Physiology Team 439

MED439
KING SAUD UNIVERSITY

Revised & Approved

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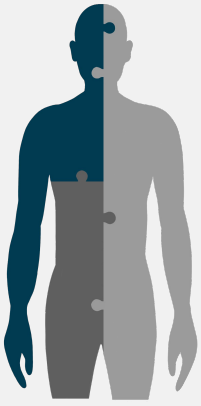


Adrenal Medulla and Pheochromocytoma

Objectives:

- Summarize the actions of adrenal androgens.
- Describe the causes and major manifestations of hyperadrenocorticism and Hypoadrenocorticism
- Describe circumstances in which catecholamines are released from the adrenal gland.
- List the major actions of catecholamines.

Color index:

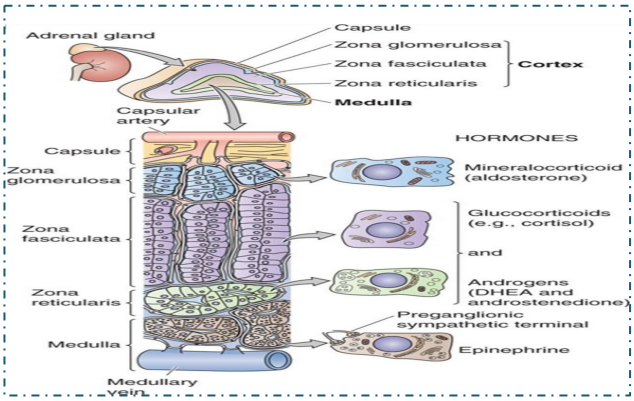
- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

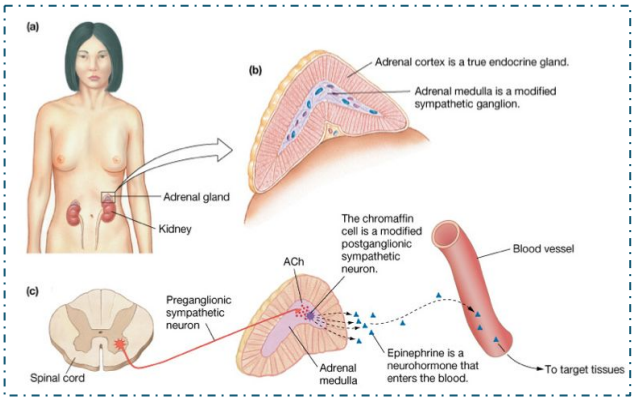
Editing File

Adrenal Medulla

Overview:

- The adrenal medulla is the inner part or core of each adrenal gland.
- It is considered as part of **sympathetic nervous system**.
- The adrenal medulla is functionally integral part (تعتبر جزء لا يتجزأ) of the sympathetic system.
- Medullary cells are derived from the embryonic neural crest, simply modified neurons (Chromaffin cells, also pheochromocytes).
- Innervated by cholinergic preganglionic sympathetic neurons.
- They synthesize the catecholamine secrete epinephrine, and 20% secrete norepinephrine . The neurotransmitter **norepinephrine** is from tyrosine.
- However, high levels of cortisol that drain into the medulla from the adrenal cortex induce expression of the enzyme **phenylethanolamine N-methyl transferase (PNMT)**, which converts norepinephrine to **epinephrine**.
- Phenylethanolamine N-methyltransferase (PNMT) is an enzyme found in the adrenal medulla that converts norepinephrine (noradrenaline) to epinephrine (adrenaline).



