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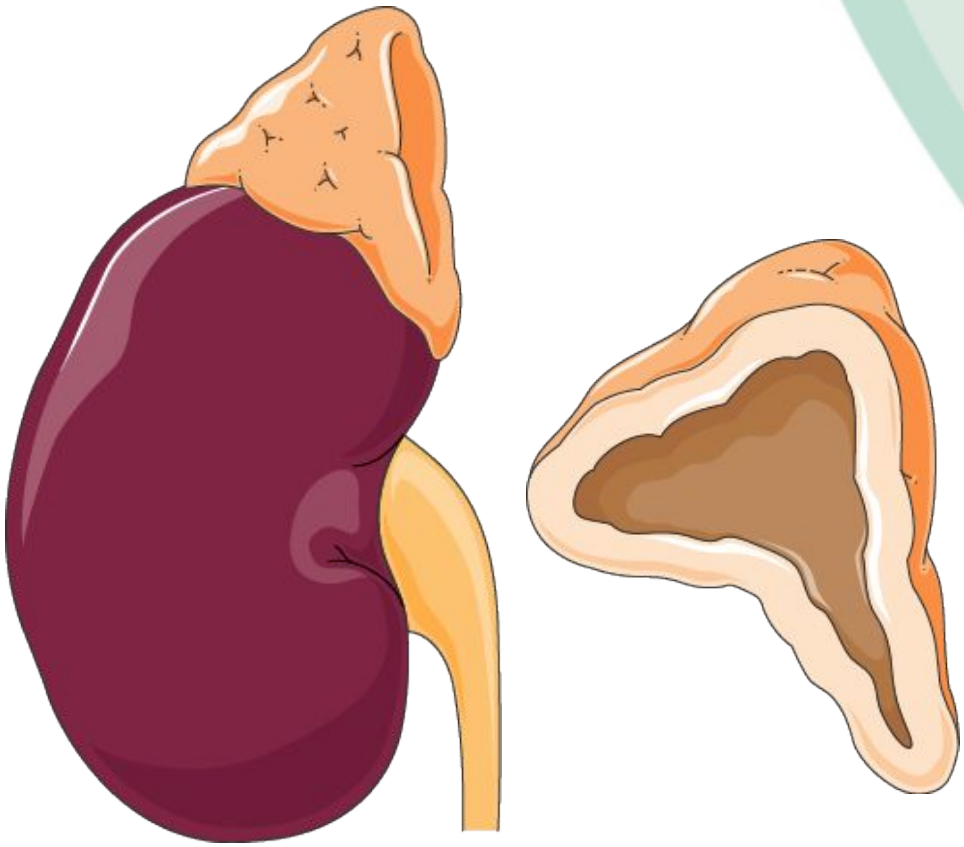

Adrenal Medulla and Pheochromocytoma

Color Index :

- Main Text
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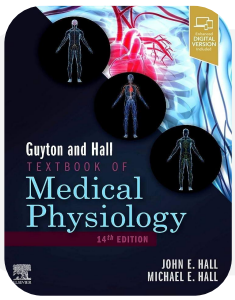
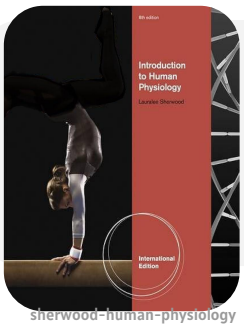
Objectives

- 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.

Resources

Only ENDO chapters included





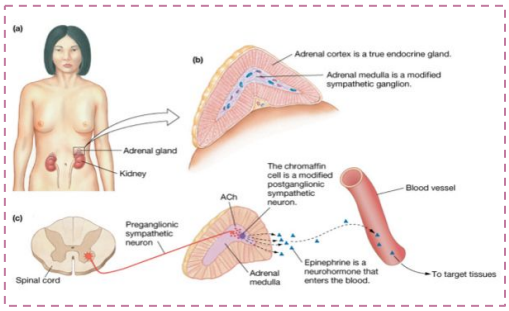
sherwood-human-physiology

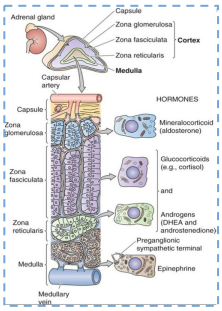
This lecture was presented by:
Dr. Abeer Ghumlas - Dr. Khalid Alregaiey

