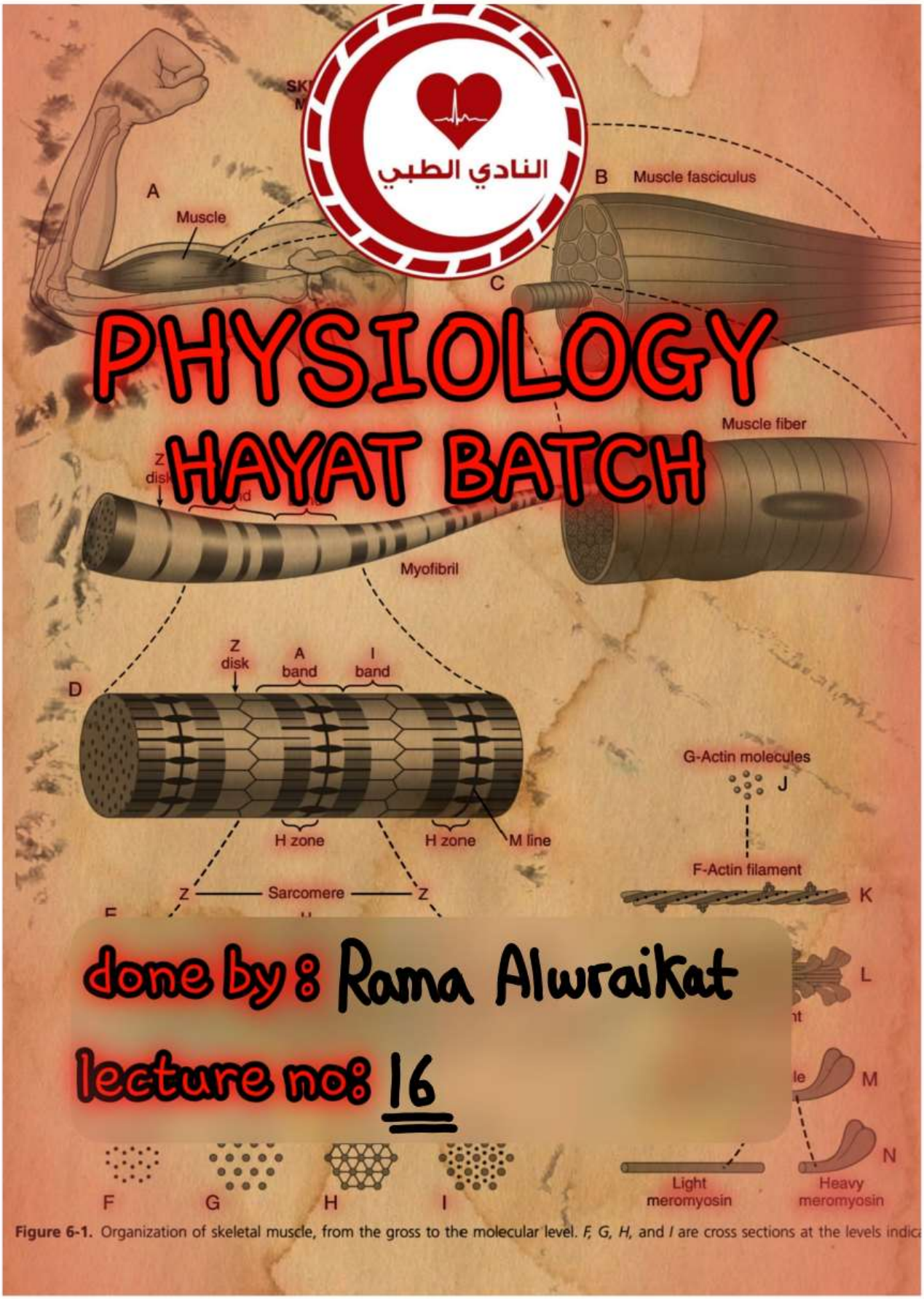


Figure 6-1. Organization of skeletal muscle, from the gross to the molecular level. *F, G, H,* and *I* are cross sections at the levels indica

Intercellular Communication

Physiology Lecture 16

Dr. Waleed R. Ezzat

Lecture Objectives:

- Understand how neural and endocrine integrate to maintain homeostasis.
- Recognize extra cellular regulators: nervous, endocrine, paracrine, autocrine.
- Compare and contrast autocrine, paracrine, and endocrine signaling in the control of cell function.
- Differentiate chemical nature of hormones.
- Explain how the electrical components of the nervous system and the chemical components of the endocrine system work together to influence body function.

