.

• If less hormone is required, there has been an increase in sensitivity of the target tissue

Dose response curve of hormone action



We are measuring hormone concentration to the response of the cell ,so we the hormone concentration increases the response of the cell will be increased until it reaches it maximum

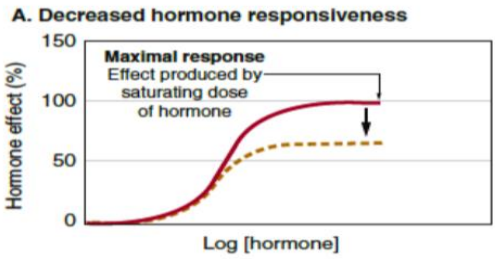
ED50: is defined as the concentration of the hormone in which it is needed to produce the the 50% of the response

A Hormone responsiveness.

• Decreased responsiveness to hormone effects and can be due decreased number of hormone receptors

• decreased number of target cells.

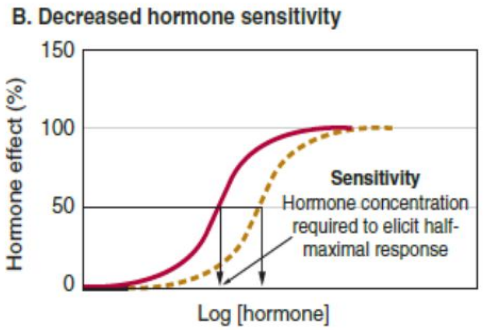
• When responsiveness is decreased, then no matter how high the hormone concentration is, a maximal response will not be achieved



Hormone concentration will not change theresponse

Hormone sensitivity.

• A decrease in hormone sensitivity requires higher hormone concentrations to produce 50% of the maximal response. **so it depends on the hormone concentration**



• Decreased sensitivity can be due to:

- decreased hormone–receptor affinity
  - Decreased hormone– receptor number
  - Hormone receptor resistance

Resistance to hormone action

• Abnormalities in receptors or events distal to the ligand-receptor interaction, often due to chronic elevation of circulating hormone (e.g., type II diabetes) or drug therapy.

In diabetes type 2 means that there is hormone(insulin) resistance that don't respond well to the action of this hormone

• Receptors are often saturated.**((the responsiveness are not good but the receptor is there))**

Permissive action

A phenomenon in which one type of hormone must be present before another hormone can act; for example,

1- cortisol must be present for glucagon to carry out gluconeogenesis and prevent hypoglycemia.

2-Thyroxine increases responsiveness to catecholamines**(because thyroxine helps in forming beta adreginc receptors in the heart)**

Regulation of receptors

■ Hormones determine the sensitivity of the target tissue by regulating the number or sensitivity of receptors.

The number of the receptors will change ..

Down-regulation of receptors

▪ A hormone decreases the number or affinity of receptors for itself or for another hormone.

▪ Is a mechanism in which a hormone decreases the number or affinity of its receptors in a target tissue.

▪ The purpose of down-regulation is to reduce the sensitivity of the target tissue when hormone levels are high for an extended period **((to prevent the excessive effect of such hormone after elevation))examples:**

1- in the uterus, progesterone down-regulates its own receptor and the receptor for estrogen**((during pregnancy))**

2- T4 or T3, decreases the sensitivity of thyrotropin-releasing hormone (TRH) receptors in the anterior pituitary.

Mechanisms of down regulation

• inactivation of some of the receptor molecules

• inactivation of some of the intracellular protein signaling molecules

• degradation of the receptors by lysosomes after they are internalized;

• Decreased synthesis of new receptors.

Up-regulation of receptors

▪ a hormone increases the number or affinity of its receptors or for another hormone .

▪ Up-regulation may occur by:

• increasing synthesis of new receptors

• decreasing degradation of existing receptors

▪ **Examples** :

1. In the ovary, estrogen up-regulates its own receptor and the receptor forLH
2. prolactin increases the number of its receptors in the breast
3. growth hormone increases the number of its receptors in skeletal muscle and liver
4. estrogen increases the number of its receptors in the uterus.

Metabolic clearance rate of hormones:

This rate reflects how fast the hormone is eliminated from the blood

Clearance: is how much the plasma is cleared from a particular hormone per unit time

They take radioactive hormone at a concentrate till the radioactivity reach steady state, they take an blood sample and measure the concentration of the hormone by radioimmunoassay ((the details is not important))

Rate of disappearance of hormone from the plasma

(nanograms per minute) /Concentration of hormone (nanograms per milliliter of plasma)

Ways of hormone clearance from plasma

• metabolic destruction by the tissues : Endocytosis of hormone receptor complex into the cell and metabolization of the complex usually receptors are recycled

• excretion by the liver into the bile, and

• excretion by the kidneys into the urine.