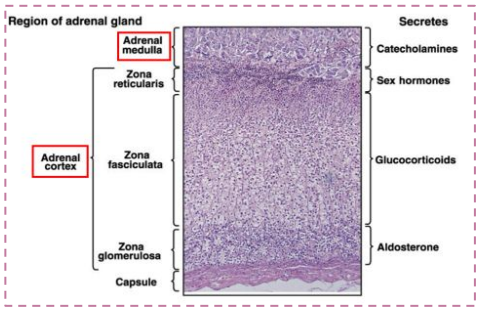
Adrenal Medulla

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 an integral part (تعتبر جزء لا يتجزء) of the sympathetic system.
- Medullary cells are derived from the embryonic neural crest, simply modified neuron (Chromaffin cells, also pheochromocytes).
- Innervated by cholinergic preganglionic sympathetic neurons.
- They synthesize the catecholamine secrete epinephrine 80%, and 20% secrete norepinephrine.
- The neurotransmitter norepinephrine is from tyrosine.
- NE in blood comes from both adrenal medulla and postganglionic sympathetic nerves.
- This is because postganglionic sympathetic nerves cannot synthesize EP from its precursor NE, because they lack enzyme (PNMT) needed for conversion of NE into EP.
- 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).







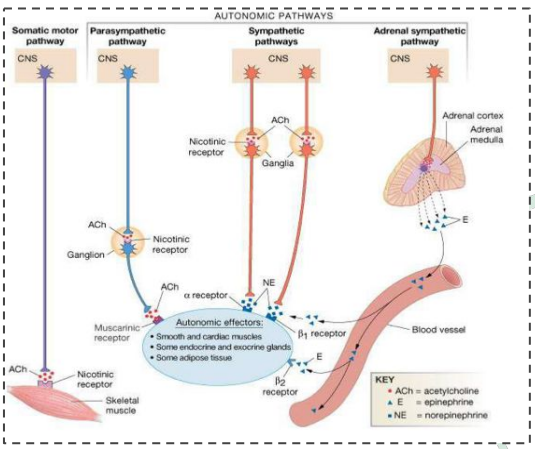
Review of Efferent Pathways: Motor and Autonomic

Doctor 442:

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).

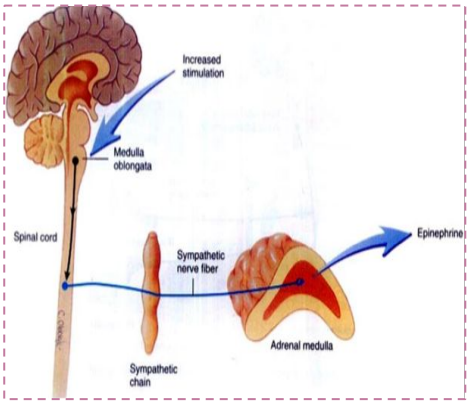
The difference between them: that the adrenal sympathetic pathway don't have axonal fibers that terminate in the effector organ. If stimulated by preganglionic, it will release neurotransmitters directly into the Blood = Systemic Effect.

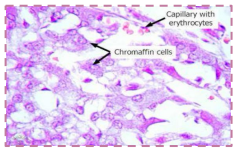


It secretes catecholamines:

1. Adrenaline (epinephrine) 80% of it is secretion, EP found in the bloodstream and comes solely from the adrenal medulla.
2. Noradrenaline (norepinephrine) 20 % of it is secretion. NE found in blood and comes from both adrenal medulla (30%) and postganglionic (70%) (sympathetic nerves.)
3. They are released from chromaffin cells.
4. Why postganglionic sympathetic nerves can not synthesize EP from its precursor NE, because they lack the enzyme (PNMT) needed for conversion of NE into EN.
5. small amount of dopamine

Doctor 442: PNMT ENZYME ONLY found in Adrenal medulla NOT found in postganglionic sympathetic nerve fibers.





Female slides

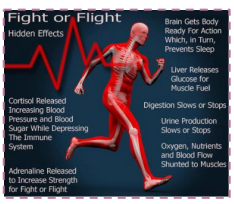
It secretion are derived from Tyrosine:

Tyrosine → Dopamine → Norepinephrine → Epinephrine

Secretions of these hormones causes:

- 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:



- Enhance the effects of the sympathetic nervous system.
- Prepare the body for a stressful event.
  - This response is known as the "fight or flight" response.