Introduction: Communication and Signaling Modes

طرق التخاطب والتواصل بين الخلايا

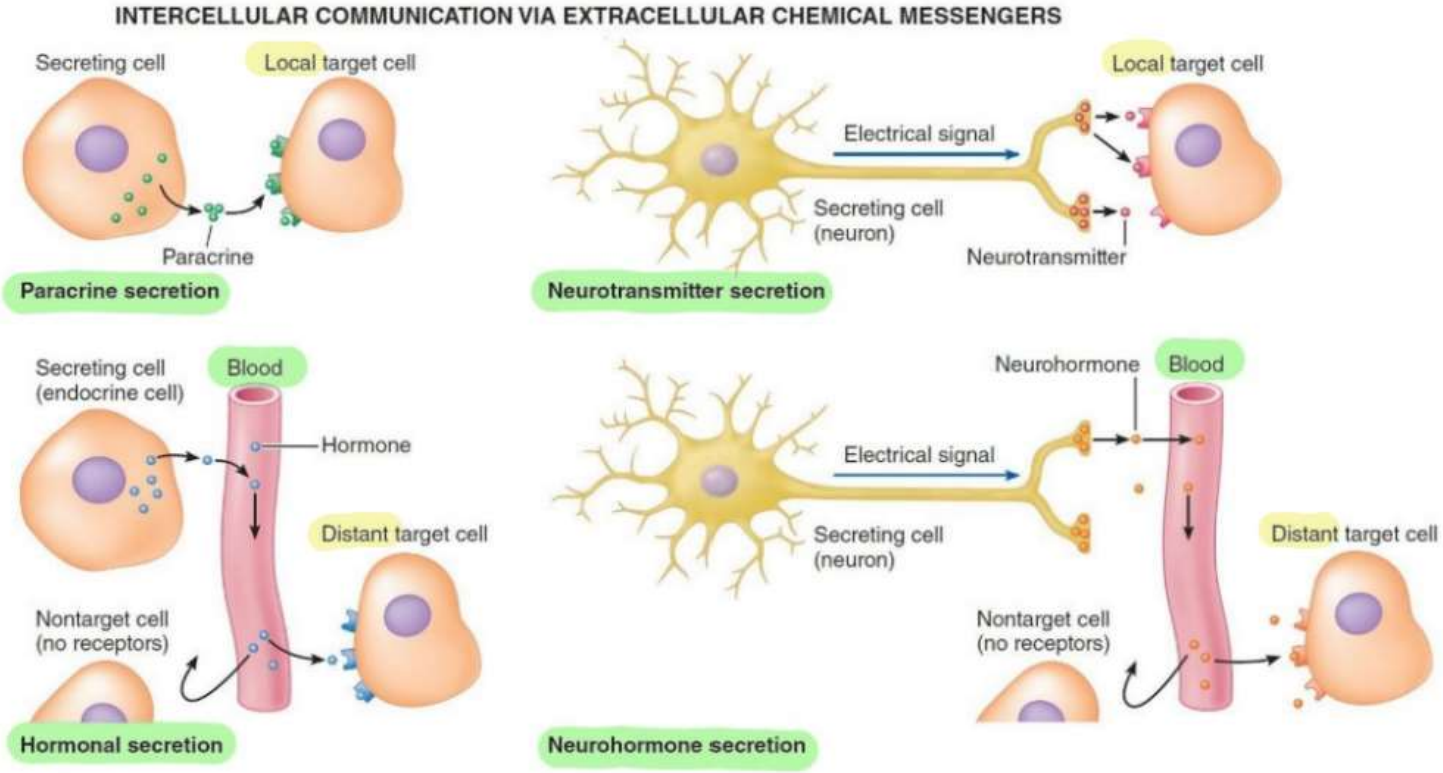
The human body has several means of transmitting information between cells.

