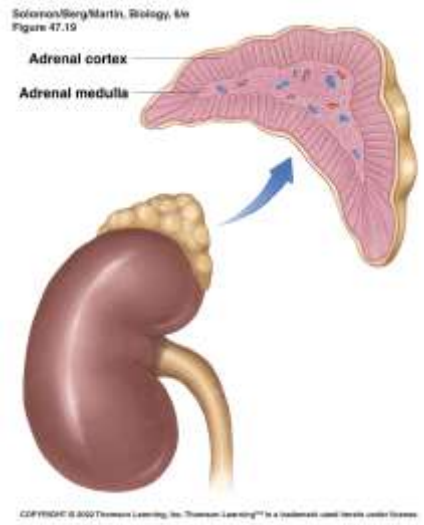
Endocrine Physiology

4

The Adrenal Medulla, Pheochromocytoma

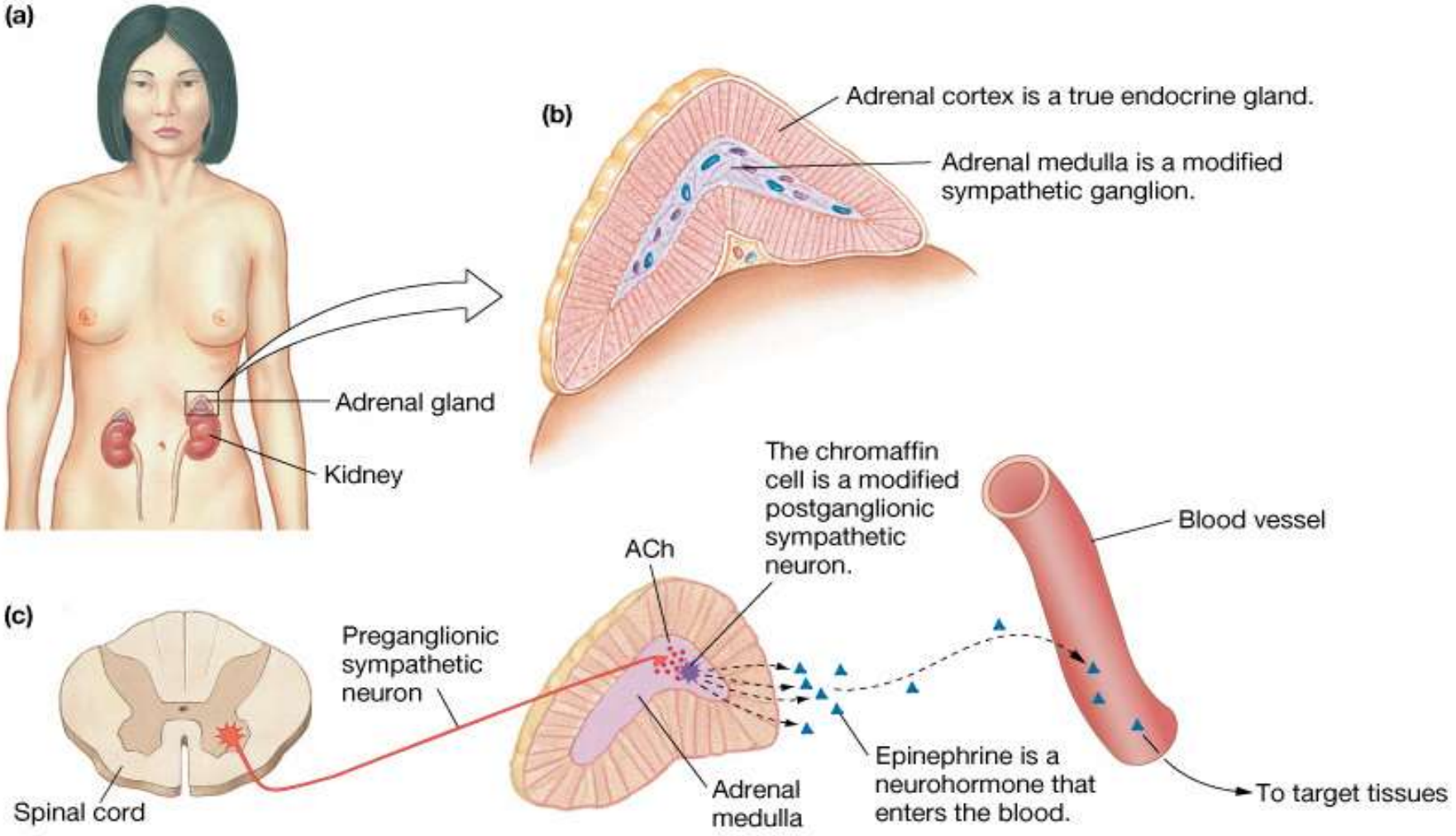
Dr. Khalid Alregaiey