Effects of Catecholamines

Female slides

	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 -Vasodilation of coronary & skeletal muscles vessels		Increase blood pressure
Respiratory	Airway dilation(5),relaxation in bronchi		Reduce the resistance of the air way
GIT	Decreased activity		Reduce motility
Bladder	Inhibition of bladder emptying, (Bladder sphincter contraction)		
CNS	Increased alertness	Free fatty acids (Lipolysis)(6)	Increase quick thinking in emergency situation
Eyes	pupillary dilation, flattened lens		More vision and quick view
sweat	Increase		Git rid of extra heat

1. Glycogenolysis and gluconeogenesis in liver and skeletal muscle (can lead to hyperglycemia) which increases blood glucose level.
2. Increase heart rate and blood pressure.
3. Cause vasoconstriction of blood vessels.
4. Mobilization of free fatty acids.
5. Increase metabolic rate.
6. 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 ?

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

Functions of Catecholamines

Male slides

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

1. Exercise is similar to the "fight-or-flight" response but without the subjective element of fear.
2. It involves a greater adrenomedullary response (i.e., endocrine role of epinephrine) than a sympathetic nervous response (i.e., neurotransmitter role of norepinephrine).
3. 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

Adrenergic receptors

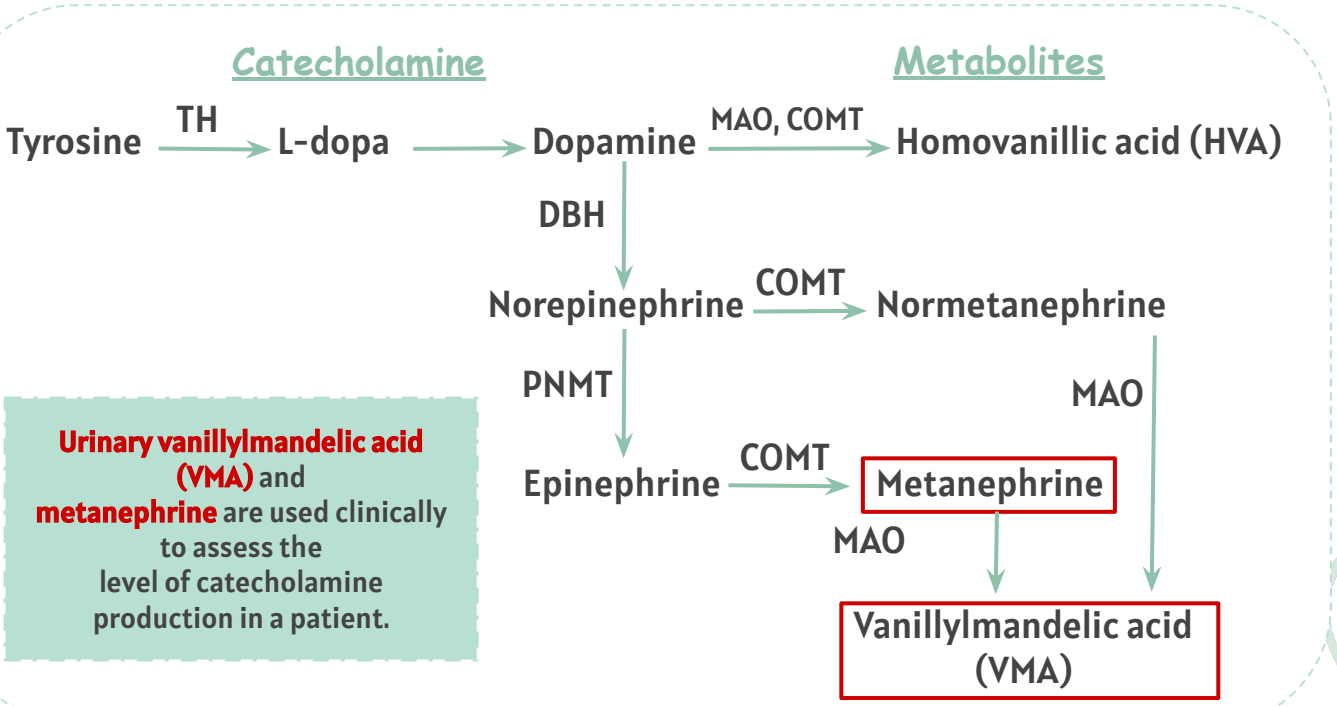
- **Beta-Adrenergic receptors**
  - Beta I: **Increase** HR and contraction, lipolysis, renin secretion.
  - Beta 2: **Vasodilation** (of heart and muscle), increase bronchodilation and glycogenolysis. Epinephrine acts more on Beta 2
  - Beta 3: increase lipolysis, brown fat thermogenesis.
- **Alpha-Adrenergic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