These mechanisms include:

A. Direct communication between adjacent cells
B. Autocrine and paracrine signaling
C. The release of neurotransmitters and hormones produced by nerves and endocrine cells

A+B حسب الموقع

حسب الزمن



Types of intercellular communication.
Paracrines, neurotransmitters, hormones, and neurohormones are all extracellular chemical messengers that accomplish indirect communication between cells. These chemical messengers differ in their source and the distance they travel to reach their target cells.

Target Cells —have→ receptors
Nontarget Cells ⟶ noreceptors

A. Direct communication between adjacent cells:

خليتين متجاورات بينهم gap junctions (فتحات) وهي سهلة وما فيها تعقيد

B. Autocrine & paracrine signaling

هنا الحزيئات تكون كبيرة وتطلع من الخلايا عن طريق عملية exocitosis بواسطة Vesicles إلى ECF وممكن المادة تطلع برا الخلية وما زالت تأثر بالخلية نفسها بسبب Negative feedback mechanism

Autocrine ← الخلية تكرف تركيز المادة اللي طلعت منها (إذا مساوي للمطلوب أو أقل من اللازم أو أكثر) إذا كان أكثر ترجع المادة ترتبط بـ receptor على سطح الخلية نفسها

Paracrine ← الخلية تطلعه مادة لخلايا قريبة منها والمسافة بينهم قليلة لكنهم ليس متلاصقين الجار بالجار وتركيز هذه المادة شبه معدوم لأنها تعمل فقط في المنطقة ولا تذهب إلى الدم

↓

ما في بينهم gap junctions

C. The release of neurotransmitters & Hormones by nerves & endocrine cells

هنا خليتين مختلفتان بيتواصلوا مع بعض متلاً خلية في الدماغ وخلية في الرجل

Neurons ← يكون لها امتداد وهو المحور Axon فمتلاً تكون على كتير الدماغ وتمتد متر إلى متر وبنهن. داخل Axon يوجد Cyctoplasm نفس الموجود داخل الخلية. يحدث على سطح الخلية Action Potential حتى تنهل إلى نهاية Axon وهنا تكون موجودة Vesicles تحمل neurotransmitters وتبدأ تتحرك عند وصول Action Potential الأن قبل نهاية Axon يوجد electrical channels للكالسيوم Threshold: -40 mV

Resting membrane potential يختلف المنطقة في
- Skeletal / cardiac muscles → -90 mV
- Brain / Spinal cord → -70 mV

RMP = -70 mV إذاً قبل وصول Action Potential لنهاية Axon يكون
عند وصوله تحدث Depolarization فيدخل Na^+ عن طريق Voltage gated channels

عند (-60 إلى -55 mV) وتبدأ السالبية تقل وعندما يصل إلى -40mV
تنفتح بوابات الكالسيوم Ca^{+2} عن طريق أيضاً Voltage gated channels
الآن تتحرك Vesicles وتلتحم مع نهاية Axon وتنفجر وتطلق محتوياتها إلى سطح الخلية المجاور

من	إلى	
Neuron	Neuron ⇒	Synapse المنطقة بينهم تسمى
Neuron	Skeletal Muscle ⇒	Neuromuscular junction المنطقة بينهم تسمى

* Action Potential سريع تصل سرعته إلى (50m/s) والذي يحدده عاملان
- Myelin Sheath
- Diameter ↓ كلما كان أكبر يزيد السرعة (أسرع شيء α neurons)

* لو زاد حجم neuron لحجم بريتقالة أو لحجم كرة السلة لأصبح طول Axon يصل إلى (7 Km).

