Medical Committee
The University of Jordan

PHARMACOLOGY

Slide # : 8

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Introduction to Autonomic Pharmacology

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Introduction to Autonomic Pharmacology

- **The autonomic nervous system activities are not under direct conscious control.**
- **It is concerned primarily with visceral functions such as cardiac output, blood flow and digestion, ..etc .**

Autonomic Nervous System

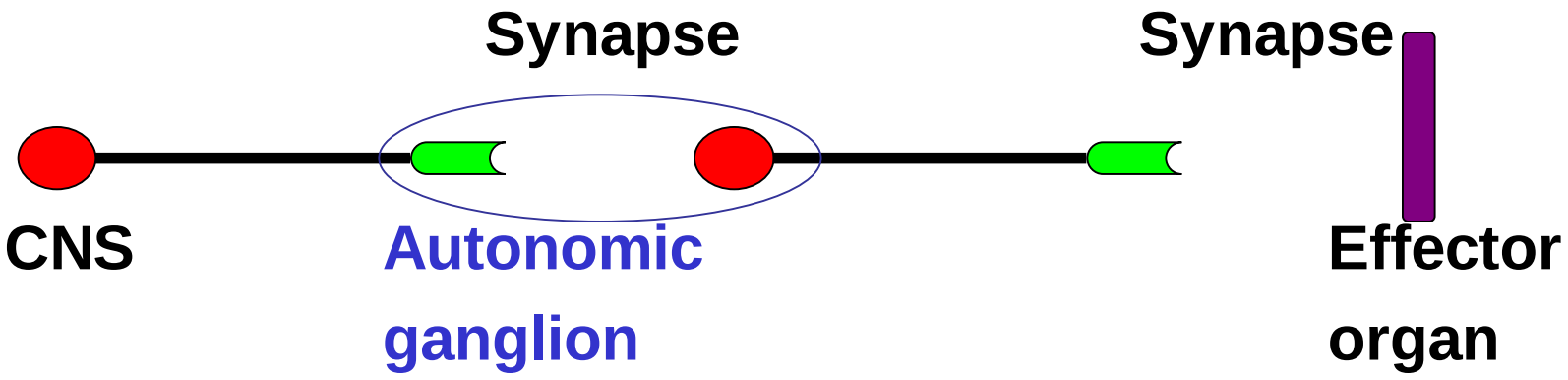
2 major divisions:

1. **Sympathetic (thoracolumbar)**
2. **Parasympathetic (craniosacral)**

- **Both divisions originate in nuclei within the central nervous system → give rise to preganglionic efferent fibers that exit from brain stem or spinal cord and terminate in autonomic ganglia.**

Autonomic Nervous System

- **From the autonomic ganglia, postganglionic fibers run to the tissues involved.**



ANS Neurotransmitters

- **Neurons of the ANS release chemicals called neurotransmitters into the synapse, which carry information to or activate the next cells.**
- **These chemicals may be:**

1. **Acetylcholine and the nerves that release it are called cholinergic nerves.**
2. **Norepinephrine (noradrenaline) and the nerves that release it are called adrenergic nerves.**

