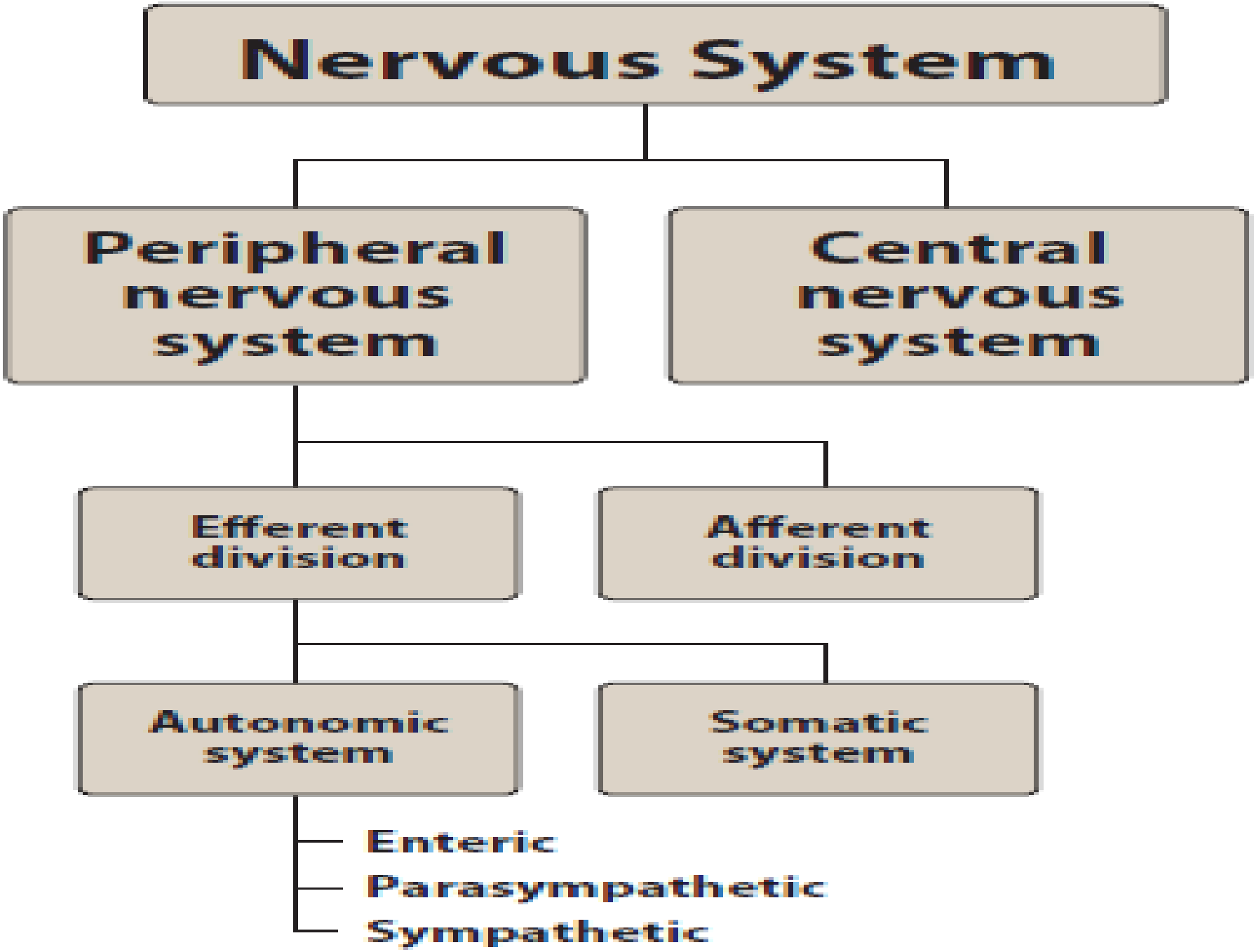
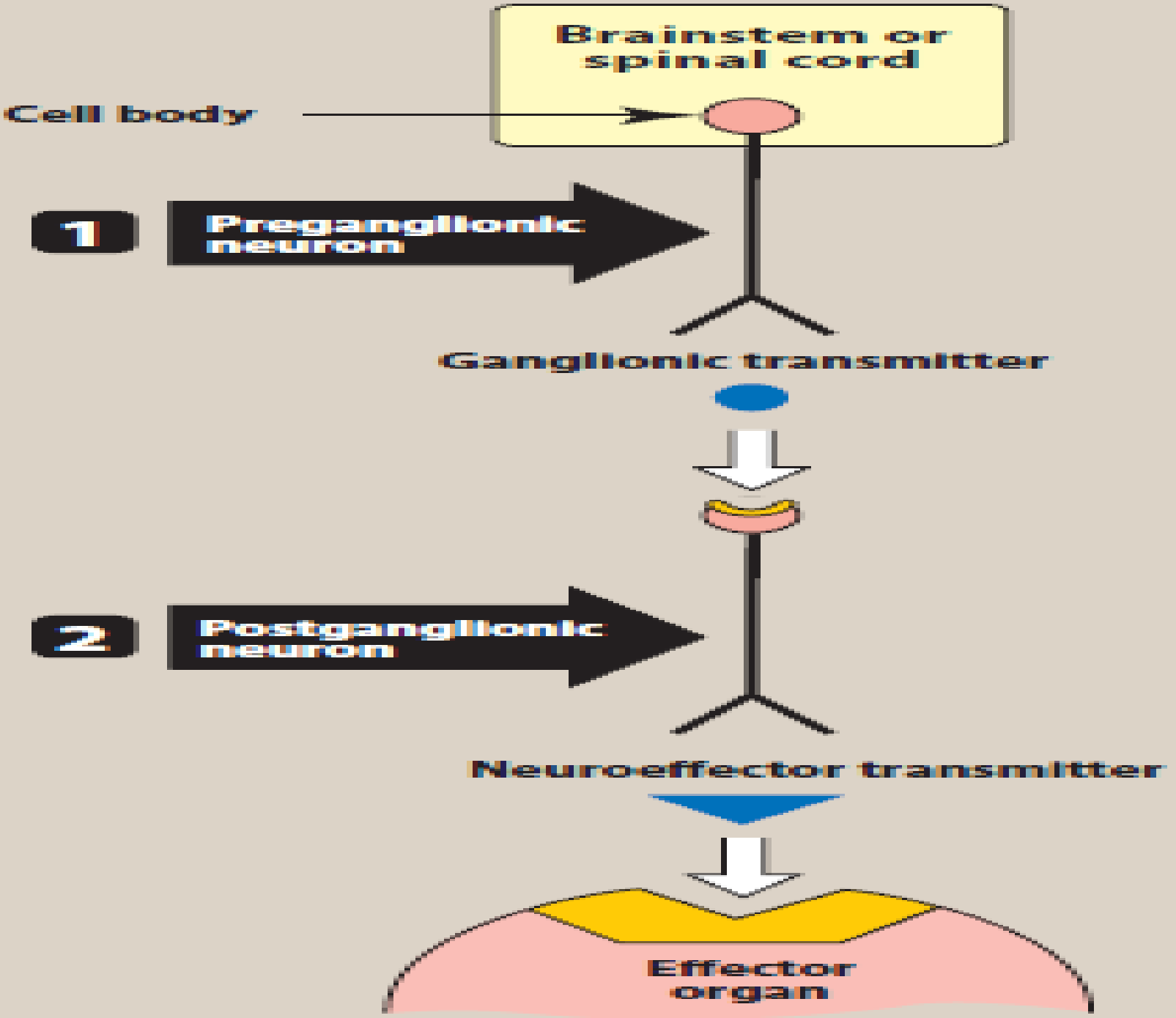
