Introduction to Autonomic Nervous System (ANS) Pharmacology

Yacoub Irshaid MD, PhD, ABCP

Department of Pharmacology

Introduction to ANS 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

It consists of 2 major divisions:

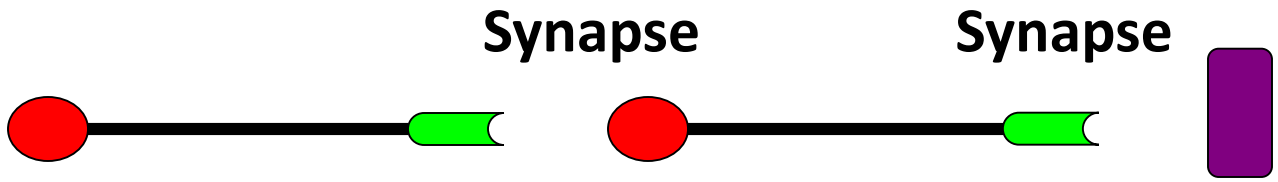
1. **Sympathetic (thoracolumbar ouflow)**
2. **Parasympathetic (craniosacral outflow)**

- **Both divisions originate in nuclei within the central nervous system, giving 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.**

Autonomic Nervous System



CNS

Autonomic ganglion

Effector organ

Preganglionic nerve

Postganglionic nerve

ANS Neurotransmitters

- **Neurons of the ANS release 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 neurones.**
2. **Norepinephrine (noradrenaline) and the nerves that release it are called adrenergic neurones.**