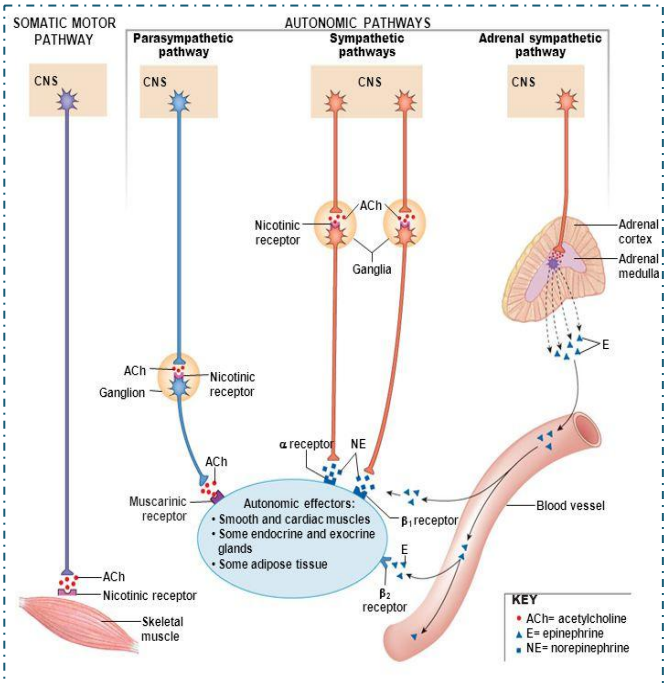


Review of Efferent Pathways: Motor and Autonomic

Sympathetic pathway: consists of preganglionic Neuron and postganglionic neuron preganglionic Neuron originates in CNS and has axonal fibers that terminate on a second postganglionic neurons that peripherally located, and terminate in the effector organ, and will release norepinephrine and epinephrine to specific receptors called adrenergic receptors.

Adrenal sympathetic pathway: has preganglionic neuron and Axon, But the postganglionic Neuron are modified Sympathetic Neuron (chromaffin cells).

The difference between them: that the adrenal sympathetic pathway don't have axonal fibers that terminate in the effector organ. If stimulated by preganglionic, it will release neurotransmitters directly into the Blood = Systemic Effect.



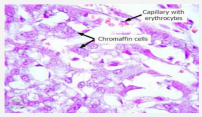
Adrenal Medulla Hormones cont..

It secretes catecholamines:

Adrenaline (epinephrine)	80% of its secretion	Ep in the bloodstream comes solely from adrenal medulla
Noradrenaline (norepinephrine)	20% of its secretion	NE in blood comes from both adrenal medulla (30%) and postganglionic (70%) (sympathetic nerves)
Small amount of dopamine*		

this is because postganglionic sympathetic nerves con not synthesize EP from its precursor NE, because they lack the enzyme (PNMT)[1] needed for conversion of NE into EN.*

They are released from **chromaffin cells.***



It secretion are derived from <u>Tyrosine</u>:*

Tyrosine → Dopamin → Norepinephrine → Epinephrine

Secretion of these hormones cause:*

- Blood to be diverted to the brain, heart and skeletal muscles
- Epinephrine Is the more potent stimulator of the heart and metabolic activities
- Norepinephrine is more influential on peripheral vasoconstriction and blood pressure

Role of the adrenal medullary hormones:*

1. Enhance the effects of the sympathetic nervous system.
2. Prepare the body for a stressful event.

The response is known as the "fight or flight" response.

1: This enzyme ONLY found in Adrenal medulla NOT found in postganglionic sympathetic nerve fibers.

Effects of Catecholamines*

Organs	Effect	Metabolic	Result
Heart	Increased heart rate, contractility and cardiac output[2]	Blood glucose level[3]	Increase blood pressure
Vessel	Generalized Vasoconstriction[4] ,Raise the vessel resistance		Increase blood pressure
Respiratory	Airway dilation[5],relaxation in bronchi		Reduce the resistance of the air way
GIT	Decreased activity		Reduce motility
Bladder	Bladder sphincter contraction		Inhibition of bladder empty
CNS	Increased alertness	Lipolysis[6]	Quick thinking in emergency situation
Eyes	pupillary dilation, flattened lens		More vision and quick view
sweat	Increase		Git rid of extra heat

- Glycogenolysis and gluconeogenesis in liver and skeletal muscle (can lead to hyperglycemia) which increases blood glucose level.
- Increase heart rate and blood pressure.
- Cause vasoconstriction of blood vessels.
- Mobilization of free fatty acids.
- Increase metabolic rate.
- Increase O2 consumption.

2: Is it important to CO to increase? Yes لأنه لو مثلاً تبين تهربين فلازم عندك قوة مضخة وقوة دفع > to meet your emergency need at this moment.