Metabolism of catecholamines

1 monoamine oxidase (MAO)

2 catechol-O-methyltransferase (COMT)

These Two primary enzymes are involved in the degradation of catecholamines:



Actions of Adrenal medullary hormones

Summary of the receptors and their responses.

Female slides

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_1
	↑ Blood sugar	β &α_1
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

Note!

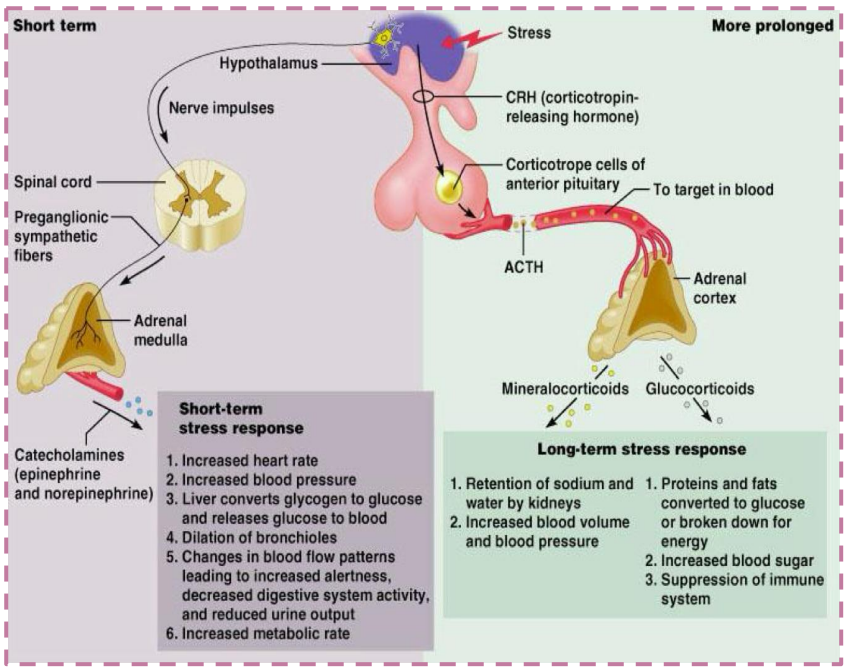
The effects of the adrenal medullary hormones underlie the role of these hormones in preparation of body for fight or flight.
The overall effect is to ensure that all requirements for increased muscle activity are available. What are these?

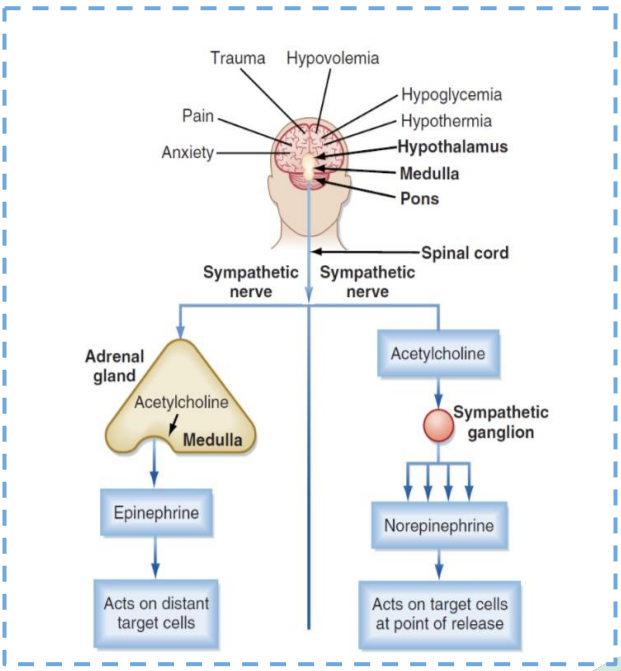
Control of secretion of adrenal medullary hormones

Female slides

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.