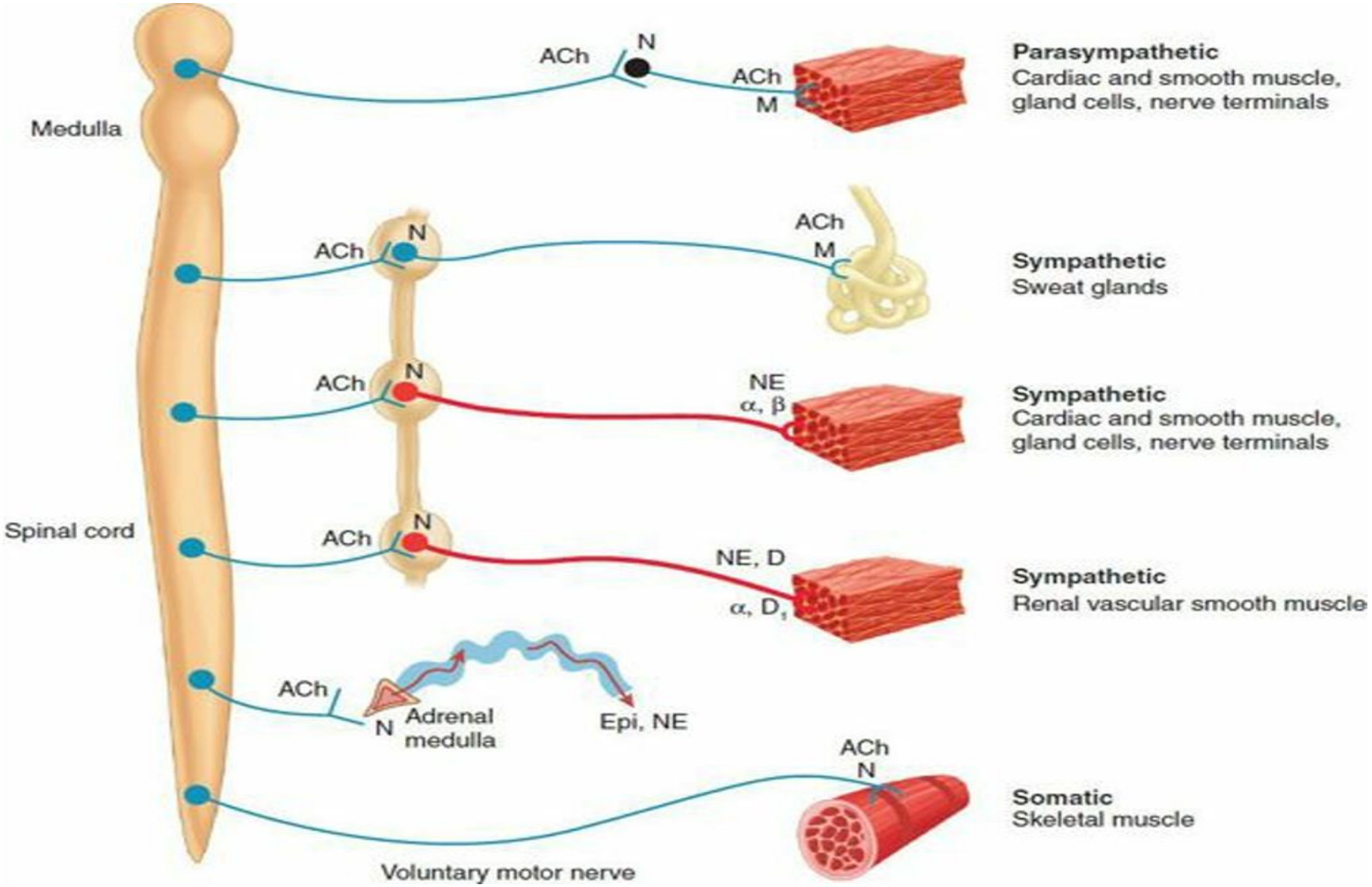


FIGURE 6–1 Schematic diagram comparing some anatomic and neurotransmitter features of autonomic and somatic motor nerves. Only the primary transmitter substances are shown. Parasympathetic ganglia are not shown because most are in or near the wall of the organ innervated. Cholinergic nerves are shown in blue, noradrenergic in red. Note that some sympathetic postganglionic fibers release acetylcholine rather than norepinephrine. Sympathetic nerves to the renal vasculature and kidney may release dopamine as well as norepinephrine during stress. 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; M, muscarinic receptors; N, nicotinic receptors; NE, norepinephrine.

ANS Neurotransmitters

Cholinergic fibers include:

1. **All autonomic preganglionic fibers.**
2. **Most 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 and norepinephrine.**

- **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. **Mechanism of termination of action.**
5. **Action on receptors.**