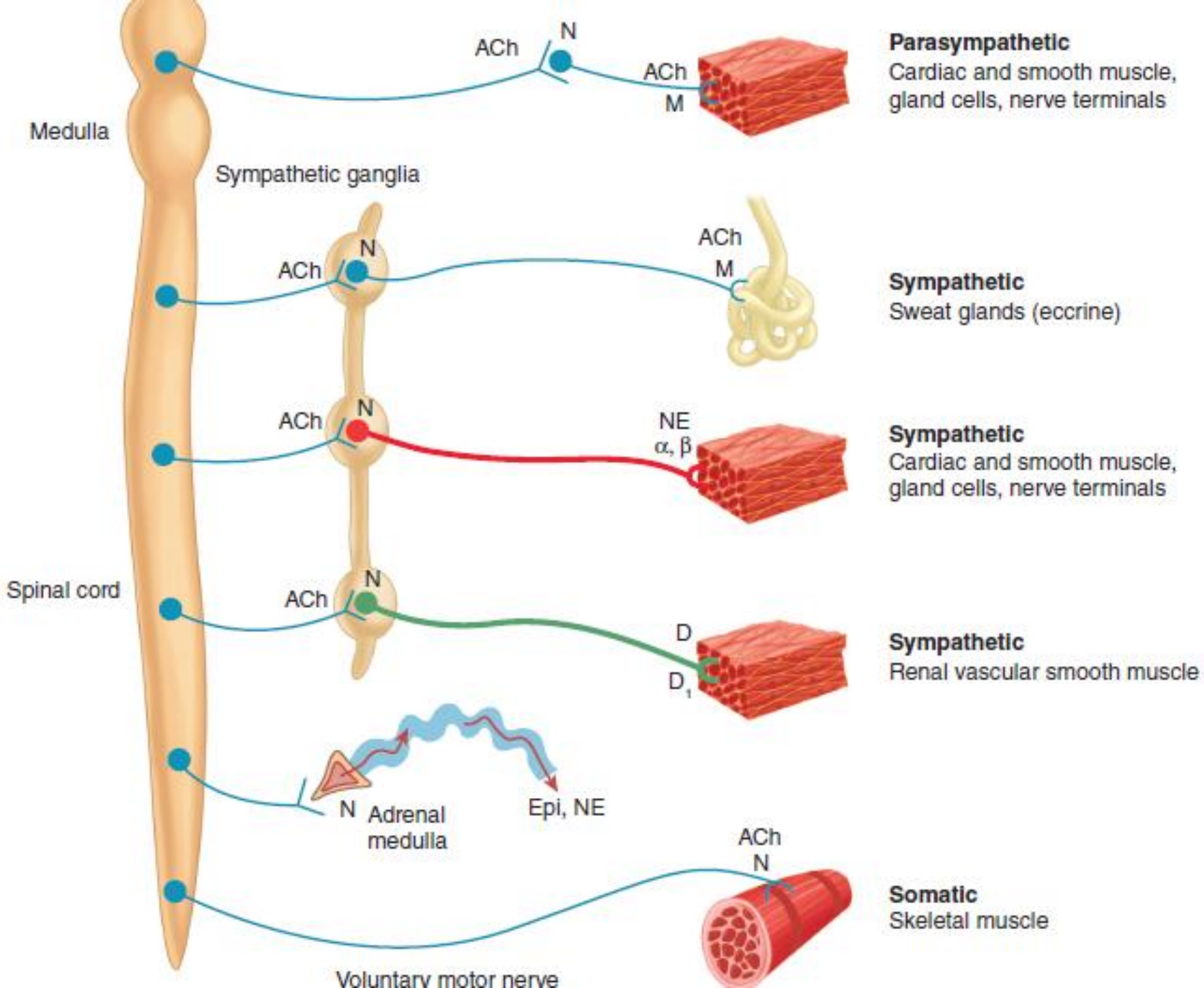
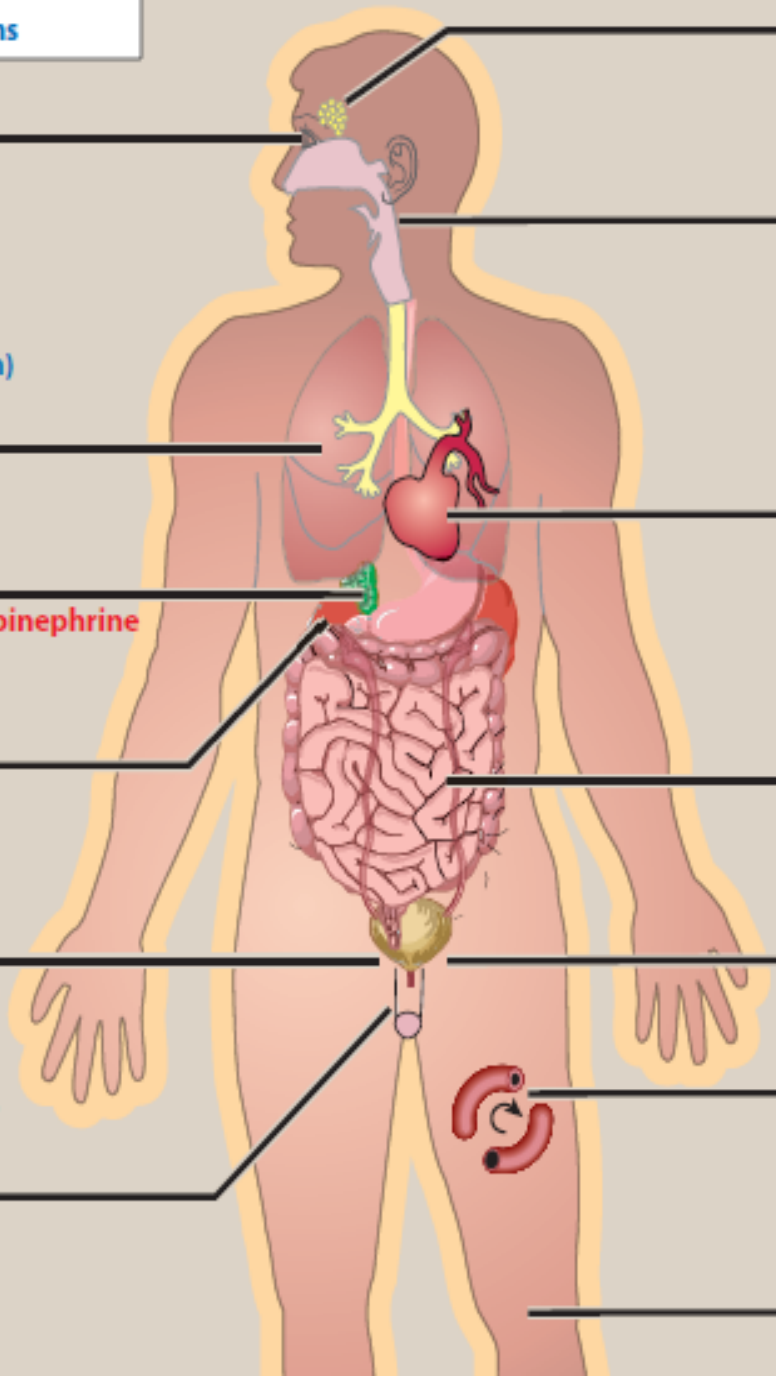