3: By:

- Stimulation of liver gluconeogenesis.
- Inhibition of insulin secretion.
- Production of glucagon, which work on the liver to break down glycogen that stored in the liver, so increase glycogenolysis and gluconeogenesis.

4: Except coronary artery and vessels in the skeletal muscles, to shift the blood to the heart and skeletal muscles.

5: To move air in and out easily without resistance.

6: Increase fatty acids.

—

- Increase glucose level and free fatty acids provide an additional fuel to increase the power of muscle movement, and adequate nourishments during crisis.
- Inhibition of insulin release ?

Free fatty ac لأن حتى العضلات ممكن تستخدم Brain لأن الخلايا الأخرى ماتحتاج جلوكوز وأهم شي ال

Functions of catecholamines*

1- Effect on carbohydrate metabolism:

Increase glycogenolysis and gluconeogenesis and decrease glycogenesis.
- Catecholamine promote the release of glucose from liver and decrease its utilization by muscle.
- Epinephrine inhibits insulin secretion but promote glucagon secretion.

2- Effect on lipid metabolism:

Both of them enhance the breakdown of TG in adipose tissue (lipolysis).
This cause increase in the free fatty acid in the circulation which are effectively utilized by the heart and muscle as fuel source.

3- Effect on physiological function:

Catecholamines increase cardiac output, blood pressure and oxygen consumption.
They cause smooth muscle relaxation in bronchi, GIT and blood vessels supplying skeletal muscle.

Exercise as an example of Adrenal Medulla activation*

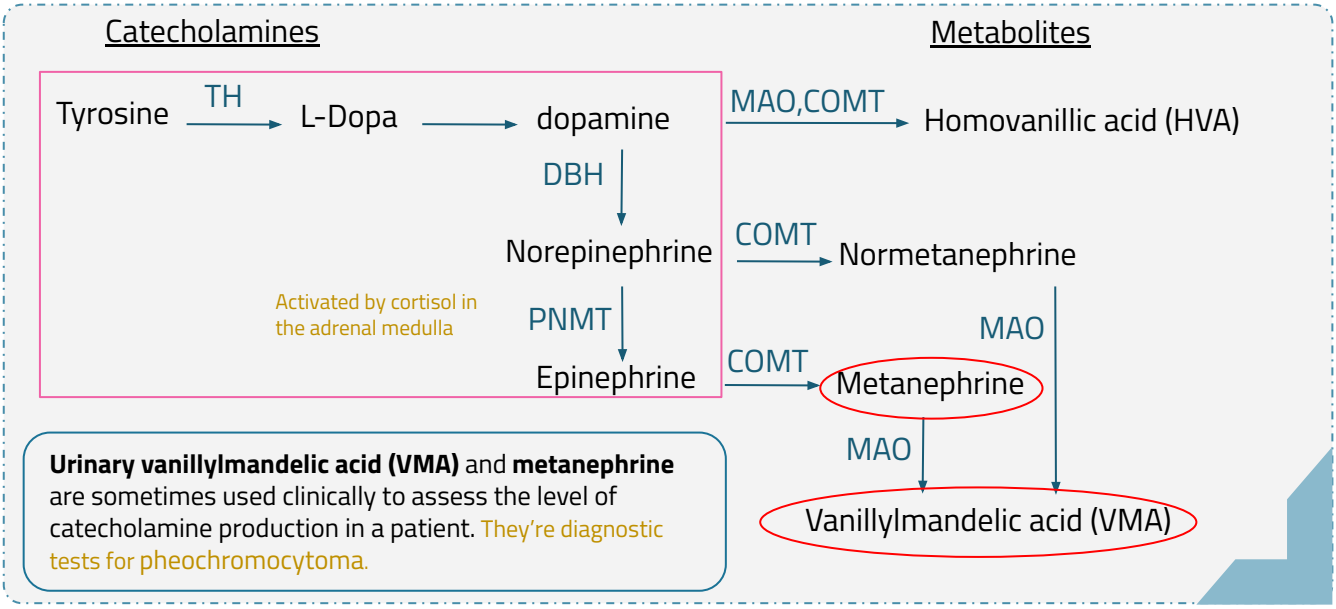
- Exercise is similar to the "fight-or-flight" response but without the subjective element of fear.
- It involves a greater adrenomedullary response (i.e., endocrine role of epinephrine) than a sympathetic nervous response (i.e., neurotransmitter role of norepinephrine).
- The overall goal of the sympathoadrenal system during exercise is to meet the increased energy demands of skeletal and cardiac muscle while maintaining sufficient oxygen and glucose supply to the brain.