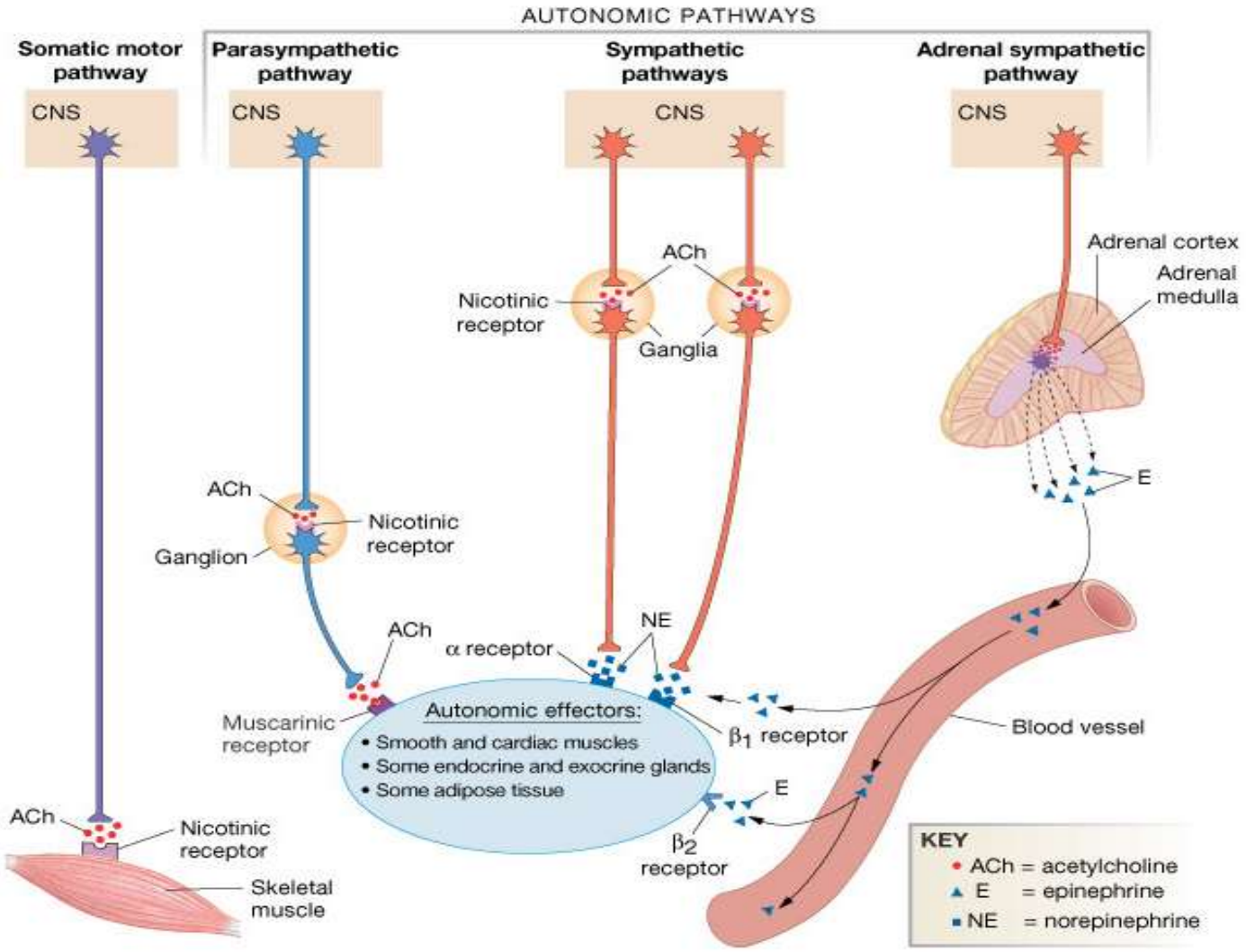
Adrenal Medulla

- Medullary cells are derived from the embryonic neural crest, simply modified neurons (Chromaffin cells, also pheochromocytes).