Nervous System
Peripheral nervous system
Central nervous system
Efferent division
Afferent division
Autonomic system
Somatic system
Enteric
Parasympathetic
Sympathetic


Brainstem or spinal cord
Cell body
1
Preganglionic neuron
Ganglionic transmitter
2
Postganglionic neuron
Neuroeffector transmitter
Effector organ


Medulla
Sympathetic ganglia
Spinal cord
ACh
N
ACh
M
Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh
N
ACh
M
Sympathetic
Sweat glands (eccrine)
ACh
N
NE
α, β
Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh
N
D
D1
Sympathetic
Renal vascular smooth muscle
N
Adrenal medulla
Epi, NE
ACh
N
Somatic
Skeletal muscle
Voluntary motor nerve

Red = Sympathetic actions
Blue = Parasympathetic actions



EYE

Contraction of iris radial muscle (pupil dilates)

Contraction of iris sphincter muscle (pupil contracts)
Contraction of ciliary muscle (lens accommodates for near vision)

TRACHEA AND BRONCHIOLES

Dilation
Constriction, increased secretions

ADRENAL MEDULLA

Secretion of epinephrine and norepinephrine

KIDNEY

Secretion of renin (β_1 increases; α_1 decreases)

URETERS AND BLADDER

Relaxation of detrusor; contraction of trigone and sphincter

Contraction of detrusor; relaxation of trigone and sphincter

GENITALIA (male)

Stimulation of ejaculation
Stimulation of erection

LACRIMAL GLANDS

Stimulation of tears

SALIVARY GLANDS

Thick, viscous secretion
Copious, watery secretion

HEART

Increased rate; increased contractility
Decreased rate; decreased contractility

GASTROINTESTINAL SYSTEM

Decreased muscle motility and tone; contraction of sphincters

Increased muscle motility and tone

GENITALIA (female)