Adrenergic Receptors

Alpha-Adrenergic Receptors	Beta Adrenergic Receptors
Alpha 1: Vasoconstriction,intestinal relaxation,uterine contraction and pupillary dilation. **Alpha 2**: Platelet aggregation, decrease insulin secretion and vasoconstriction	**Beta 1**: Increase HR and contraction,lipolysis,renin secretion **Beta 2**: Vasodilation (heart and muscle) ,bronchodilation and glycogenolysis. Epinephrine acts more on Beta 2 **Beta 3**:increase lipolysis, brown fat thermogenesis

Metabolism of Catecholamines

Male Dr: Don't worry about the enzymes, Just know that the metabolites can be used to monitor catecholamine secretion. (the pink is what the female dr. said you have to know)



Urinary vanillylmandelic acid (VMA) and **metanephrine** are sometimes used clinically to assess the level of catecholamine production in a patient. They're diagnostic tests for pheochromocytoma.

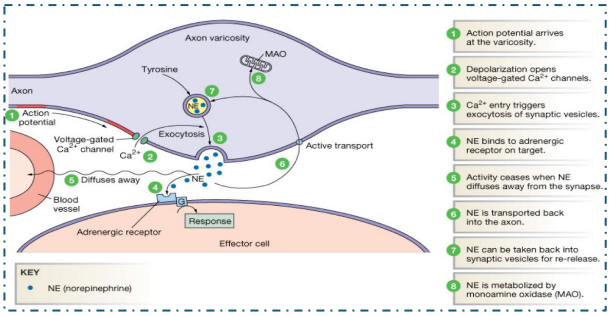
Two primary enzyme are involved in the degradation of catecholamines

1 **monoamine oxidase (MAO)**

2 **catechol-O-methyltransferase (COMT)**

Mechanism: Norepinephrine Release and Recycling*

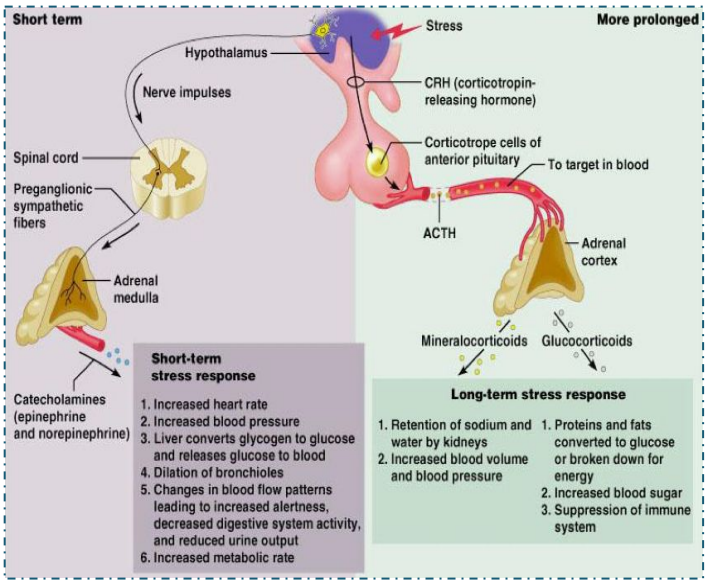
Male Dr: it's NOT important.