- Innervated by cholinergic preganglionic sympathetic neurons

Adrenal Medulla: A Modified Sympathetic Ganglion



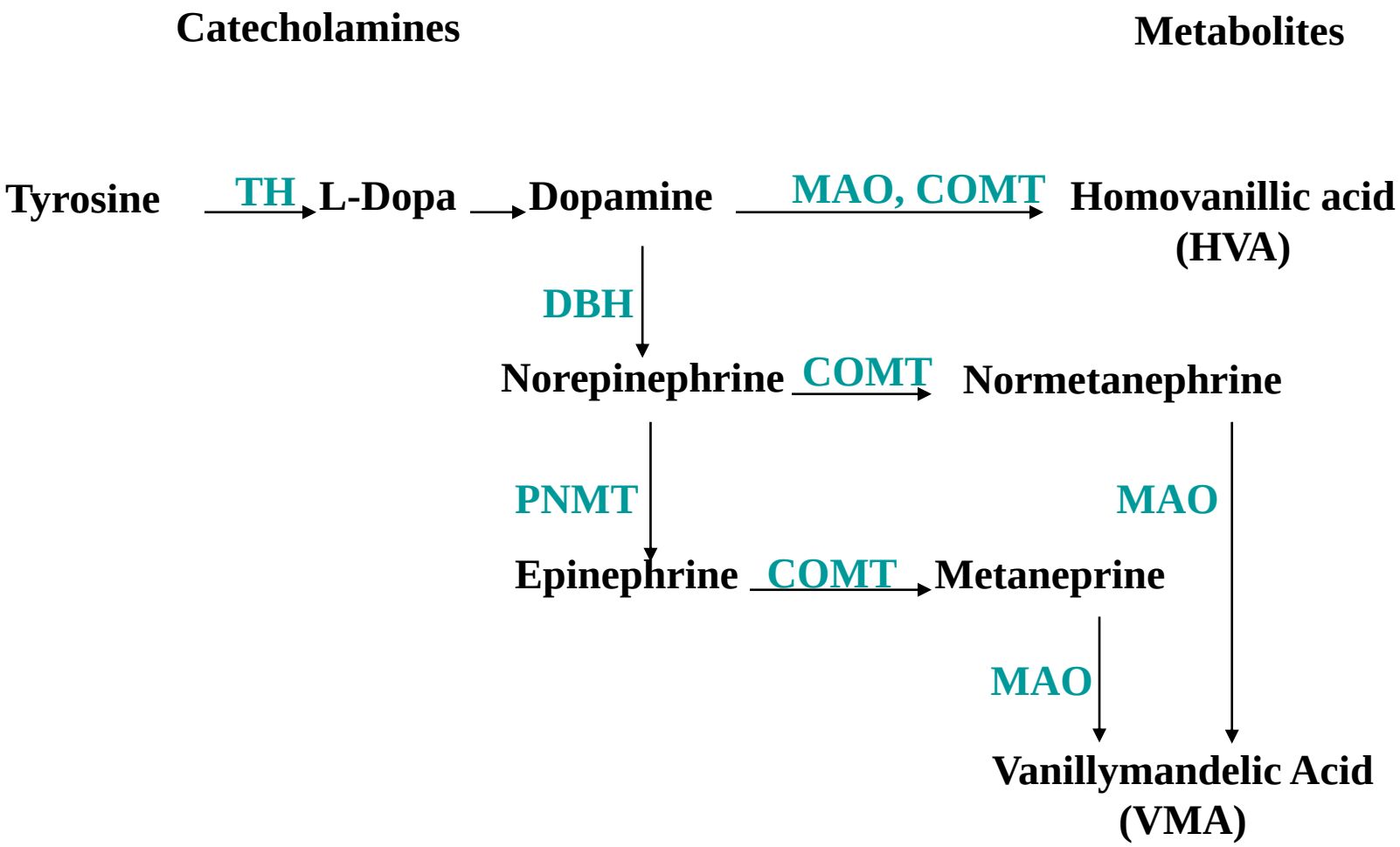
Review of Efferent Pathways: Motor and Autonomic