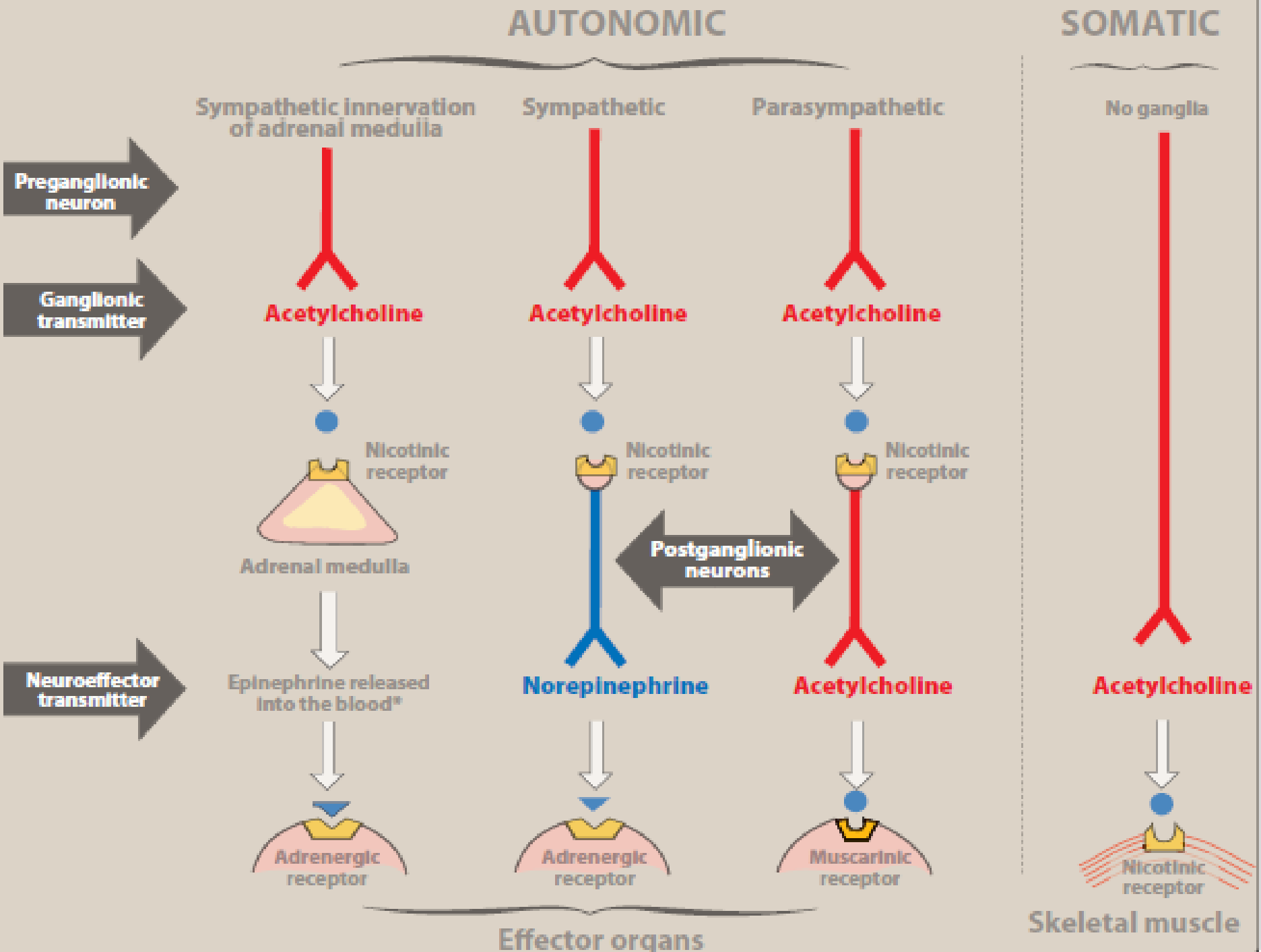
Relaxation of uterus

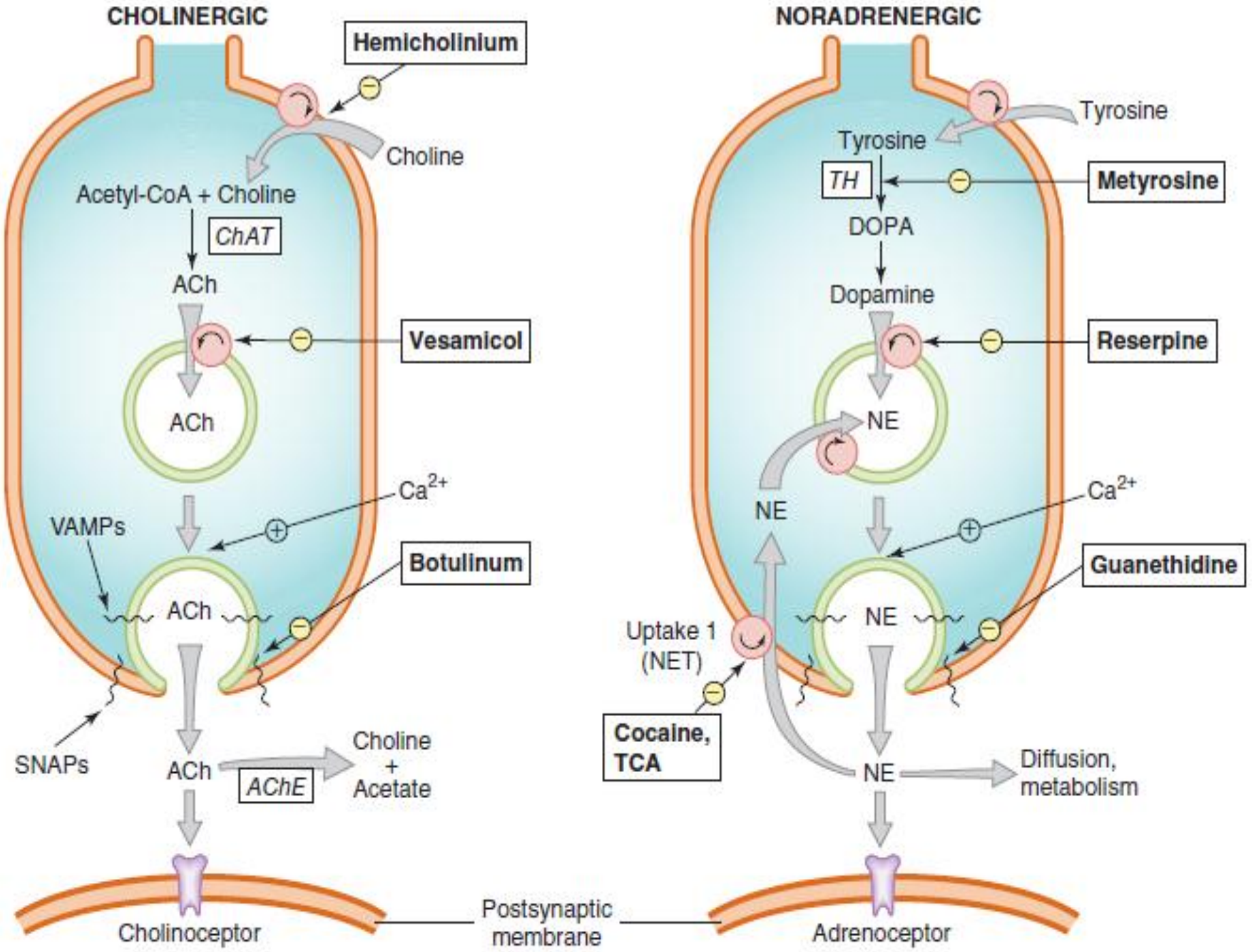
BLOOD VESSELS (skeletal muscle)