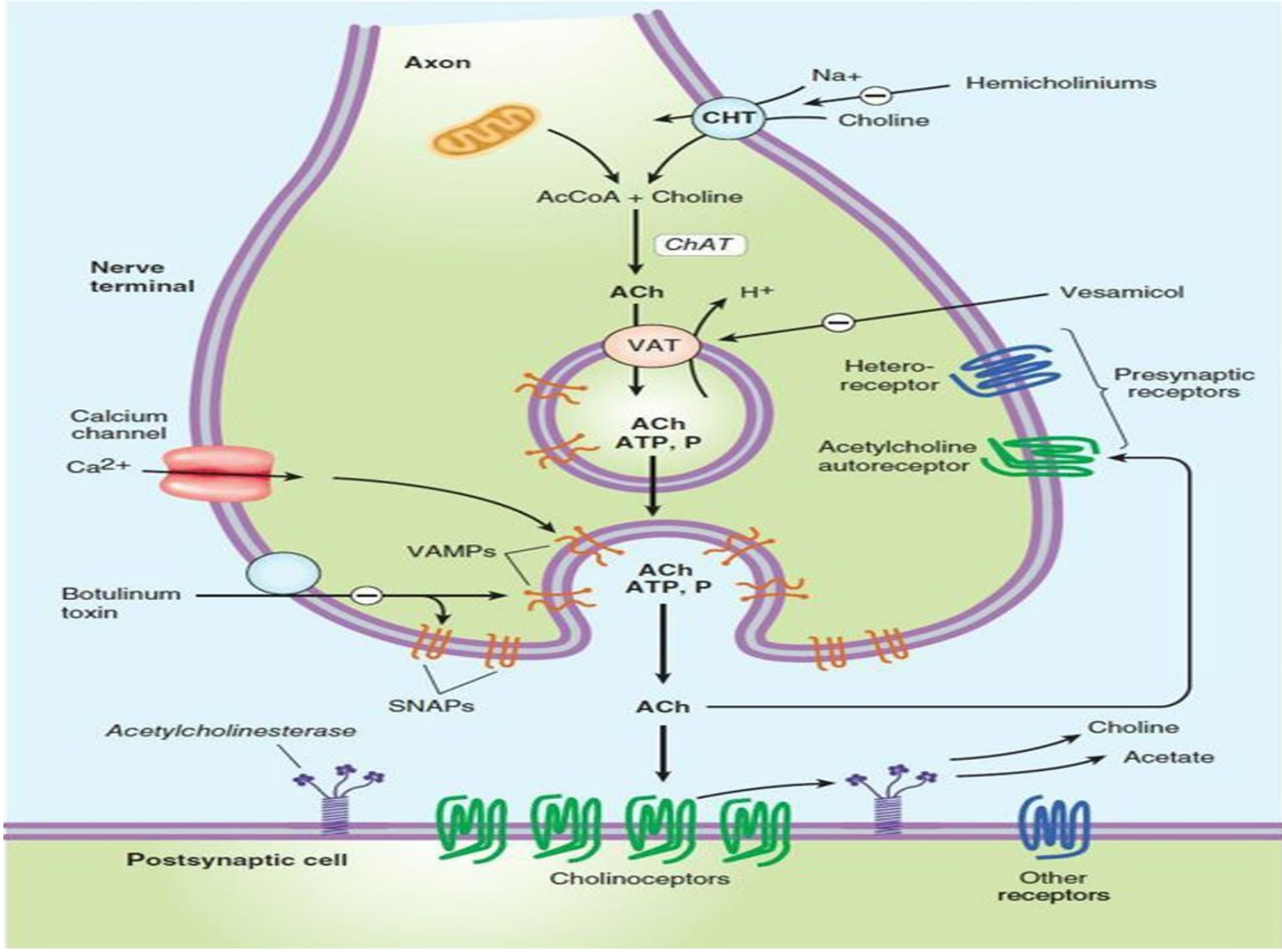

Axon
Na+
Hemicholiniums
CHT
Choline
AcCoA + Choline
ChAT
Nerve terminal
ACh
H+
Vesamicol
VAT
Hetero-receptor
Presynaptic receptors
Calcium channel
ACh ATP, P
Acetylcholine autoreceptor
Ca2+
VAMPs
ACh ATP, P
Botulinum toxin
SNAPs
ACh
Acetylcholinesterase
Choline
Acetate
Postsynaptic cell
Cholinoceptors
Other receptors

FIGURE 6–3 Schematic ilustration 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-CoA (AcCoA) by the enzyme choline acetyltransferase (ChAT). Acetylcholine (ACh) is then transported into the storage vesicle by a 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 transmitters occurs when voltage-sensitive calcium channels in the terminal membrane are opened, allowing an influx of calcium. The resulting increase in intracelular calcium causes fusion of vesicles with the surface membrane and exocytotic expulsion of acetylcholine 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 modulate transmitter release.

SNAPs, synaptosomal nerve associated proteins; VAMPs, vesicle-associated membrane proteins.