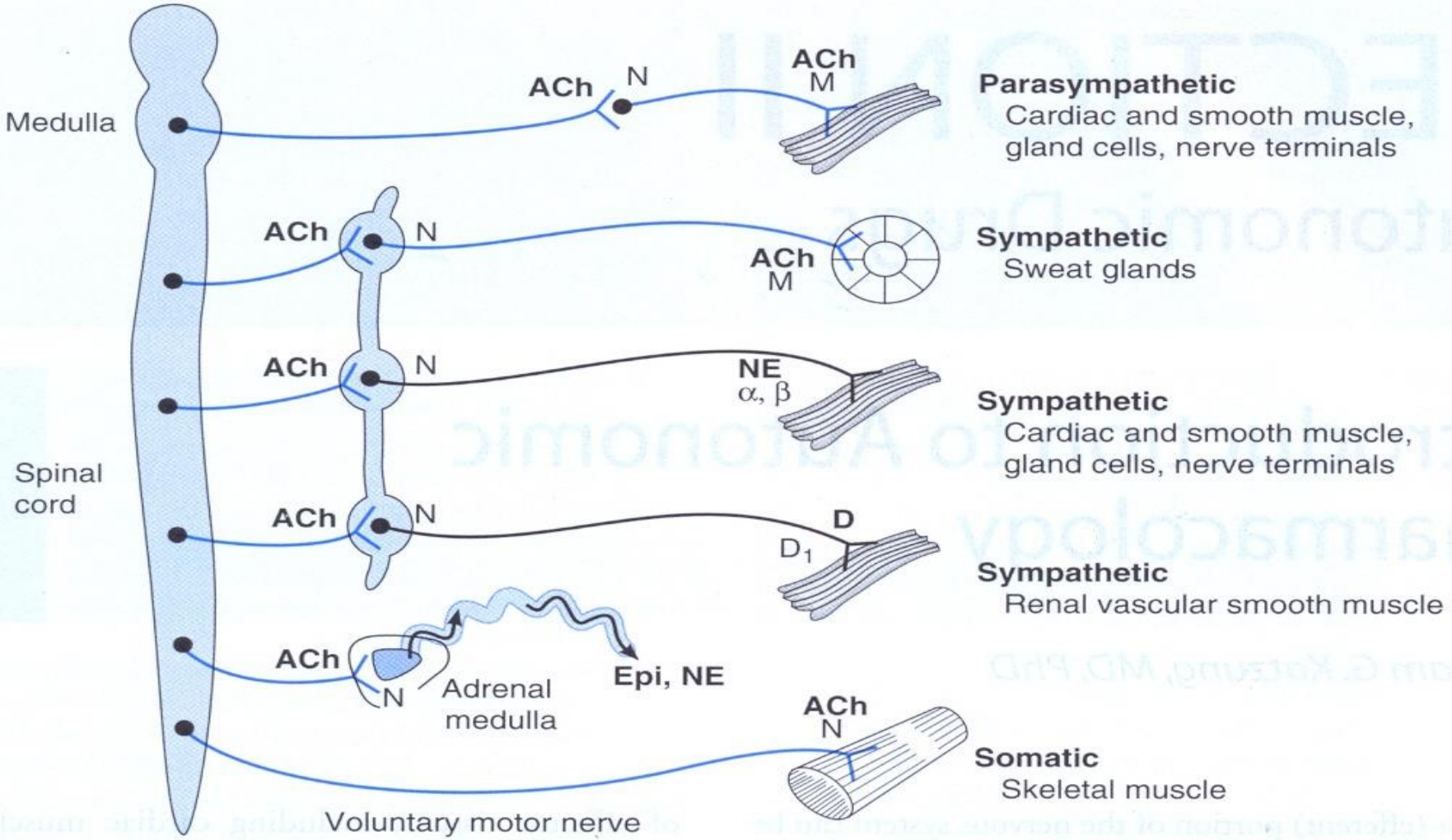


Figure 6–1. Schematic diagram comparing some anatomic and neurotransmitter features of autonomic and somatic motor nerves. Only the primary transmitter substances are shown. Parasympathetic ganglia are not shown because most are in or near the wall of the organ innervated. Cholinergic nerves are shown in color. Note that some sympathetic postganglionic fibers release acetylcholine or dopamine rather than norepinephrine. The adrenal medulla, a modified sympathetic ganglion, receives sympathetic preganglionic fibers and releases epinephrine and norepinephrine into the blood. (ACh, acetylcholine; D, dopamine; Epi, epinephrine; NE, norepinephrine; N, nicotinic receptors; M, muscarinic receptors.)