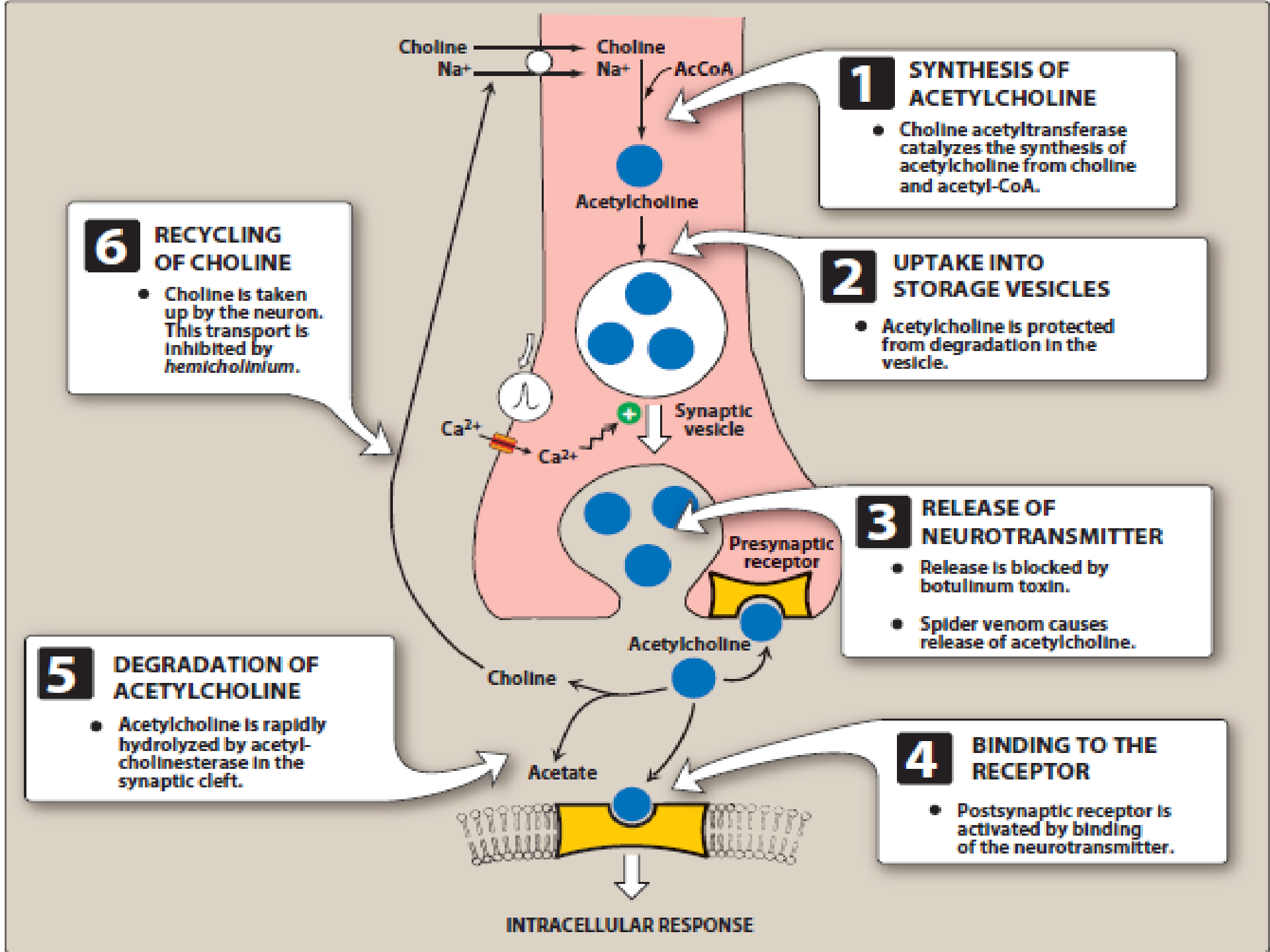
Dilation

BLOOD VESSELS (skin, mucous membranes, and splanchnic area)