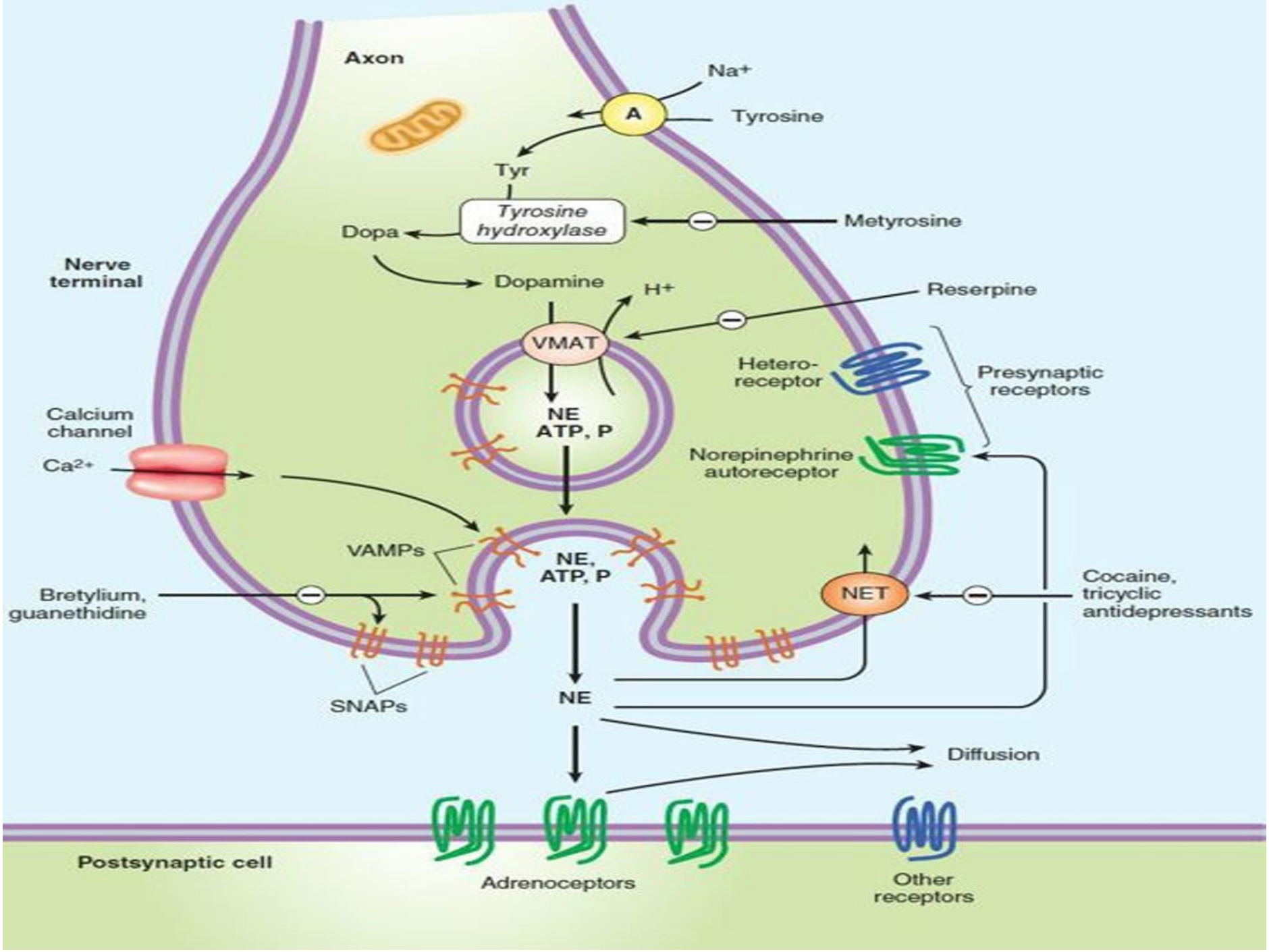

Axon
Na+
A
Tyrosine
Tyr
Tyrosine hydroxylase
Dopa
Metyrosine
Nerve terminal
Dopamine
H+
Reserpine
VMAT
Hetero-receptor
Presynaptic receptors
Calcium channel
Ca2+
NE ATP, P
Norepinephrine autoreceptor
VAMPs
NE, ATP, P
Bretylium, guanethidine
NET
Cocaine, tricyclic antidepressants
SNAPs
NE
Diffusion
Postsynaptic cell
Adrenoceptors
Other receptors

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), and transported into the vesicle by the vesicular monoamine transporter (VMAT), which can be blocked by reserpine. The same carrier transports norepinephrine (NE) and several related amines into these vesicles. 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 certain antidepressants, or into postjunctional or perijunctional cells. Regulatory receptors are present on the presynaptic terminal.

SNAPs, synaptosome-associated proteins; VAMPs, vesicle-associated membrane proteins.