Response to stress and adrenal gland





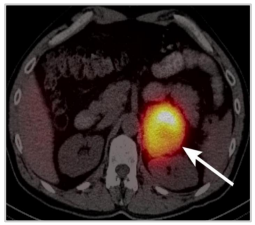
42: Explanation of the figure:

- 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

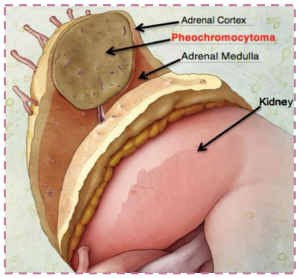
Case study

"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.



Overview

Pheochromocytoma is a relatively rare 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 impaired
-About 10% of pheochromocytomas are malignant.
-Most tumors secrete epinephrine, NE, and dopamine and can cause episodic hypertension.
-Associated with neurofibromatosis.
-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.

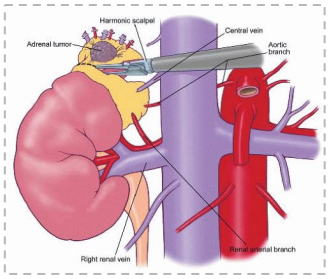


Sign and symptoms/ clinical features

Palpitations 64%, **E**pisodic sweating, **H**eadache 80% (These 3 are the classic triad), chest pain, anxiety, glucose intolerance, increased metabolic rate such as profuse sweating and mild to moderate weight loss, Fast heartbeat are typical symptoms, usually associated with markedly high blood pressure. Resistant Hypertension 95%: often severe, occasionally malignant, and may be resistant to treatment with standard antihypertensive drugs.
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.
Sinus tachycardia, sinus bradycardia, supraventricular arrhythmias, and ventricular premature contractions have all been noted.
Angina and acute myocardial infarction. Perspiration 71% pallor 42%

PHEochromocytome are the three most common symptoms.

Pheochromocytoma

Diagnosis	The diagnosis is established by the demonstration of: - **Increased production of plasma 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, PET.
Treatment	 -Treatment is surgical resection -Laparoscopic Adrenalectomy: • Pre-op (operation): I- Control of hypertension. 2- α blockers (e.g. Phenoxybenzamine) to prevent hypertensive crisis due to tumor manipulation and release of catecholamines and to prevent hypertension after b-blockers administration. 3- β -blocker 4- 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

MCQs:

Q1: How can epinephrine increase blood sugar levels?

A: Suppression of lipolysis | B: Stimulating glycogenolysis | C: Increase glucose uptake | D: inhibiting gluconeogenesis

Q2: NEPN & EPN will cause vasodilation in which of the following?

A: Liver | B: Bladder | C: Skeletal muscles | D: Adipose tissue

Q3: Patient came to the ER with a headache and palpitation, hypertension and elevated blood sugar levels (hyperglycemia). The patient complained that there had been similar episodes in the past where it appears and then suddenly declines. What is the provisional diagnosis?

A: Cushing syndrome | B: DM | C: Addison's disease | D: Pheochromocytoma

Q4: Pheochromocytoma is a tumor arise from which of the following?

A: spongiocytes | B: chromaffin cell | C: spindle cells | D: kupffer cells

Q5: which one of the following is expected to be high in pheochromocytoma?

A: dopamine | B: Ach | C: VMA | D: protein

Q6: All of the following are correct regarding B-adrenergic receptors except?

A: ↑lipolysis | B: ↑glycogenolysis | C: ↑ heart rate | D: dilation of pupils

Q7: Hypertension is a direct characteristic of which of the following?

A: DM | B: dwarfism | C: pheochromocytoma | D: cancer

1-B,2-C,3-D,4- B, 5- C, 6- D, 7-C

SAQs:

- Q1: Why postganglionic sympathetic nerves can not synthesize EP from its precursor NE?
- Q2: What is the classic triad of PHEochromocytoma?

A1: because they lack the enzyme (PNMT) needed for conversion of NE into EN.
A2: Palpitation, Headache, Episodic sweating are the most common symptoms.

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