Channels
- chemical
- mechanical
- electrical

* Fibers → A → A alpha / A beta / A gamma / A delta → myelinated يحتاف النخاع
  → B
  → C → nonmyelinated / small / thin رفيعة

قطرها من ١ ميكرون وأقصر والسرعة بطيئة

↓

Sympathetic/parasympathetic Nerves

Hormones ← طا تكون المنظومة الزمنية طويلة الأمد وليست عاجلة

مثلاً هرمون النمو لا يتوقف منذ لحظة الولادة لأن جميع الخلايا تقوم ماعدا الخلايا العصبية، فعملية الانقسام للخلايا عملية مستمرة مدى الحياة

مثال آخر: هرمون الانسولين عند تناول glucose عملية metabolism تحتاج مدة زمنية وليست بثواني

Coordination of Body Functions by Chemical Messengers:

Cellular and tissue activities are coordinated by **chemical messenger systems**. These systems include:

1. **Neurotransmitters** are released by axon terminals of neurons into the synaptic junctions and act locally to control nerve cell functions. The nervous system is also organized for rapid discrete activities; it has an enormous number of "private lines" for sending messages from one distinct locus to another.

2. **Endocrine hormones** are released by glands or specialized cells into the circulating blood and influence the function of target cells at another location in the body. In contrast to the rapid, directed effects resulting from neuronal stimulation, responses to hormones are much slower (seconds to hours) in onset, and the effects often last longer.

Glands مثل
- Thyroid gland
- Adrenal gland
- Pancreas gland

Specialized Cells ⟹

* عضلات القلب في الأذين تفرز هرمون Atrial Natriuretic Peptide ← يفرز natrium صوديوم

* الكلية تفرز هرمون erthyropoietin فالأشخاص الي بعانوا من فجز الكلى يكون معهم Anemia لأن الكلية فقدت القابلية على إفراز هذا الهرمون الذي يجعل نخاع العظم ينتج خلايا دم حمراء

* المشيمة عند الأم الحامل Placenta تفرز لبروجين وبروجسترون وهو وظيفة الأساسية تبادل الغاز و الغذاء بين الأم والجنين

* المعدة تفرز هرمون Gastrin

* Duodenum تفرز هرمون Secretin

3. **Neuroendocrine hormones** are secreted by neurons into the circulating blood and influence the function of target cells at another location in the body.

ADH ⟵ Antidiuretic Hormone ⟵ from Axon to circulating blood

pituitary gland — تفرزه الغدة النخامية — وليس إلى خلية مقابلة

↓

مبنية بـ neurons

إذا الدماغ حس إنه ↑osmolarity يعطي أمر يحدث Action Potential ويصل إلى Axon تفرز ADH إلى الدورة الدموية إلى خلية بعيدة Kidney فيأمرها أن تحبس الماي وهكذا يزداد التركيز

4. **Paracrines** are secreted by cells into the extracellular fluid and diffuses a short distance and affect **neighboring target cells** of a different type. They do not gain entry to the blood in any significant quantity because they are rapidly inactivated by locally existing enzymes or bound to extracellular matrix, thus preventing their widespread diffusion. *Histamine* and *Nitric oxide* (NO) are an example of a paracrine-signaling molecules.

* ترطبة النخلة تسبب تقرح بسبب الخلايا في المنطقة تشعر بمادة غريبة وتفرز مادة Histamine تذهب للمنطقة نفسها وإذا وصلت لجدران الأوعية الدموية تتوسع Vasodilation فتزداد كمية السوائل فيها فتهيج نهايات nerve endings في المنطقة فتسبب شعور بالألم والحكة

5. **Autocrines** are secreted by cells into the extracellular fluid and affect the function of the same cells that produced them. **Eicosanoids (e.g., prostaglandins)** are examples of signaling molecules that can act in an autocrine manner.

6. **Cytokines** are peptides (cannot cross the lipid bilayer of cells to enter the cytoplasm) secreted by cells into the extracellular fluid and can function as autocrines, paracrines, or endocrine hormones as **immune-modulating agents**. Cytokines are important in health and disease, specifically in host immune responses to infection, inflammation, trauma, sepsis, cancer, and reproduction. Examples; are interleukins, lymphokines and chemokines. Example of cytokine hormones is the **leptin** (synthesized by adipose cells and enterocytes in the small intestine).