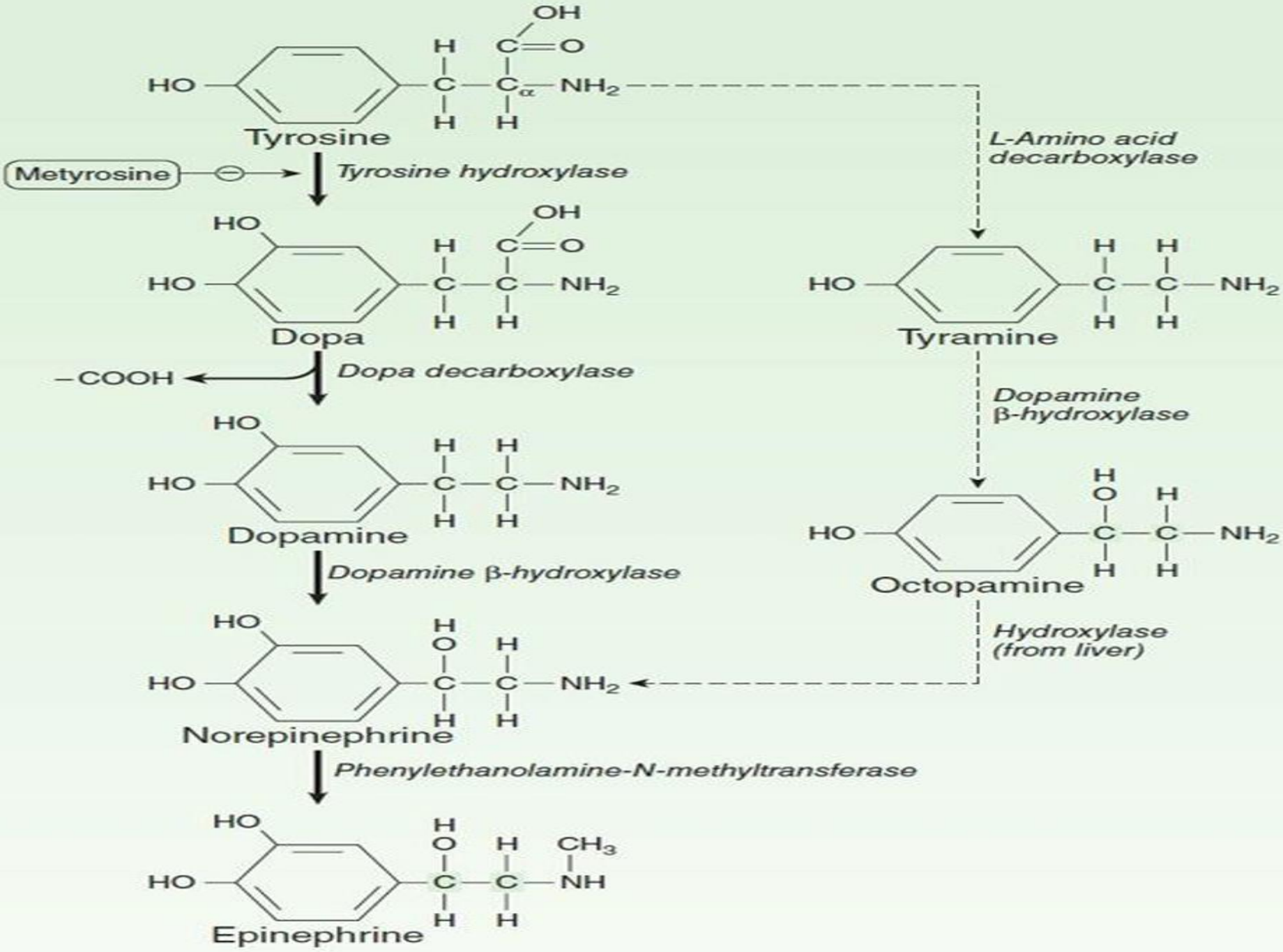

Tyrosine
Metyrosine
Tyrosine hydroxylase
L-Amino acid decarboxylase
Dopa
Dopa decarboxylase
–COOH
Tyramine
Dopamine β-hydroxylase
Dopamine
Dopamine β-hydroxylase
Octopamine
Hydroxylase (from liver)
Norepinephrine
Phenylethanolamine-N-methyltransferase
Epinephrine

FIGURE 6–5 Biosynthesis of catecholamines.
The rate-limiting step, conversion of tyrosine to dopa, can be inhibited by metyrosine (α methyltyrosine). The alternative pathway shown by the dashed arrows has 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 Gardner DG, Shoback D [editors]: Greenspan's Basic & Clinical Endocrinology, 9th ed. McGraw-Hil, 2011. Copyright © The McGraw-Hil Companies, Inc.)