ANS Neurotransmitters

Cholinergic fibers include:

1. **Autonomic preganglionic fibers.**
2. **Parasympathetic postganglionic fibers.**
3. **Few sympathetic postganglionic fibers (sweat gland).**

ANS Neurotransmitters

Adrenergic fibers include:

1. **Most sympathetic postganglionic fibers.**
2. **Some sympathetic postganglionic fiber release dopamine.**
3. **Adrenal medulla releases a mixture of epinephrine (adrenaline) and norepinephrine (noradrenaline).**

- **Most autonomic nerves also release co-transmitters in addition.**

ANS Neurotransmitters

Key features of neurotransmitters as potential targets for pharmacologic agents:

1. **Synthesis.**
2. **Storage.**
3. **Release.**
4. **Termination of action.**
5. **Function of the receptor.**

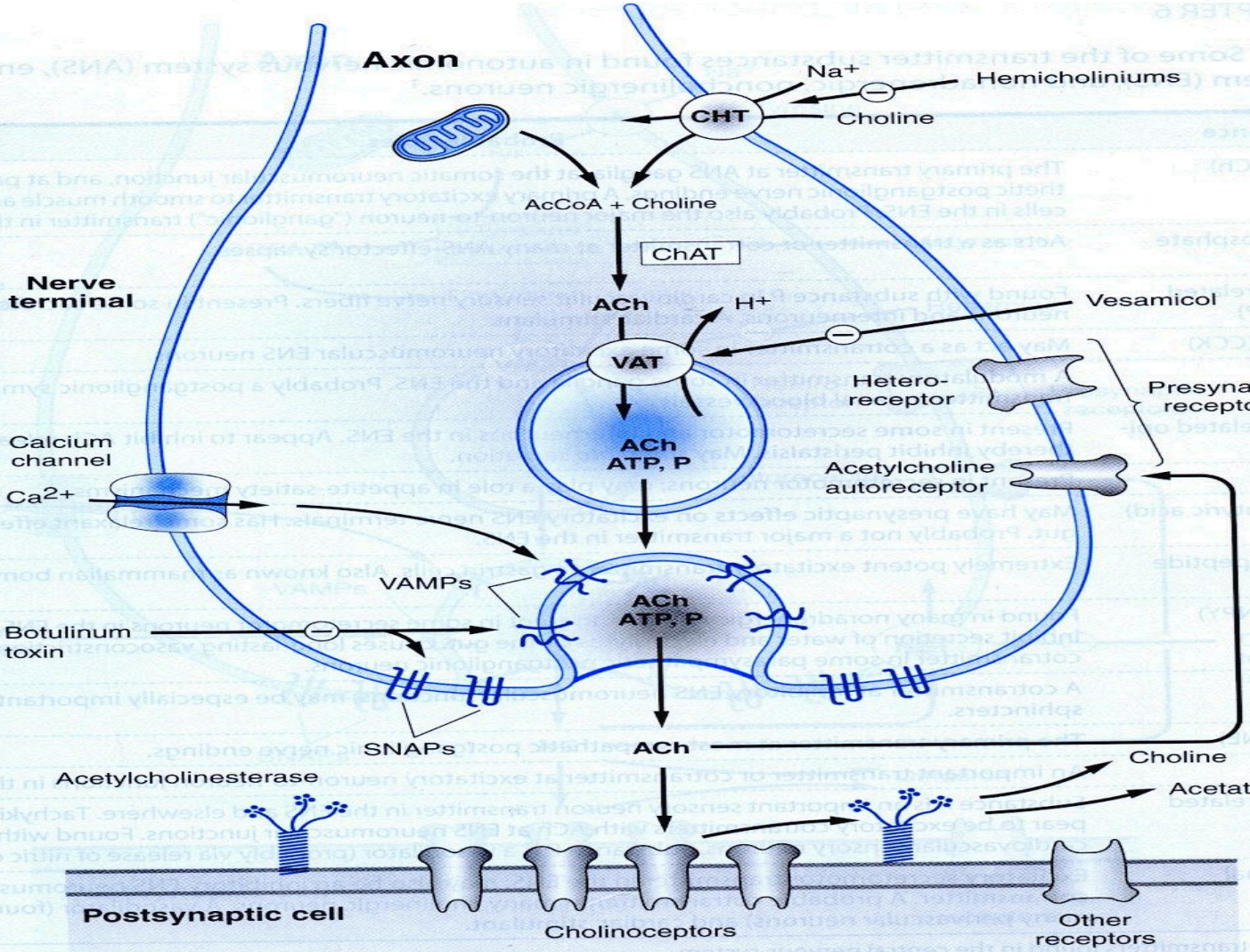


Figure 6–3. Schematic illustration of a generalized cholinergic junction (not to scale). Choline is transported into the presynaptic nerve terminal by a sodium-dependent choline transporter (CHT). This transporter can be inhibited by hemicholinium drugs. In the cytoplasm, acetylcholine is synthesized from choline and acetyl Co-A (AcCoA) by the enzyme choline acetyltransferase (ChAT). ACh is then transported into the storage vesicle by a second carrier, the vesicle-associated transporter (VAT), which can be inhibited by vesamicol. Peptides (P), adenosine triphosphate (ATP), and proteoglycan are also stored in the vesicle. Release of transmitter occurs when voltage-sensitive calcium channels in the terminal membrane are opened, allowing an influx of calcium. The resulting increase in intracellular calcium causes fusion of vesicles with the surface membrane and exocytotic expulsion of ACh and cotransmitters into the junctional cleft (see text). This step can be blocked by botulinum toxin. Acetylcholine's action is terminated by metabolism by the enzyme acetylcholinesterase. Receptors on the presynaptic nerve ending regulate transmitter release. (SNAPs, synaptosome-associated proteins; VAMPs, vesicle-associated membrane proteins.)