يؤثر على الشهية

sepsis → تعفن الدم
trauma → صدمة

* مثلاً دخلت بكتيريا للجلد شعرت فيها الكريات البيضاء التابعة لجهاز المناعة فتطلقه مواد هذه المواد تذهب للدورة الدموية فتصل إلى نخاع العظم لأن ٩٠٪ من الكريات البيضاء موجودة في نخاع العظم فكأنها إشارة للدعم فعوضاً نخاع العظم يطلقه الكريات البيضاء الموجودة عنده

- The nervous system exerts control over endocrine gland function, most if not all endocrine glands are innervated by the PNS, and these nerves can directly control the endocrine function of the gland.
- This overlap between the nervous and endocrine systems maintains **homeostasis**. Example; the adrenal medullae and the posterior pituitary gland secrete their hormones primarily in response to neural stimuli. Therefore, it is sometimes difficult to classify a particular molecule as either a hormone or a neurotransmitter.
- On the other hand, hormones can affect the CNS to alter behavior and mood.

تغيير

- The word "**hormone**" is derived from the Greek *hormaein*, which means to "**excite**".
- The endocrine hormones are carried by the circulatory system to cells throughout the body, including the nervous system in some cases, where they bind with receptors and initiate many cell reactions.
- A particular cell can only respond to a hormone if it possesses the appropriate hormone receptor.

PNS → Perifpheral Nervous System

* إذاً كما يؤثر الدماغ على إفراز الهرمونات فإن الهرمونات تؤثر على الدماغ تحديداً السلوك الفرق بين طفلة ٤ سنوات وشابة هو السلوك الذي يؤثر عليه إفراز الهرمونات كالاستروجين و البروجستون

Chemical Structure and Synthesis of Hormones:

chemical signal

The three chemical classes of hormones include:

1. **Proteins and polypeptides**. Example; anterior and posterior pituitary hormones, the pancreatic hormones (insulin and glucagon), the parathyroid hormone, and many others.

Protein ← amino acids سلسلة طويلة من

Polypeptide ← amino acids سلسلة قصيرة من ← 3 amino acids أقصر من

para ← مجاور

* يذوب في الماء
* مصنوعة ومخزونة وجاهزة عند الطلب

الهرمون المصنوع قبل الإطلاقه يكون inactive يكون عنده amino acids إضافية تجعله inactive بعدين بصير له activation وينطلق (ينفصل)

* Receptor يكون برا على cell membrane من خارج لأنه لا يستطيع اختراقه
* الأغلب لا تحتاج إلى carrier
* هي عرضة للتدمير لأنه لا يوجد مادة تبقى في الجسم إلى الأبد

(Half life) ← مثلاً مادة half life = 6 h إذاً بعد 6 ساعات تنقص نسبتها 50٪

بعد كمان 6 ساعات بتنقص 25٪ وبعد كمان 6 ساعات بتنقص 12.5٪ ← بالتدريج

← إذاً هرمونات البروتينات عمرها قصير

*you can never give it by mouth but intravenously (injection)

حتى ما تنهضم بسرعة وتتحول إلى amino acids

Polypeptide and Protein Hormones:

- Most of the body hormones are polypeptides and proteins. They range in size from small peptides with as few as **three amino acids** (thyrotropin-releasing hormone, TRH) to proteins with almost 200 amino acids (growth hormone and prolactin).
- Protein and peptide hormones are synthesized as **prohormones** on the rough end of the endoplasmic reticulum, and then transferred to the Golgi apparatus for packaging into secretory vesicles.
- Polypeptide hormones are synthesized and stored in advance of need.
- Enzymes in the vesicles cleave the prohormones to produce smaller, biologically active hormones and inactive fragments. تتكون
- Secretion of the hormones (as well as the inactive fragments) occurs by **exocytosis** into the interstitial fluid or directly into the blood stream.
- Exocytosis is initiated either by **increased cytosolic calcium** concentration caused by depolarization of the plasma membrane. Or, by stimulation of an endocrine cell surface receptor that increases **cAMP**, and the subsequent activation of protein kinases that initiate secretion of the hormone.
- The peptide hormones are water soluble (**hydrophilic**) and carried by plasma to their target tissues.

cAMP → cyclic adenosine monophosphate

---

2. **Steroids** (cholesterol-derived). Example; adrenal cortical hormones (cortisol and aldosterone), the ovarian hormones (estrogen and progesterone), the testicular hormones (testosterone), and the placental hormones (estrogen and progesterone).