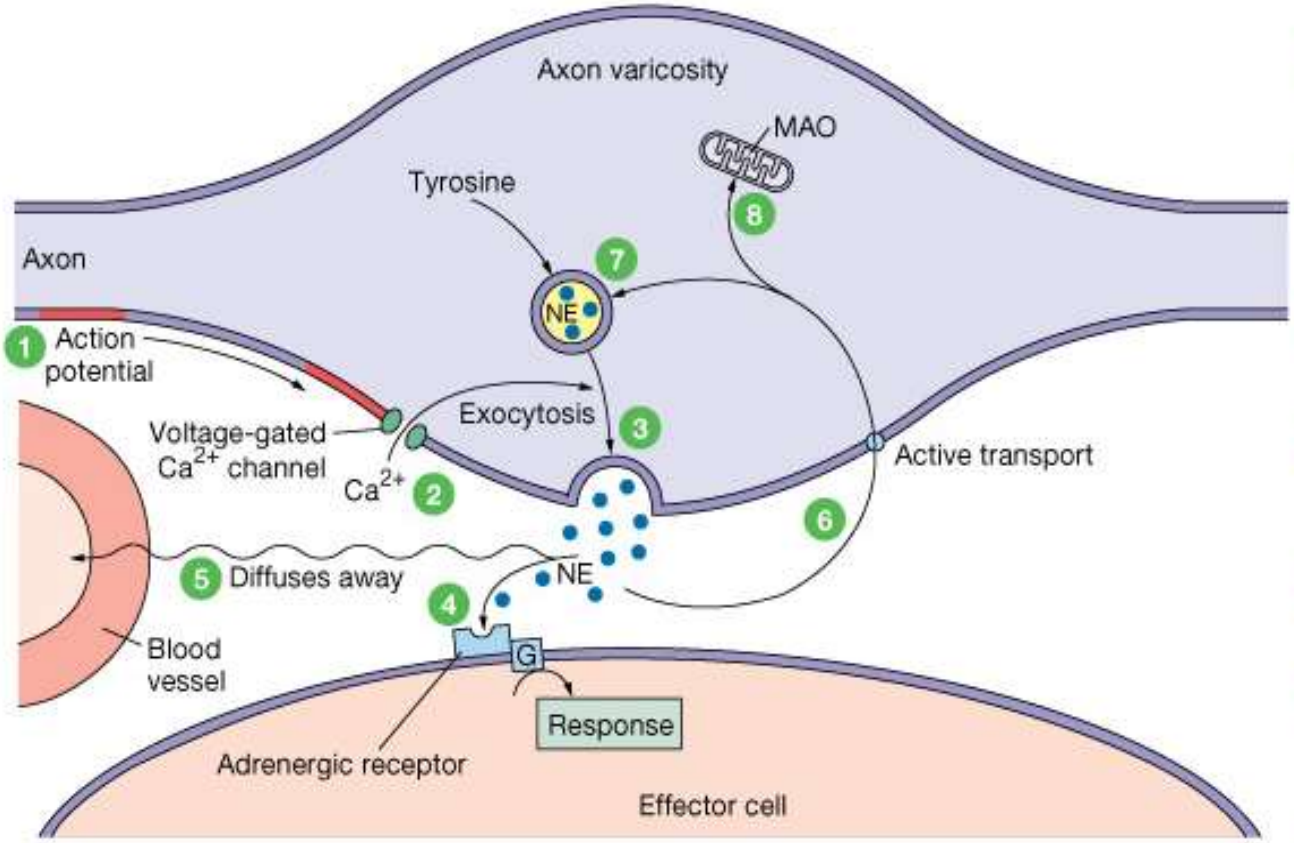
Adrenal Medulla

- They synthesize the catecholamine neurotransmitter **norepinephrine** 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.**
- About 80% of the cells of the adrenal medulla secrete **epinephrine,** and 20% secrete **norepinephrine.**