Constriction


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
No ganglia
Preganglionic neuron
Ganglionic transmitter
Acetylcholine
Acetylcholine
Acetylcholine
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Neuroeffector transmitter
Epinephrine released into the blood*
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Skeletal muscle


CHOLINERGIC
Hemicholinium
Choline
Acetyl-CoA + Choline
ChAT
ACh
Vesamicol
ACh
Ca2+
VAMPs
Botulinum
ACh
SNAPs
ACh
AChE
Choline
+
Acetate
Cholinoceptor
NORADRENERGIC
Tyrosine
Tyrosine
TH
Metyrosine
DOPA
Dopamine
Reserpine
NE
NE
Ca2+
Guanethidine
NE
Uptake 1
(NET)
Cocaine,
TCA
NE
Diffusion,
metabolism
Adrenoceptor
Postsynaptic
membrane


Choline
Na+
Choline
Na+
AcCoA
Acetylcholine
1 SYNTHESIS OF ACETYLCHOLINE
• Choline acetyltransferase catalyzes the synthesis of acetylcholine from choline and acetyl-CoA.
2 UPTAKE INTO STORAGE VESICLES
• Acetylcholine is protected from degradation in the vesicle.
Synaptic vesicle
Ca2+
Ca2+
3 RELEASE OF NEUROTRANSMITTER
• Release is blocked by botulinum toxin.
• Spider venom causes release of acetylcholine.
Presynaptic receptor
Acetylcholine
4 BINDING TO THE RECEPTOR
• Postsynaptic receptor is activated by binding of the neurotransmitter.
INTRACELLULAR RESPONSE
5 DEGRADATION OF ACETYLCHOLINE
• Acetylcholine is rapidly hydrolyzed by acetylcholinesterase in the synaptic cleft.
Choline
Acetate
6 RECYCLING OF CHOLINE
• Choline is taken up by the neuron. This transport is inhibited by *hemicholinium*.

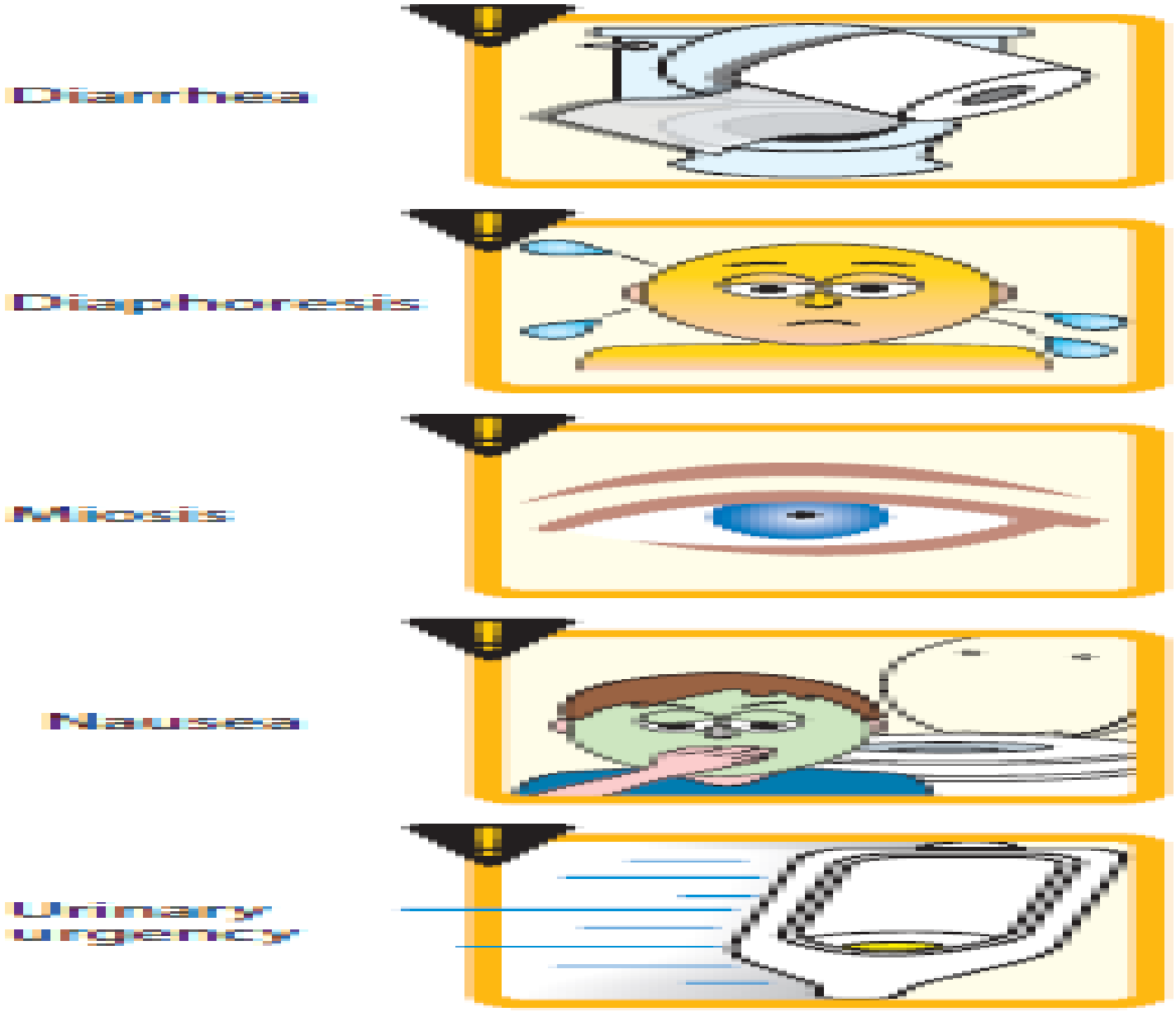


Figure 4.6
Some adverse effects observed with cholinergic agonists.