دهنية

يستخدم في الصناعة: • الهرمونات • كل cell membrane فيها cholestrol

* يخترق cell membrane ف Receptor يكون عند جهة ICF

* لا تذوب في الماء فتحتاج carrier protein (90٪ تحمل الخلية الهدف و 10٪ ينفصل عن carrier protein ويدخل الخلية الهدف هذا هو active)

* عمرها طويل

* لا تتأثر عن طريق العم فمثلاً حبوب منع الحمل هي شبيهة بهرمونات الاستروجين والبروجسترون

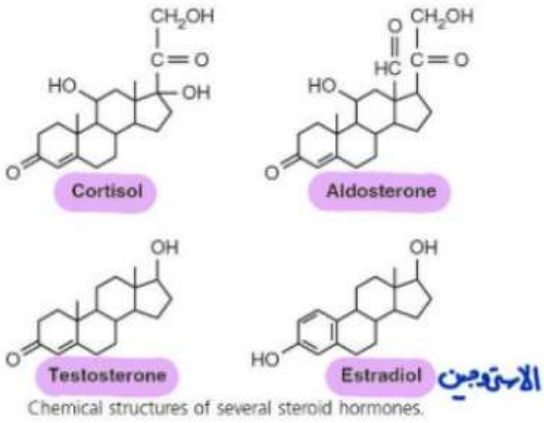
* ليست موجودة دائمًا في vesicles فهي تصنع عند الطلب.

Gonads
- Testies → تنتج testosterone + Sperm → عند الذكور
- ovaries → تنتج estrogen + progesteronet + Ovum → عند الإناث

Gametes → Cell with half number of chromosomes
- ↓ Ovum/Sperm

Steroid hormones:

- The chemical structure of steroid hormones is similar to that of **cholesterol**, and in most instances, hormones are synthesized from cholesterol.
- They are lipid soluble (**hydrophobic**) and once they are synthesized, they diffuse across the cell membrane and enter the interstitial fluid and then the blood.
- Steroid hormones are synthesized and secreted on demand.
- In most cases, 90% or more of steroid hormones in the blood are **bound to plasma proteins**. Some of the plasma proteins that bind hormones are specialized, in that they have a considerably higher affinity for one hormone over another (such as *corticosteroid-binding globulin*).
- The liver synthesizes and secretes these plasma proteins.
- For hormones that bind to carrier proteins, only 1% to 10% of the total hormone present in the plasma exists **free** in solution. However, only this free hormone is biologically active.
- Bound hormone cannot directly interact with its receptor and, thus, is part of a temporarily inactive pool.
- Protein binding greatly slows the rate of clearance of hormones from plasma.



Chemical structures of several steroid hormones.

Amine hormones (Tyrosine derivative):

- These hormones are small in size.
- Two groups of hormones are derived from tyrosine, the thyroid and the adrenal medullary hormones.
- The thyroid hormones are synthesized and stored in the thyroid gland as the protein **thyroglobulin**. Thyroglobulin is stored in large follicles within the **thyroid gland**.
- Hormone secretion occurs when the amines are split from thyroglobulin, and the free hormones are then released into the blood stream.
- After entering the blood, most of the thyroid hormones combine with plasma proteins, **thyroxine-binding globulin**, which slowly releases the hormones to the target tissues.
- Epinephrine (E) and norepinephrine (NE) are formed in the **adrenal medulla**. The gland secretes about four times more epinephrine than norepinephrine.
- Similar to the protein hormones stored in secretory granules, catecholamines are also released from adrenal medullary cells by **exocytosis**.

& triiodothyronine

ينقسم

from liver (carrier protein)

Epinephrine = Adrenaline = E

Norepinephrine = Noradrenaline = NE

*يذوبوا في الماء و Receptor يكون خارج الخلية

*ليس كل خلية لها Receptor لكل الهرمونات

Adrenal Gland → Cortex

Adrenal Gland → Adrenal Medulla تفرز → E / NE

Thyrosine → لا توجد خلية في الجسم ما بستغل عليها → Cell membrane يخزنه

Thyrosine → Receptor → ICF

Notes:

- The **liver** is quantitatively the most important site of degradation; for a few others, the **kidneys** play a significant role as well.
- Diseases of the liver and kidneys may, therefore, indirectly influence endocrine status as a result of altering the rates at which hormones are removed from the circulation.
- Urine is the primary route of excretion of hormone degradation products. In some cases, measuring the urinary content of a hormone metabolite provides a useful, indirect, noninvasive means of assessing endocrine function.