Metabolism


Catecholamines
Metabolites
Tyrosine
TH
L-Dopa
Dopamine
MAO, COMT
Homovanillic acid
(HVA)
DBH
Norepinephrine
COMT
Normetanephrine
PNMT
MAO
Epinephrine
COMT
Metaneprine
MAO
Vanillymandelic Acid
(VMA)

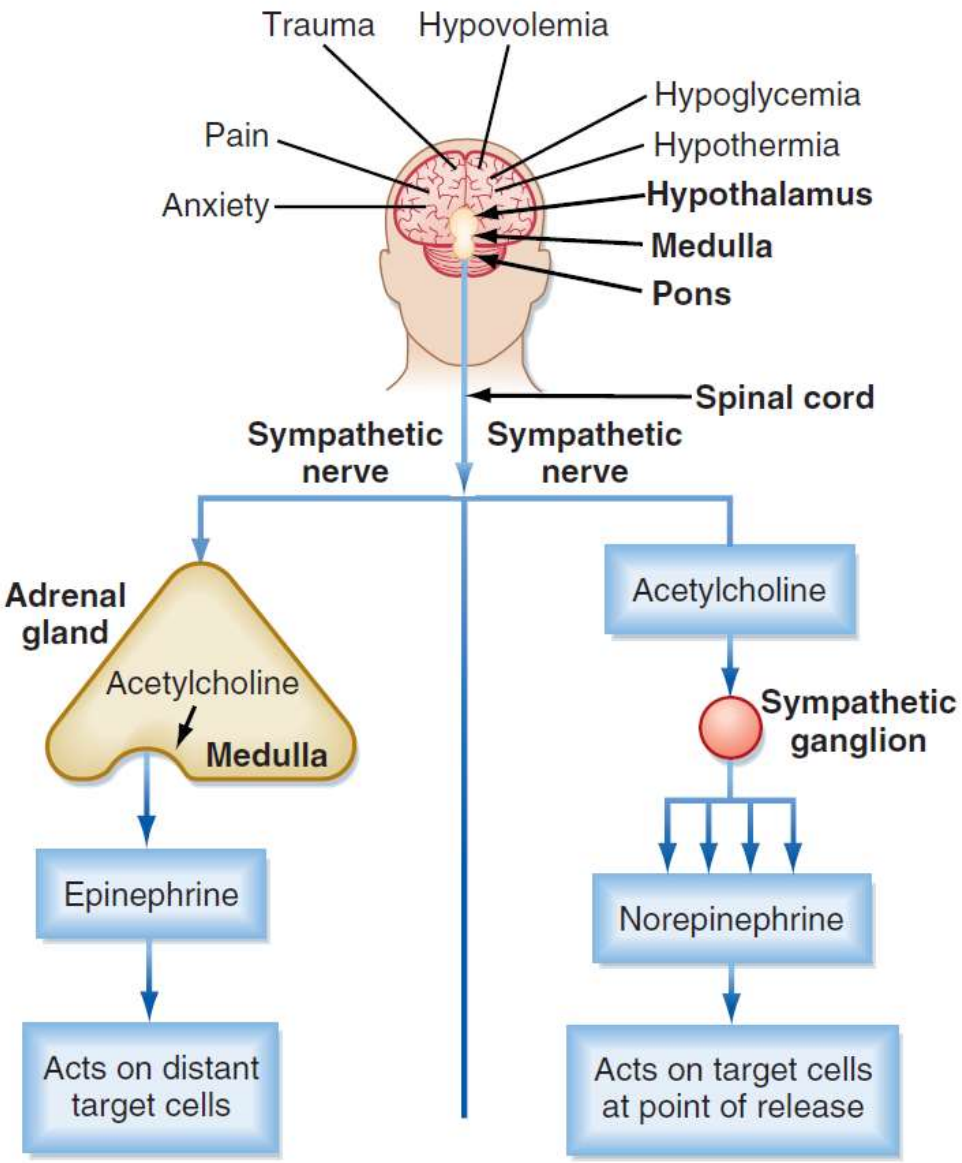
Mechanism: Norepinephrine Release and Recycling