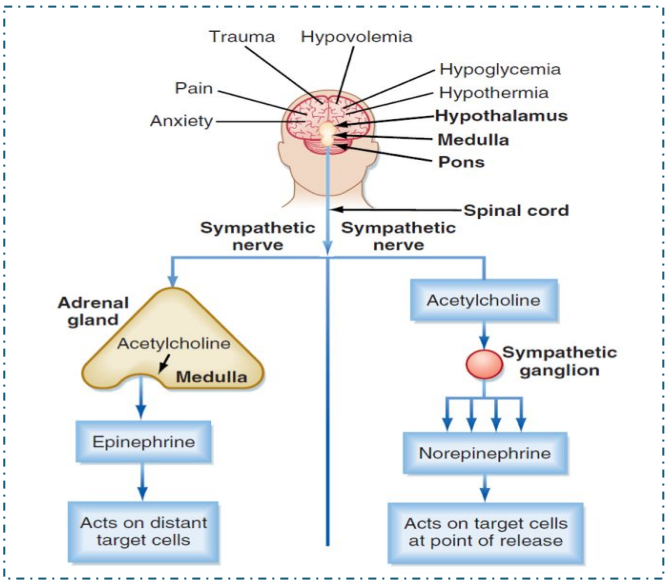


Control of secretion of adrenal medullary hormones*

1. The adrenal medulla is innervated by the sympathetic nervous system.
2. Adrenal hormones are released from the medulla in response to signals from the sympathetic nervous system.
3. The sympathetic nervous system is activated in response to stress also known as the "fight or flight" response. Stress can be physical (exercise), physiological (hypoglycemia, hemorrhage), or emotional.
4. Cortisol, when secreted from the adrenal cortex in response to stress, causes release of these hormones from the medulla.

Stress and the Adrenal Gland





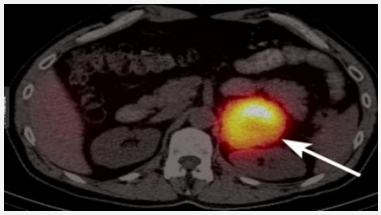
Explanation of the figure:

- Stress ⇒ sympathetic nervous system ⇒ secrete epinephrine and norepinephrine. Also stress will stimulate ACTH release which lead to production of glucocorticoids and mineralocorticosteroids.
- Long time stress:
  increase glucocorticoids ⇒ diabetes
  Increase mineralocorticosteroids ⇒ hypertension.
- Sympathetic nervous system and cortisol can act directly on the adrenal medulla.

Pheochromocytoma

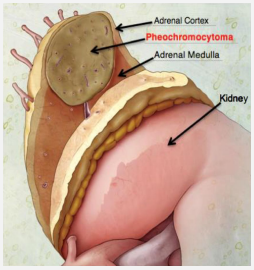
A case study?

"James" a 35-year-old husband and father of three children, has been experiencing:
headaches and palpitations of increasing frequency and severity over the past six months.
In addition, he has had periods of intense anxiety and panic attacks.



Pheochromocytoma

- **Pheochromocytoma** is a relatively rare (800-1000 cases in the us per year) tumor of the adrenal medulla or of similar specialized cells outside of the adrenal glands.
- Most often occurs in middle age.*
- Originates from the chromaffin cells (arise from neural crest) along the paravertebral sympathetic chain extending from pelvis to base of skull
- Secretes excessive amounts of epinephrine and norepinephrine.* because it isn't supplied well with cortisol like normal tissue. Epinephrine conversion will be impared
- About 10% of pheochromocytomas are malignant.*
- Most tumors secrete epinephrine, NE, and dopamine and can cause episodic hypertension.*
- Associated with neurofibromatosis 1.*
- It can occur in combination with other tumors, conditions and in some familial (inherited) syndromes.* MEN2 and von hippel-lindau syndrome
- >95% are abdominal*
- >90% in adrenal medulla*
- 80% occur unilateral*
- Surgically correctable forms of hypertension*
- It can be life threatening if not recognized & not treated.*



Clinical Features:

- Chest pain*
- Anxiety*
- Glucose intolerance*
- Increased metabolic rate
- Palpitations
- Headache
- Episodic Sweating (diaphoresis)

Classic Triad
PHEochromocytoma
3 most common symptoms

Fast heartbeat are typical symptoms, usually associated with markedly high blood pressure.*

Pheochromocytoma Cont..

Resistant Hypertension (95%): often severe, occasionally malignant, and may be resistant to treatment with standard antihypertensive drugs. Levels could be 220/180
Classical symptoms : episodic hypertension.