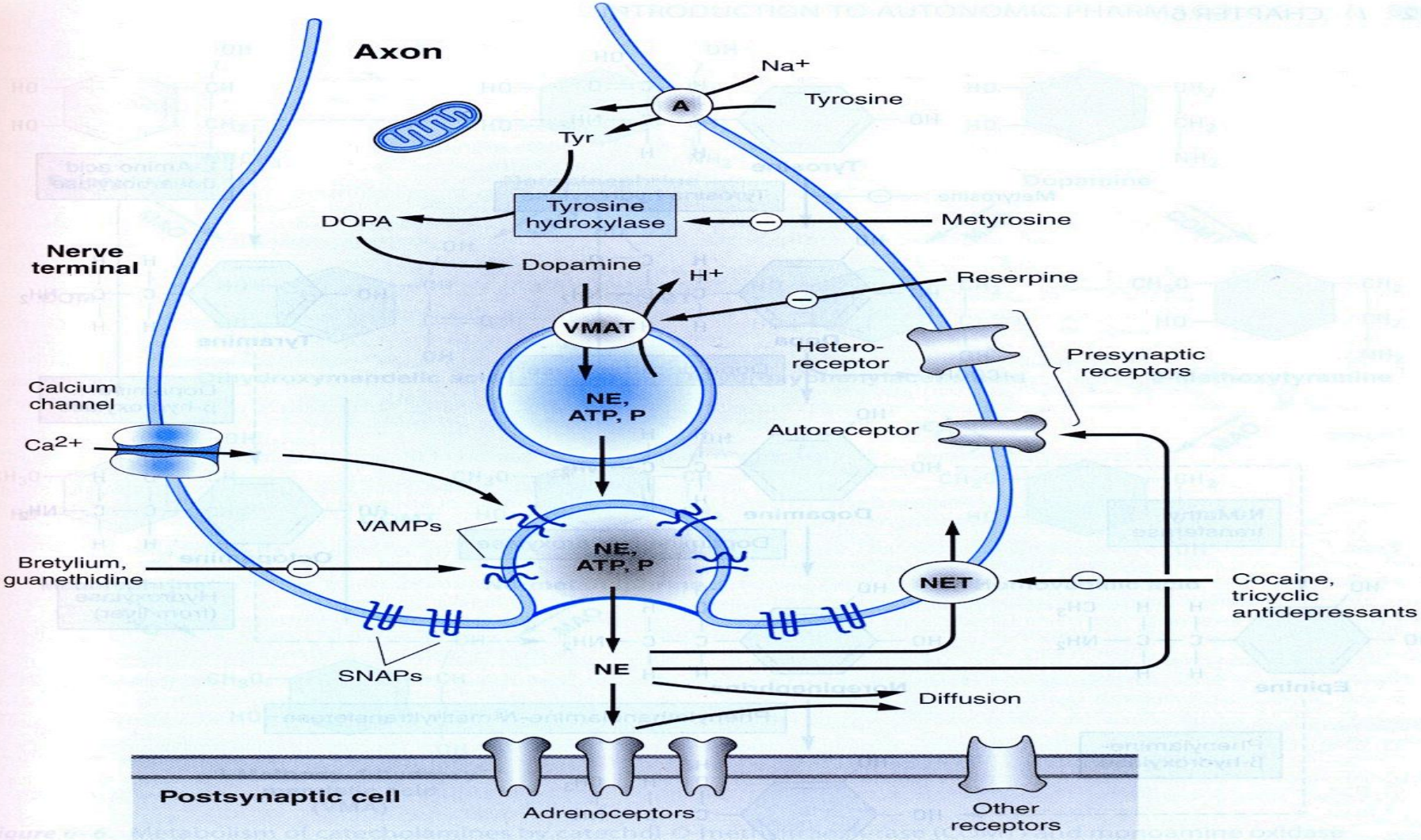


Figure 6–4. Schematic diagram of a generalized noradrenergic junction (not to scale). Tyrosine is transported into the noradrenergic ending or varicosity by a sodium-dependent carrier (A). Tyrosine is converted to dopamine (see Figure 6–5 for details), which is transported into the vesicle by the vesicular monoamine transporter (VMAT), which can be blocked by reserpine. The same carrier transports norepinephrine (NE) and several other amines into these granules. Dopamine is converted to NE in the vesicle by dopamine-β-hydroxylase. Physiologic release of transmitter occurs when an action potential opens voltage-sensitive calcium channels and increases intracellular calcium. Fusion of vesicles with the surface membrane results in expulsion of norepinephrine, cotransmitters, and dopamine-β-hydroxylase. Release can be blocked by drugs such as guanethidine and bretylium. After release, norepinephrine diffuses out of the cleft or is transported into the cytoplasm of the terminal by the norepinephrine transporter (NET), which can be blocked by cocaine and tricyclic antidepressants, or into postjunctional or perijunctional cells. Regulatory receptors are present on the presynaptic terminal.