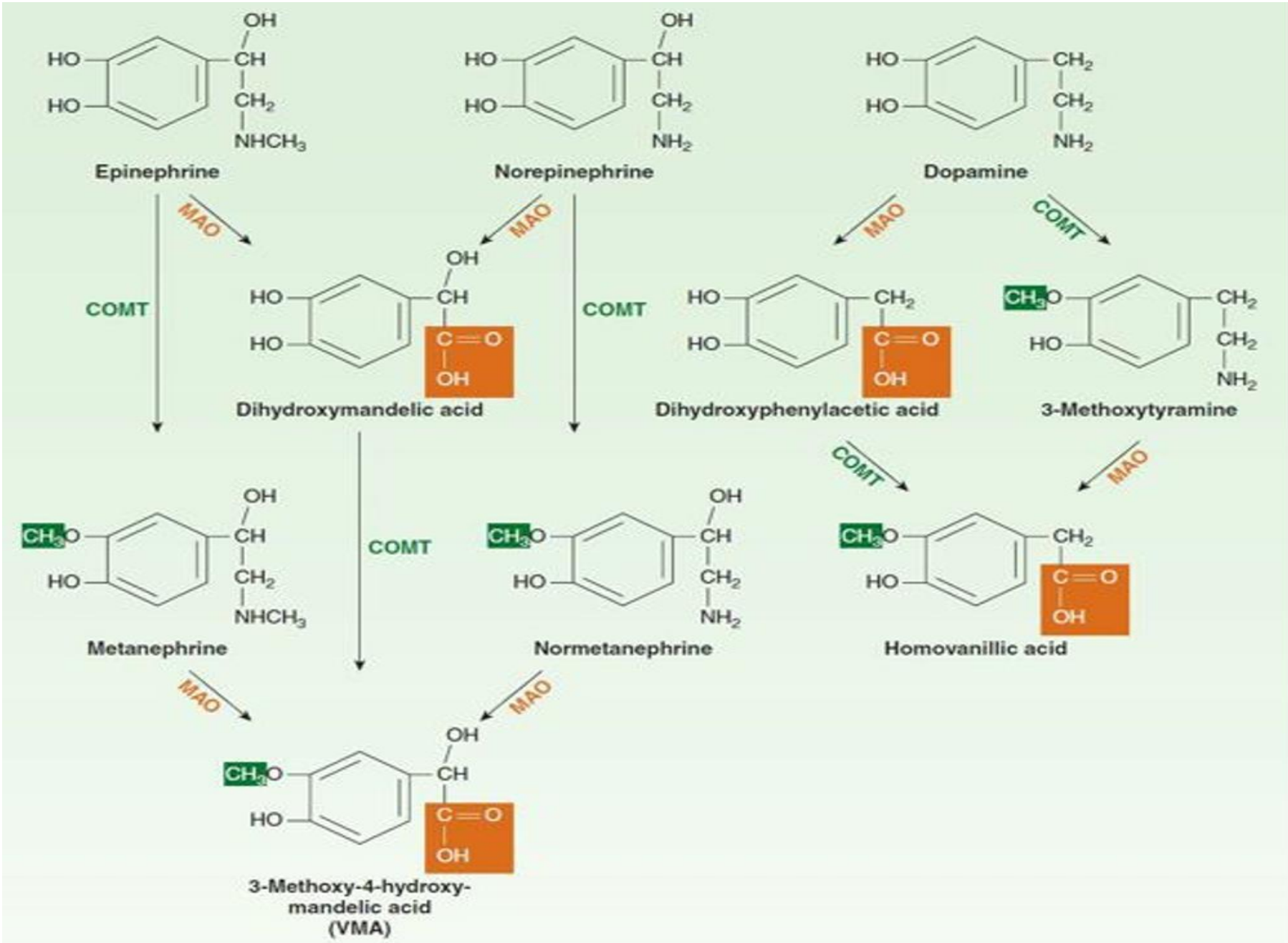


FIGURE 6–6 Metabolism of catecholamines by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). (Reproduced,

Autonomic Receptors

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

Autonomic Receptors

TABLE 6–2 Major autonomic receptor types.