KEY

- NE (norepinephrine)

1. Action potential arrives at the varicosity.
2. Depolarization opens voltage-gated Ca^{2+} channels.
3. Ca^{2+} entry triggers exocytosis of synaptic vesicles.
4. NE binds to adrenergic receptor on target.
5. Activity ceases when NE diffuses away from the synapse.
6. NE is transported back into the axon.
7. NE can be taken back into synaptic vesicles for re-release.
8. NE is metabolized by monoamine oxidase (MAO).


Trauma
Hypovolemia
Hypoglycemia
Pain
Hypothermia
Anxiety
Hypothalamus
Medulla
Pons
Spinal cord
Sympathetic nerve
Sympathetic nerve
Adrenal gland
Acetylcholine
Medulla
Epinephrine
Acts on distant target cells
Acetylcholine
Sympathetic ganglion
Norepinephrine
Acts on target cells at point of release

Adrenergic Receptors

- Alpha-Adrenergic Receptors
  - **α_1:** vasoconstriction, intestinal relaxation, uterine contraction, pupillary dilation
  - **α_2:** platelet aggregation,vasoconstriction, ↓ insulin secretion
- Beta-Adrenergic Receptors
  - **β_1:** ↑ HR/contractility, ↑ lipolysis, ↑ renin secretion
  - **β_2:** vasodilation, bronchodilation, ↑ glycogenolysis
  - **β_3:** ↑ lipolysis, ↑ brown fat thermogenesis

Functions of catecholamines

1. **Effect on carbohydrate metabolism:** Both of them can increase glycogenolysis and gluconeogenesis and decrease glycogenesis.

i. Catecholamine promote the release of glucose from liver and decrease its utilization by muscle; ii. Epinepherine inhibits insulin secretion but promote glucagon secretion.

2. Effect on lipid metabolism: Both of them enhance the breakdown of TAG 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: Catecchcholamines 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.