Hormone metabolite ↑ ⟶ Hormone ↑

↓ ⟶ Hormone ↓

Test Question:

Q. Within the endocrine system, specificity of communication is determined by:

A. The chemical nature of the hormone
B. The distance between the endocrine cell and its target cell(s) ✗
C. The presence of specific receptors on target cells
D. Anatomic connections between the endocrine and target cells ✗
E. The affinity of binding between the hormone and its receptor

Another Questions

What is an organic compound that is made by glands in the body (pituitary, thyroid, etc) that is used in long distance communication between cells?

- [x] Hormones
- [ ] Neurotransmitters
- [ ] Synapse
- [ ] Carbohydrates

Which of the following can activate a protein by transferring a phosphate group to it?

- [x] cAMP
- [ ] G Protein
- [ ] protein kinase
- [ ] protein phosphatase

A signal molecule that binds to a plasma-membrane protein is a

- ligand
- second messenger
- protein kinase
- receptor protein

Q) One of the following hormones isn't made by adrenal cortex:

1) Aldosterone

2) Cortisol

3) Noradrenaline

4) None of these hormones

*Mechanisms & modes for communication & signaling & transmitting information between cells

- Direct communication between adjacent cells
  - ↓ gap junctions
- Autocrine & paracrine signaling
- release of neurotransmitters & Hormons
  - ↓ nerves
  - ↓ endocrine cells

* Chemical Messenger Systems:

Type of Chemical Messenger System	Secreting Cell	Target Cell	Examples
Neurotransmitters	Axon terminals of neuron	Local nerve cell (another neuron)	-
Endocrine Hormones	Endocrine Cells (specialized cells) & glands	Circulating Blood (distant target cell)	-Erythropoietin -estrogen & progesterone -Atrial Natriuretic Peptide -Gastrin -secretin
Neuroendocrine	Neurons	Circulating Blood (distant target cell)	ADH (Antidiuretic Hormone)
Paracrine signaling	Cells	Local (neighbouring target cell)	-Histamine & nitric oxide
Autocrine signaling	Cells	Same cells that produced them	Eicosanoids (prostaglandins)
Cytokines	Cells	Cells	-Interlukines -Lymphokines -Chemokines -Leptin

	Speed	Effect
Neurotransmitters	rapid	Direct effect
Endocrine Hormones	slow	Last longer effect

*Chemical Structure & Synthesis of Hormones:

Type of Hormone	Is it water soluble (hydrophilic)?	Is it lipid soluble (hydrophobic)?	Examples	Where are the receptors?
Protein Hormones	Yes	NO	-Anterior & posterior pituitary hormones -Parathyroid Hormones -Pancreatic Hormones: *Insulin *Glucagon -Growth Hormones -Prolactin Thyrotropin releasing Hormone (TRH)	ECF
Steroid Hormones	NO	Yes	-Ovarian Hormones: *Progesterone *Estrogen (Estradoil) -Testicular Hormones: Testosterone -Placental Hormones: *Progesterone *Estrogen (Estradoil) -Adrenal Cortical Hormones: *Aldosterion *Cortisol	ICF
Amine Hormones (Tyrosine derivate)	Tyrosine: No Adrenal Medulla Hormones: Yes		-Thyroid Hormones: *Tyrosine Hormone *Triiodothyronine -Adrenal Medulla Hormones: *Epinephrin (Adrenaline) *Norepinephrine (Noradrenaline)	Tyrosine: ICF. Adrenal Medulla Hormones: ECF.

قليلًا مِن التفاؤلِ يَصنعُ ألف طريق نَحو السَّعادةِ..

بالتوفيق

#النادي_الطبي

#معكم_خطوة_بخطوة