• The rate of clearance of water-soluble molecules is faster than hormones bound to plasma proteins

• The rate of steroid hormones is decreased and their levels in blood increase when the liver is diseased because these hormones are conjugated mainly in the liver and then "cleared" into bile

Hormonal transport

• Dissolved in plasma **((freely))**

• Bound to plasma proteins:

Transport Protein	Principle Hormone Transported
Specific	
Corticosteroid binding globulin (CBG, transcortin)	Cortisol, aldosterone
Thyroxine binding globulin (TBG)	Thyroxine, triiodothyronine
Sex hormone-binding globulin (SHBG)	Testosterone, estrogen
Nonspecific	
Albumin	Most steroids, thyroxine, triiodothyronine
Transthyretin (prealbumin)	Thyroxine, some steroids

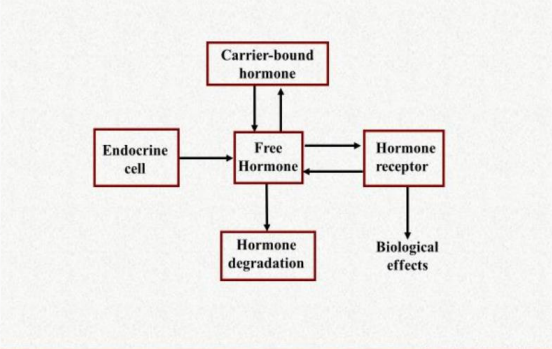
The bound hormone has low metabolic clearance and high half life while freely hormone has high metabolic rate and low half life

As shown here we are comparing the bound hormone with freely hormone in(protien binding/half life/metabolic clearnance)

Hormones with Degree of Protein Binding

Hormone	Protein binding (%)	Plasma half-life	Metabolic clearance (ml/minute)
Thyroid			
Thyroxine	99.97	6 days	0.7
Triiodothyronine	99.7	1 day	18
Steroids			
Cortisol	94	100 min	140
Testosterone	89	85 min	860
Aldosterone	15	25 min	1100
Proteins			
Thyrotropin	little	50 min	50
Insulin	little	8 min	800
Antidiuretic hormone	little	8 min	600

The relationship between hormone secretion, carrier protein binding, and hormone degradation.



Measurement of Hormone Levels(tests for endocrine disorders)

Plasma analysis

• Provides information at the time of sampling only and may not reflect the overall secretion rate(**the best time that you have to do it one time in the morning and one time in the evening because there is hormone fluctuation for example like glucocorticosteriods)**

• When hormone secretion is episodic (pulsatile), a single sampling may reflect peaks (erroneous hyperfunction) or nadirs (erroneous hypofunction).

• Pulsatile secretion, diurnal and cyclic variation, age, sleep entrainment, and hormone antagonism must all be considered in evaluating circulating levels.

• Growth hormone is secreted in pulses and mainly at night. Such peak is not observed or reflected a fasting morning sample.

• However, growth hormone stimulates the secretion of IGF-I which circulates attached to protein and has a long half-life (20 hours). Plasma IGF-I measured at any time during the day is usually a good index of overall growth hormone secretion.

• Thyroid is a fairly constant system (no pulsatile) release and T4 has a half-life of about 6–7 days. Thus, a random measurement of total T4 is usually a good estimate of daily plasma levels.**((can be measured at any time))**

Urine analysis

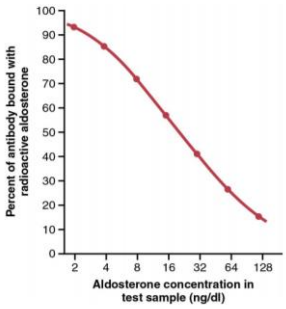
• **Restricted to the measurement of catecholamines , steroid hormones (Cortisol for example) , and water-soluble hormones such as hCG((during preganancy)) and LH.**

• A distinct advantage of urine analysis is that it provides anintegrated sample.

• – A "24-hour urine free cortisol" is often necessary to pickup a low-level in Cushing's syndrome and to eliminate the highs and lows of the normal circadian rhythm.

• Please note steroid levels can be estimated in blood as well

Principles of Radioimmunoassay

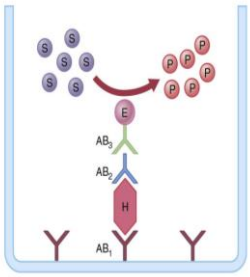


They bring specific Antibody for specific hormone and mix it with radioactive hormone standard hormone .. ((radioactive hormone standard hormone will compete with antibody))

they will take a plasma sample so if the radioactivity is high means that we have little hormone levels and then radioactivity declined because hormones bind to their specific antibodies

((not important the doctor said☺))

Principles of the ELISA
(Enzyme-Linked Immunosorbent Assay)