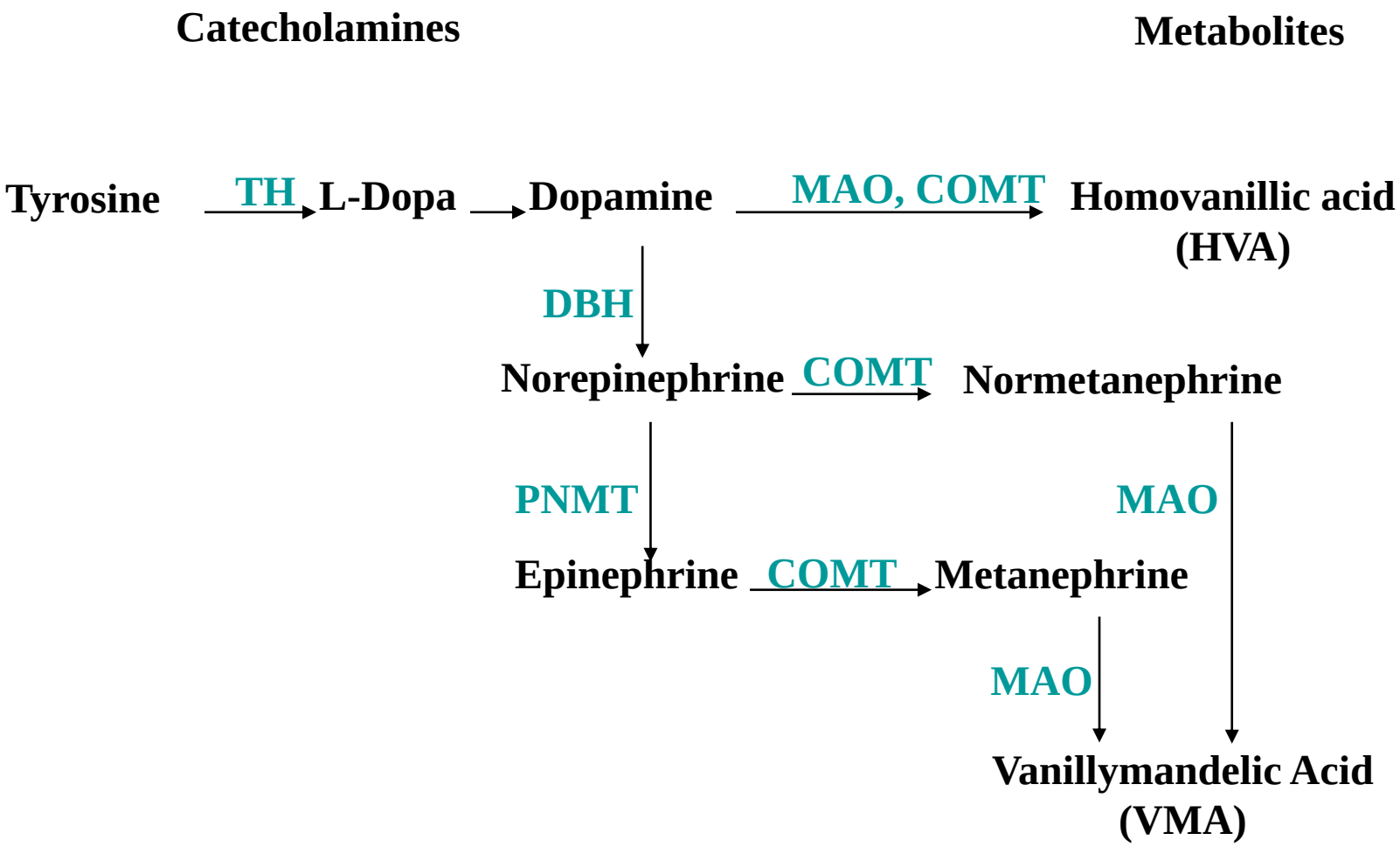
Metabolism of Catecholamines

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

1. **monoamine oxidase (MAO)** and
2. **catechol-*O*-methyltransferase (COMT)**.

- Urinary **vanillylmandelic acid (VMA)** and **metanephrine** are sometimes used clinically to assess the level of catecholamine production in a patient.

Metabolism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(VMA)

Pheochromocytoma

- Pheochromocytoma is a relatively rare tumor of the adrenal glands or of similar specialized cells outside of the adrenal glands.
- Originates from the chromaffin cells along the paravertebral sympathetic chain extending from pelvis to base of skull
- Secretes excessive amounts of epinephrine and norepinephrine
- About 10% of pheochromocytomas are malignant.
- It can occur in combination with other tumors, conditions and in some familial (inherited) syndromes.
- >95% are abdominal
- >90% in adrenal medulla
- 80% occur unilateral
- Surgically correctable forms of hypertension

Clinical Features

- Headache, sweating, palpitation, and a fast heartbeat are typical symptoms, usually in association with markedly high blood pressure.
- **Hypertension:** 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