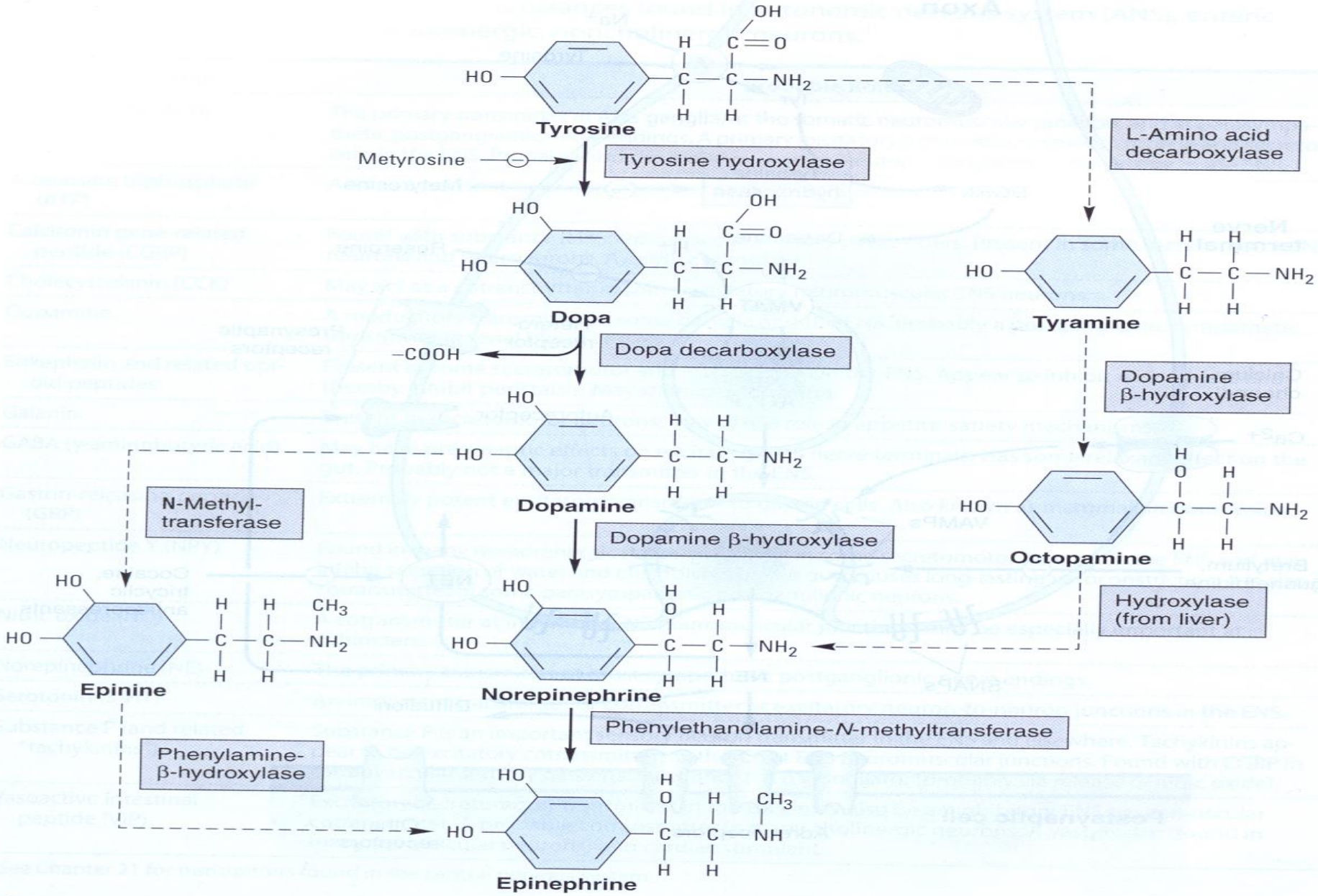


Figure 6–5. Biosynthesis of catecholamines. The rate-limiting step, conversion of tyrosine to dopa, can be inhibited by metyrosine (α-methyltyrosine). The alternative pathways shown by the dashed arrows have not been found to be of physiologic significance in humans. However, tyramine and octopamine may accumulate in patients treated with monoamine oxidase inhibitors. (Reproduced, with permission, from Greenspan FS, Gardner DG (editors): *Basic and Clinical Endocrinology,* 7th ed. McGraw-Hill, 2003.)