Paroxysms or Crisis: frequent or sporadic,occurring at intervals as long as weeks or months. With time, the paroxysms usually increase in frequency, duration, and severity*

Other Distinctive Clinical Features:*

- Increased metabolic rate, such as profuse sweating and mild to moderate weight loss.
- Sinus tachycardia, sinus bradycardia, supraventricular arrhythmias, and ventricular premature contractions have all been noted.
- Angina and acute myocardial infarction.
- Headache 80%
- Perspiration 71%
- Palpitation 64%
- Pallor 42%

Diagnosis:

- The diagnosis is established by the demonstration of:
  - Increased production of catecholamines.
    Or
  - Increased catecholamine metabolites:
    Metanephrine and vanillylmandelic acid VMA (a breakdown product of norepinephrine) in plasma and/or urine.
- The diagnosis can usually be made by the analysis of a **single 24-h urine** sample, provided the patient is hypertensive or symptomatic at the time of collection.
- Imaging: CT, MRI

Treatment:

- Treatment is surgical resection
- Laparoscopic Adrenalectomy
  - Pre-op:
    1- Control of hypertension.
    2- α blockers (e.g. Phenoxybenzamine) to prevent intraoperative hypertensive crisis due to tumor manipulation and release of catecholamines.
    3- Fluid resuscitation to prevent circulatory collapse after removal of the catecholamine-secreting tumor. Hypotension is common post op because the body has adapted to high levels of catecholamines

Actions of Adrenal medullary hormones*

Typical Responses to stimulation of the adrenal medulla

Target	Responses	Receptor
Cardiovascular system		
Heart	↑ Frequency and rate of contraction	
	↑ Conduction	β
	↑ Blood flow (dilation of coronary arterioles)	β
	↑ Glycogenolysis	α
Arterioles		
Skin	Constriction	α
Mucosae	Constriction	α
Skeletal muscle	Constriction	α
	Dilation	β
Metabolism		
Fat	↑ Lipolysis	β
	↑ Blood FFA and glycerol	β
Liver	↑ Glycogenolysis and gluconeogenesis	β & α,
	↑ Blood sugar	β &α,
Muscle	↑ Glycogenolysis	β
	↑ Lactate and pyruvate release	β

Typical Responses to stimulation of the adrenal medulla

Target	Responses	Receptor
Bronchial muscle	Relaxation	β
Stomach and intestines	↓ Motility	β
	↑ Sphincter contraction	α
Urinary bladder	↑ Sphincter contraction	α
Skin	↑ Sweating	α
Eyes	Contraction of radial muscle of the iris	α

- The effects of the adrenal medullary hormones underlie the role of these hormones in preparation of body for fight or flight
- The overall effect is to ensue that all requirements for increased muscle activity are available. What are these?

MCQ & SAQ:

Q1: what is the effect of alpha 1 adrenergic Receptor ?

A.lipolysis
B.increase HE
C. vasodilation
D. Vasoconstriction

Q2: Which one of the following result can be used to confirm pheochromocytoma:

A.Low vanillin mandelic acid
B. High ACTH
C. High vanillin mandelic acid
D. Low ACTH

Q3: which enzyme helps Norepinephrine converted to Normetanephrine?

A.COMT
B. MAO
C. DBH
D. PNMT

Q4: Which of the following is not an effect of catecholamines?

A.Increasing heart rate
B. Pupil dilation
C.Increasing oxygen consumption
D.Increasing GI secretion & motility

Q5: what is the correct sentence?

A.Norepinephrine Is more potent stimulator of the heart
B.beta 3 receptor enhanced lipolysis
C.epinephrine is more influential on peripheral vasoconstriction
D.A and B

Q6: Which of the following is not a sign of pheochromocytoma?

A. Resistant hypotension
B. Glucose intolerance
C. Anxiety
D. Sweating

answer key:
1: D
2: C
3: A
4: D
5: B
6: A

1- What is the function of alpha 2

2- What is the function DBH enzyme in the degradation of catecholamine ?

3-From which cells does pheochromocytoma originate?

A1: vasoconstriction,intestinal relaxation,uterine contraction and pupillary dilation.

A2: convert dopamine to NE

A3: Originates from the chromaffin cells (arise from neural crest) along the paravertebral sympathetic chain extending from pelvis to base of skull

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