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

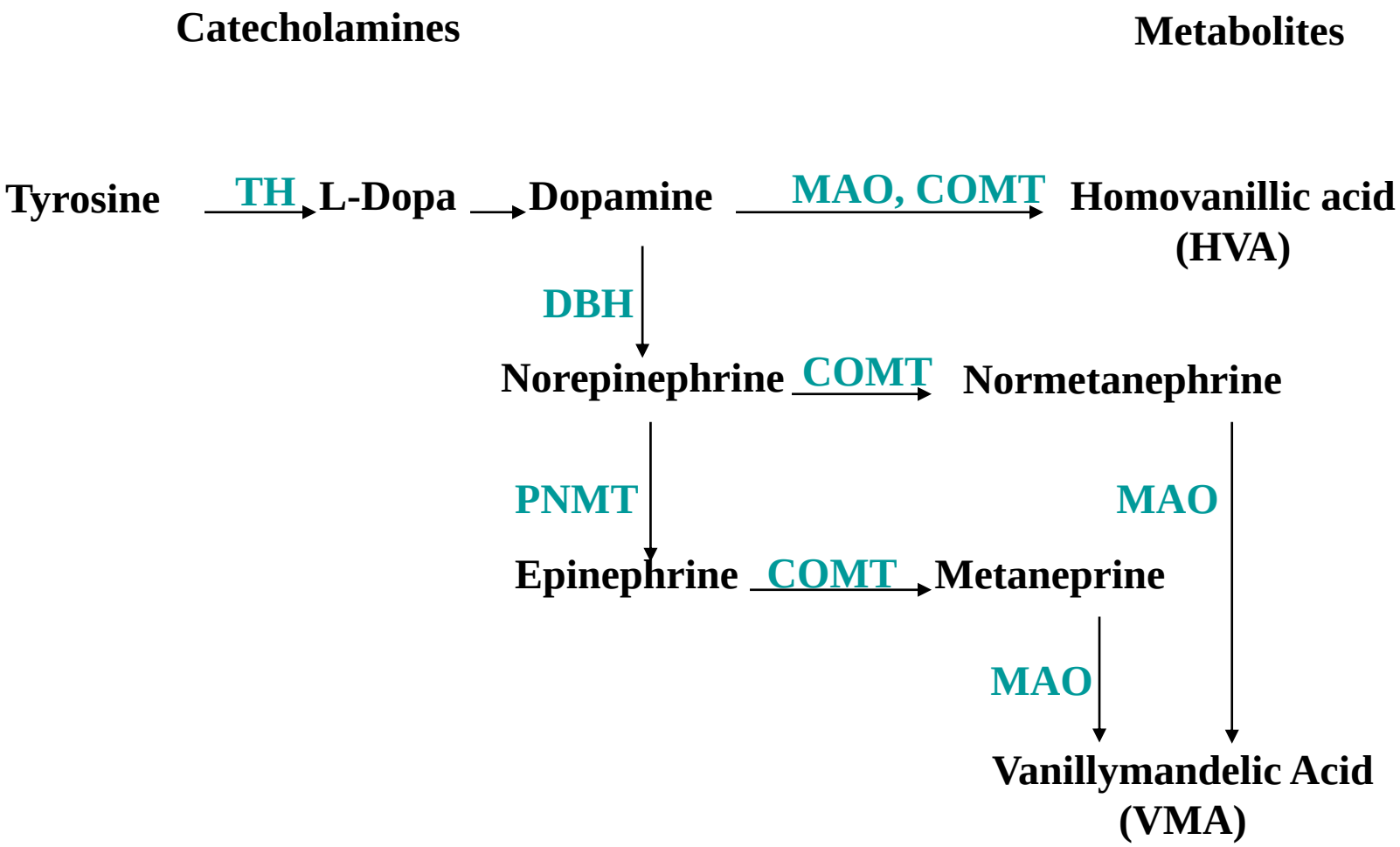
- **Catecholamine metabolites:**

metanephrine and **vanillylmandelic acid** (VMA) 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

Metabolism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Treatment

- Laparoscopic Adrenalectomy

Pre-op:

(1) Control of hypertension

(2) α blockers 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