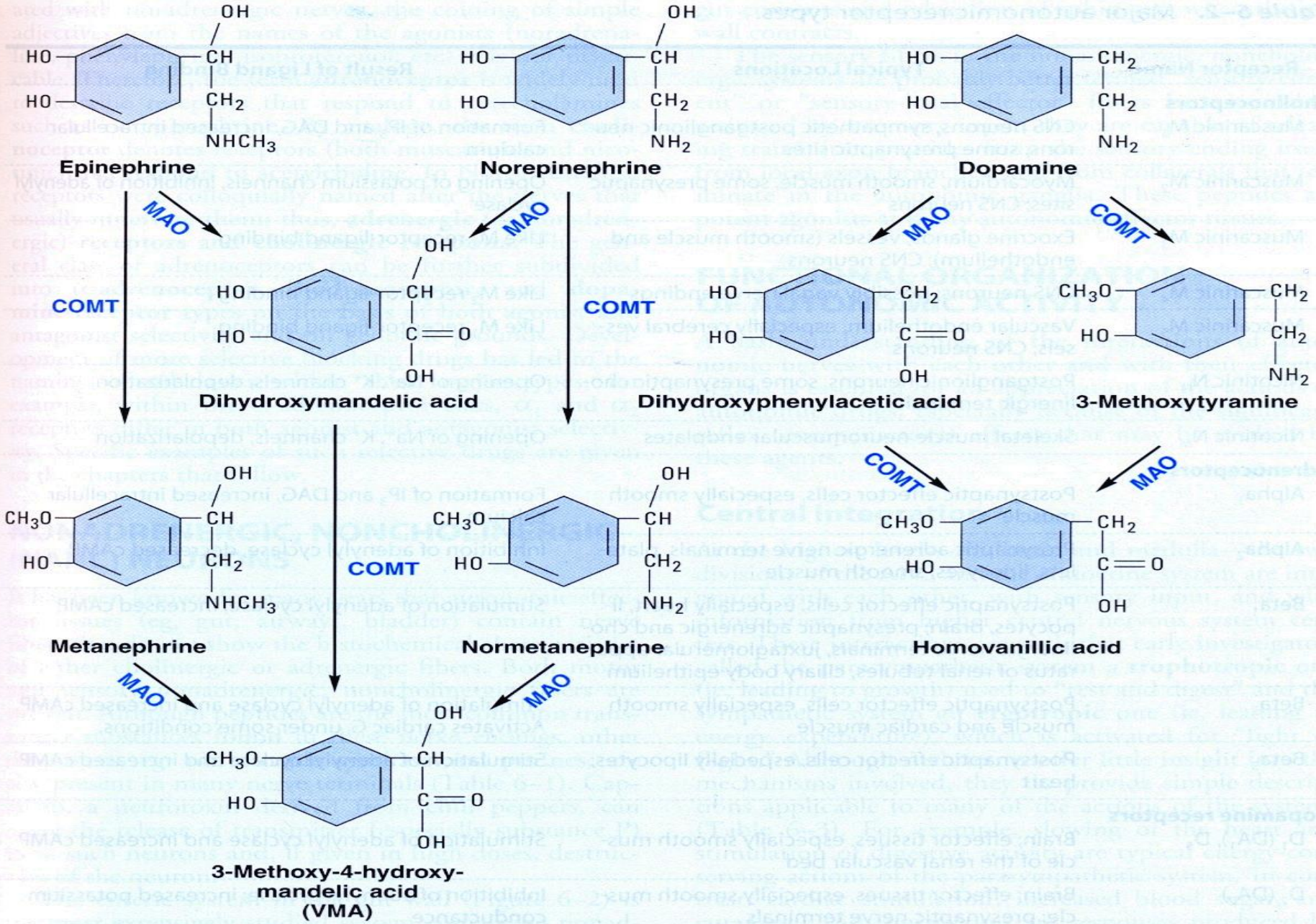


Figure 6–6. Metabolism of catecholamines by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). (Modified and reproduced, with permission, from Greenspan FS, Gardner DG (editors): *Basic and Clinical Endocrinology,* 7th ed. McGraw-Hill, 2003.)

Autonomic Receptors

- **Cholinoceptors (Cholinergic): Receptors stimulated by acetylcholine. Muscarinic and nicotinic receptors stimulated by the alkaloids muscarine and nicotine, respectively.**
- **Adrenoceptors (Adrenergic): Receptors stimulated by catecholamines such as norepinephrine (noradrenaline).**
- **Dopamine receptors (Dopaminergic): Receptors stimulated by dopamine.**

Autonomic Receptors

Receptor Name	Typical Locations
Cholinoceptors	
Muscarinic M_1	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites
Muscarinic M_2	Myocardium, smooth muscle, some presynaptic sites; CNS neurons
Muscarinic M_3	Exocrine glands, vessels (smooth muscle and endothelium); CNS neurons
Muscarinic M_4	CNS neurons; possibly vagal nerve endings
Muscarinic M_5	Vascular endothelium, especially cerebral vessels; CNS neurons
Nicotinic N_N	Postganglionic neurons, some presynaptic cholinergic terminals
Nicotinic N_M	Skeletal muscle neuromuscular endplates

Autonomic Receptors

Adrenoceptors	
$Alpha_1$	Postsynaptic effector cells, especially smooth muscle
$Alpha_2$	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle
$Beta_1$	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals, juxtaglomerular apparatus of renal tubules, ciliary body epithelium
$Beta_2$	Postsynaptic effector cells, especially smooth muscle and cardiac muscle
$Beta_3$	Postsynaptic effector cells, especially lipocytes; heart

Autonomic Receptors

Dopamine receptors	
D_1 (DA_1), D_5	Brain; effector tissues, especially smooth muscle of the renal vascular bed
D_2 (DA_2)	Brain; effector tissues, especially smooth muscle; presynaptic nerve terminals
D_3	Brain
D_4	Brain, cardiovascular system