Bethanechol

- Used in treatment of urinary retention
- Binds preferentially at muscarinic receptors

Physostigmine

- Increases intestinal and bladder motility
- Reverses CNS and cardiac effects of tricyclic antidepressants
- Reverses CNS effects of *atropine*
- Uncharged, tertiary amine that can penetrate the CNS

Rivastigmine, galantamine, donepezil

- Used as first-line treatments for Alzheimer's disease, though confers modest benefit
- Have not been shown to reduce healthcare costs or delay institutionalization
- Can be used with *memantine* (N-methyl-D-aspartate antagonist) with moderate to severe disease

Carbachol

- Produces miosis during ocular surgery
- Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to *pilocarpine*

Neostigmine

- Prevents postoperative abdominal distention and urinary retention
- Used in treatment of myasthenia gravis
- Used as an antidote for competitive neuromuscular blockers
- Has intermediate duration of action (0.5 to 2 hrs)

Echothiophate

- Used in treatment of open-angle glaucoma
- Has long duration of action (100 hours)

Pilocarpine

- Reduces intraocular pressure in open-angle and narrow-angle glaucoma
- Binds preferentially at muscarinic receptors
- Uncharged, tertiary amine that can penetrate the CNS

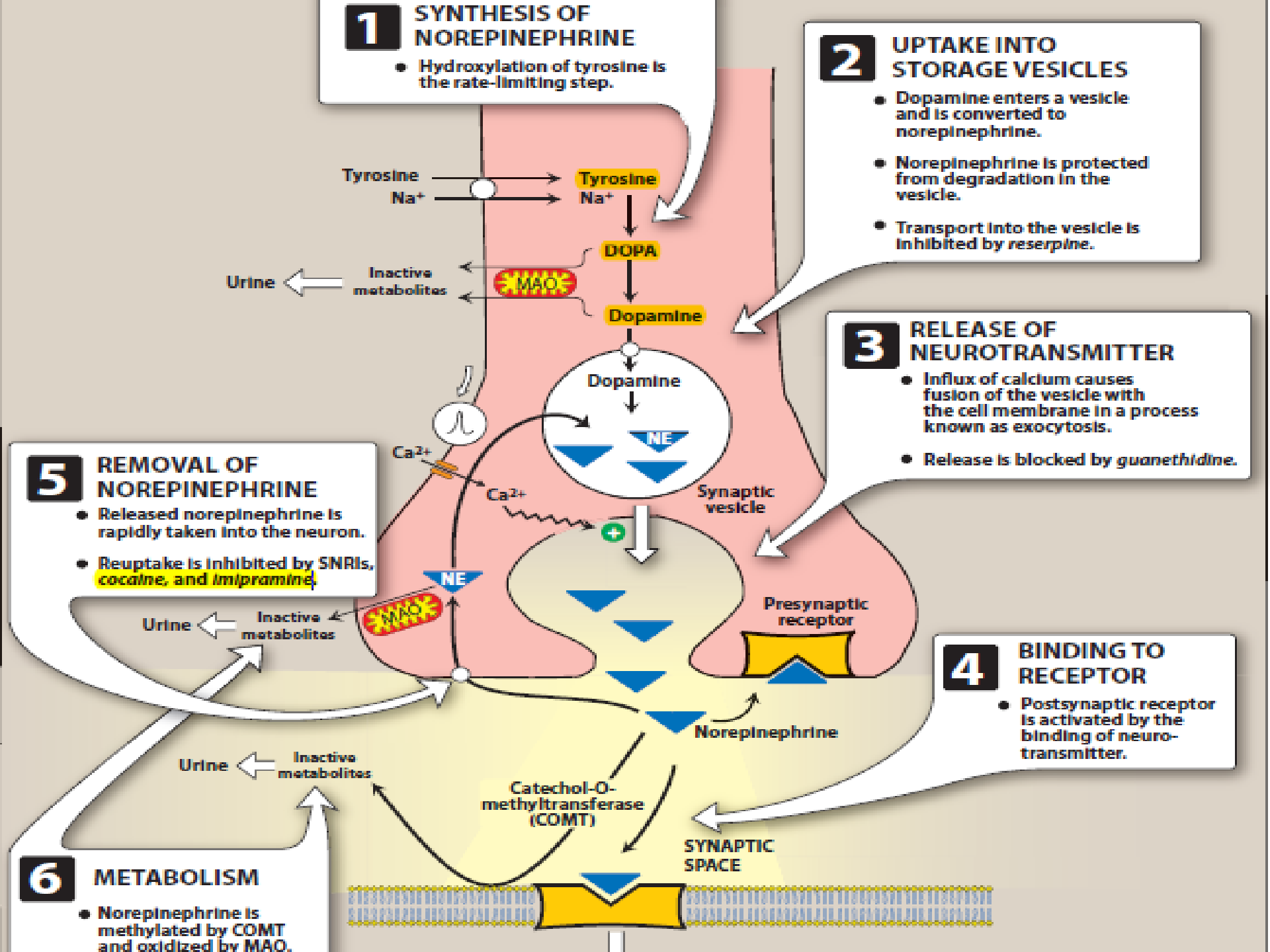
Edrophonium

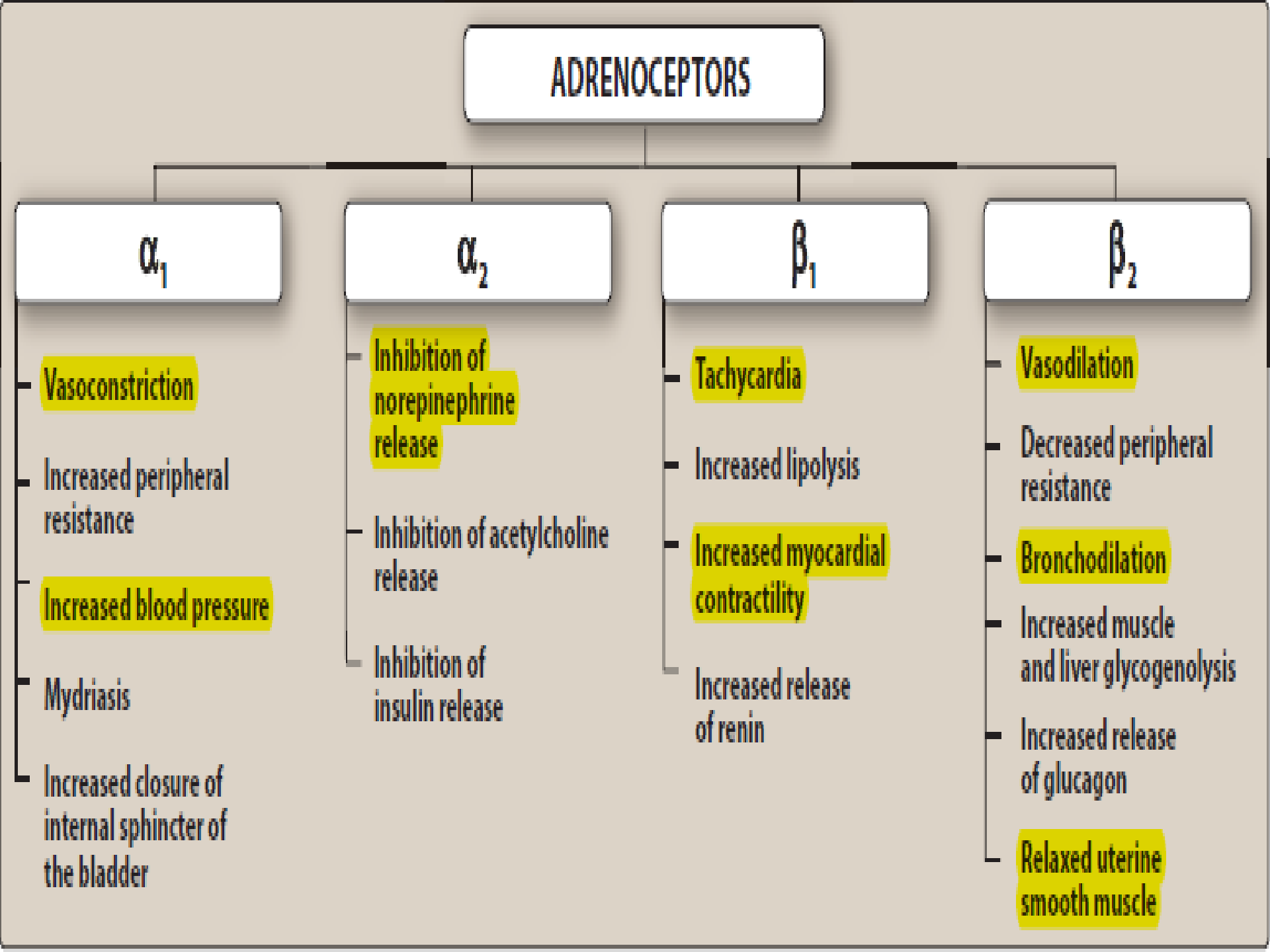
- Used for diagnosis of myasthenia gravis
- Used as an antidote for competitive neuromuscular blockers
- Has short duration of action (10 to 20 min)

Acetylcholine

- Used to produce miosis in ophthalmic surgery

Drug	Therapeutic uses