Receptor Name	Typical Locations	Result of Ligand Binding
Cholinoceptors		
Muscarinic M_1	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites	Formation of IP_3 and DAG, increased intracellular calcium
Muscarinic M_2	Myocardium, smooth muscle, some presynaptic sites; CNS neurons	Opening of potassium channels, inhibition of adenylyl cyclase
Muscarinic M_3	Exocrine glands, vessels (smooth muscle and endothelium); CNS neurons	Like M_1 receptor-ligand binding
Muscarinic M_4	CNS neurons; possibly vagal nerve endings	Like M_2 receptor-ligand binding
Muscarinic M_5	Vascular endothelium, especially cerebral vessels; CNS neurons	Like M_1 receptor-ligand binding
Nicotinic N_N	Postganglionic neurons, some presynaptic cholinergic terminals; receptors typically contain two $\alpha 3$ and one $\beta 4$ type subunits in addition to γ and δ subunits	Opening of Na^+, K^+ channels, depolarization
Nicotinic N_M	Skeletal muscle neuromuscular end plates; receptors typically contain two $\alpha 1$ and $\beta 1$ type subunits in addition to γ and δ subunits	Opening of Na^+, K^+ channels, depolarization

Autonomic Receptors

Adrenoceptors		
$Alpha_1$	Postsynaptic effector cells, especially smooth muscle	Formation of IP_3 and DAG, increased intracellular calcium
$Alpha_2$	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle	Inhibition of adenylyl cyclase, decreased cAMP
$Beta_1$	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals, juxtaglomerular apparatus of renal tubules, ciliary body epithelium	Stimulation of adenylyl cyclase, increased cAMP
$Beta_2$	Postsynaptic effector cells, especially smooth muscle and cardiac muscle	Stimulation of adenylyl cyclase and increased cAMP. Activates cardiac G_i under some conditions.
$Beta_3$	Postsynaptic effector cells, especially lipocytes; heart	Stimulation of adenylyl cyclase and increased cAMP[1]
Dopamine receptors		
D_1 (DA_1), D_5	Brain; effector tissues, especially smooth muscle of the renal vascular bed	Stimulation of adenylyl cyclase and increased cAMP
D_2 (DA_2)	Brain; effector tissues, especially smooth muscle; presynaptic nerve terminals	Inhibition of adenylyl cyclase; increased potassium conductance
D_3	Brain	Inhibition of adenylyl cyclase
D_4	Brain, cardiovascular system	Inhibition of adenylyl cyclase

[1] Cardiac β_3-receptor function is poorly understood, but activation does *not* appear to result in stimulation of rate or force.

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

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

Presynaptic Regulation

1. **Serotonin (5-HT) stimulation of its receptors at cholinergic preganglionic sites inhibits cholinergic transmission.**
2. **Adenosine and ATP stimulation of their receptors (P_1 and P_2 respectively) at adrenergic autonomic neurons inhibit adrenergic function.**
3. **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 by antagonist.**
2. **Down regulation of receptors: Decreased number of receptors upon continued increased receptor activation by 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[3]	M_3	…	…
Endothelium of vessels in heart, brain, viscera	…	…	Synthesizes and releases EDRF[4]	M_3, M_5[5]
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M_3

Effects of Autonomic Nerve Activation

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			…	…
Eccrine	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	…	…

[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. Parasympathetic fibers innervate muscarinic receptors in vessels in the viscera and brain, and sympathetic cholinergic fibers innervate skeletal muscle blood vessels. The muscarinic receptors in the other vessels of the peripheral circulation are not innervated and respond only to circulating muscarinic agonists.

[5]Cerebral blood vessels dilate in response to M_5 receptor activation.

[6]Probably through presynaptic inhibition of parasympathetic activity.