Presynaptic Regulation

- **Negative feedback control is found at the presynaptic level of autonomic function, such as:**
- **Presynaptic α_2-adrenoceptors when activated by norepinephrine and similar substances lead to reduction of further norepinephrine release.**

Presynaptic Regulation

- **Conversely, Presynaptic β-adrenoceptors when activated by norepinephrine and similar substances facilitate further norepinephrine release.**
- **These receptors are called autoreceptors.**
- **Heteroreceptors may also be involved in presynaptic regulation. They are activated by substances released from other nerve terminals.**

Presynaptic Regulation

1. **Some vagal fibers in the myocardium synapse on sympathetic noradrenergic nerve terminals and inhibit norepinephrine release.**
2. **Alternatively, some substances move to these receptors from the blood or nearby tissues.**

Presynaptic Regulation

3. Serotonin (5-HT) stimulation of its receptors at cholinergic preganglionic sites inhibits cholinergic transmission.
4. Adenosine and ATP stimulation of their receptors (P_1 and P_2 respectively) at adrenergic autonomic neurons inhibit adrenergic function.
5. Angiotensin II stimulates its receptor (AT_2-1) at adrenergic nerve terminals & stimulates adrenergic transmission.

Postsynaptic regulation

1. **Up-regulation of receptors: Increased number of receptors upon continued decreased receptor activation (antagonist).**
2. **Down regulation of receptors: Decreased number of receptors upon continued increased receptor activation (agonist).**

Effects of Autonomic Nerve Activation

Table 6–3. Direct effects of autonomic *nerve* activity on some organ systems. Autonomic *drug* effects are similar but not identical (see text).

	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
Organ	Action[1]	Receptor[2]	Action	Receptor[2]
Eye				
Iris radial muscle	Contracts	α_1	…	…
Iris circular muscle	…	…	Contracts	M_3
Ciliary muscle	[Relaxes]	β	Contracts	M_3
Heart				
Sinoatrial node	Accelerates	β_1,β_2	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1,β_2	…	…
Contractility	Increases	β_1,β_2	Decreases (atria)	M_2
Blood vessels				
Skin, splanchnic vessels	Contracts	α	…	…
Skeletal muscle vessels	Relaxes	β_2	…	…
	[Contracts]	α	…	…
	Relaxes	M[3]	…	…
Endothelium			Releases EDRF[4]	M_3, M_5[5]
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M_3

Effects of Autonomic Nerve Activation

Gastrointestinal tract				
Smooth muscle				
Walls	Relaxes	α_2[6], β_2	Contracts	M_3
Sphincters	Contracts	α_1	Relaxes	M_3
Secretion	…	…	Increases	M_3
Genitourinary smooth muscle				
Bladder wall	Relaxes	β_2	Contracts	M_3
Sphincter	Contracts	α_1	Relaxes	M_3
Uterus, pregnant	Relaxes	β_2	…	…
	Contracts	α	Contracts	M_3
Penis, seminal vesicles	Ejaculation	α	Erection	M
Skin				
Pilomotor smooth muscle	Contracts	α	…	…
Sweat glands			…	…
Thermoregulatory	Increases	M	…	…
Apocrine (stress)	Increases	α	…	…
Metabolic functions				
Liver	Gluconeogenesis	β_2,α	…	…
Liver	Glycogenolysis	β_2,α	…	…
Fat cells	Lipolysis	β_3	…	…
Kidney	Renin release	β_1	…	…

Effects of Autonomic Nerve Activation

[1]Less important actions are shown in brackets.

[2]Specific receptor type: α = alpha, β = beta, M = muscarinic.

[3]Vascular smooth muscle in skeletal muscle has sympathetic cholinergic dilator fibers.

[4]The endothelium of most blood vessels releases EDRF (endothelium-derived relaxing factor), which causes marked vasodilation, in response to muscarinic stimuli. However, unlike the receptors innervated by sympathetic cholinergic fibers in skeletal muscle blood vessels, these muscarinic receptors are not innervated and respond only to circulating muscarinic agonists.

[5]Cerebral blood vessels dilate in response to M_3 receptor activation.

[6]Probably through presynaptic inhibition of parasympathetic activity.