Here we have to bring antibodies for the antibodies of a specific hormone and some substrates ,we have to mix it together until there is a change of the color and the amount of dye

DISORDERS OF THE ENDOCRINE SYSTEM

Primary versus Secondary Disorders

• A primary disorder

means **dysfunction originating in the endocrine gland itself, ither hyper- or hypo-function.**

Examples of a primary disorder include:

▪ excess cortisol from an adrenal adenoma (Conn's disease)

▪ pheochromocytoma**((excess epinephrine and noreepipherine//tumor of adrenal gland))**

▪ decreased thyroid secretion (Hashimoto's thyroiditis)

▪ reduced ADH secretion (central diabetes insipidus)

• A secondary disorder

• indicates that **a disturbance is secondary to diseases of other organs causing the gland to secrete more or less of the hormone.(like in pituitary gland or any other organ)**

• Examples of a secondary disorder :

• hyperparathyroidism that develops in chronic renal failure**(because of low calcium ions)**

• Cushing disease (pituitary adenoma secreting ACTH) resulting in hypercortisolism

• SIADH: ectopic secretion of ADH by tumors cancers

• Secondary adrenal insufficiency is adrenal hypofunction dueto a lack of adrenocorticotropic hormone (ACTH)

• Pituitary hypothyroidism

Suppression and stimulating test**(help us in diagnose the abnormalities of endocrine system)**

Suppression tests :

usually used to test hyperfunctions

• Failure of glucose to suppress growth hormone diagnostic for acromegaly**((because if you give glucose the GH will be low but a patient in acromegaly after giving him GLUCOSE the GH is still high))**

• Overnight Dexamethasone Suppression Test :

• Failure of dexamethasone (low dose) to suppress cortisol diagnostic for hypercortisolism

If the levels of cortisol can't get normal after giving dexamethasone it means that there is hyepercorticolism

Stimulating tests :

usually used to test hypofunction

• Hypothalamic hormones test anterior pituitary reserve

• Injection of the pituitary trophic hormone (e.g., ACTH) tests target gland reserve.

• Failure of growth hormone release after arginine injection

Hypofunction

• Can be caused by autoimmune disease (Hashimotothyroiditis)

• primary adrenal insufficiency

• gonadal failure, hemorrhage,

• Infection

• damage by neoplasms

• Evaluated by a stimulation test

• Hypothalamic hormones test anterior pituitary

• Injection of the pituitary trophic hormone (e.g., ACTH) tests target gland reserve.

• Failure of growth hormone release after arginine injection

Hyperfunction

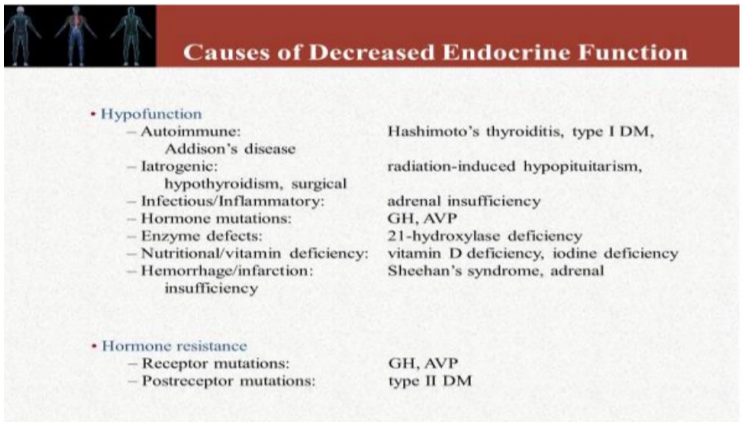
• Caused by hormone-secreting tumors, hyperplasia,autoimmune stimulation, ectopically produced peptide hormones (e.g., ACTH)

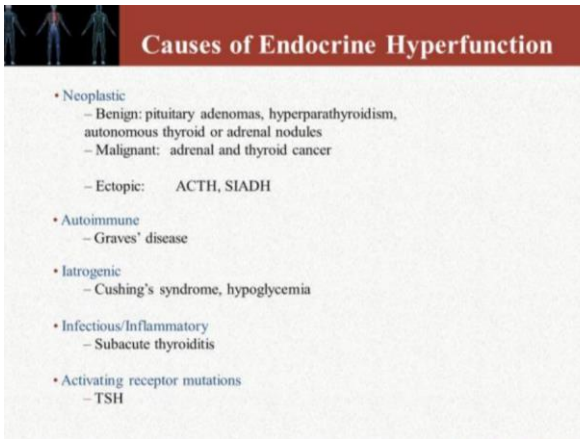
• Evaluated by a suppression test

• Multiple endocrine neoplasia

• hyperparathyroidism, endocrine pancreas, and pituitary Adenomas

• medullary carcinoma of the thyroid, pheochromocytoma,





GOOD LUCK HOPE ☺