Muscarinic blockers	
Trihexyphenidyl *Benztropine*	• Treatment of Parkinson's disease
Darifenacin *Fesoterodine* *Oxybutynin* *Solifenacin* *Tolterodine* *Trospium*	• Treatment of overactive urinary bladder
Cyclopentolate *Tropicamide* *Atropine**	• In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
*Atropine**	• To treat spastic disorders of the GI tract • To treat organophosphate poisoning • To suppress respiratory secretions prior to surgery • To treat bradycardia
Scopolamine	• To prevent motion sickness
Ipratropium *Tiotropium*	• Treatment of COPD
Ganglionic blockers	
Nicotine	• Smoking cessation


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
2 UPTAKE INTO STORAGE VESICLES
Dopamine enters a vesicle and is converted to norepinephrine.
Norepinephrine is protected from degradation in the vesicle.
Transport into the vesicle is inhibited by reserpine.
3 RELEASE OF NEUROTRANSMITTER
Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
Release is blocked by guanethidine.
4 BINDING TO RECEPTOR
Postsynaptic receptor is activated by the binding of neuro-transmitter.
5 REMOVAL OF NOREPINEPHRINE
Released norepinephrine is rapidly taken into the neuron.
Reuptake is inhibited by SNRIs, cocaine, and imipramine.
6 METABOLISM
Norepinephrine is methylated by COMT and oxidized by MAO.
Tyrosine
Na+
Tyrosine
Na+
DOPA
Dopamine
MAO
Urine
Inactive metabolites
Dopamine
NE
Ca2+
Ca2+
Synaptic vesicle
NE
MAO
Urine
Inactive metabolites
Presynaptic receptor
Norepinephrine
Urine
Inactive metabolites
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE


ADRENOCEPTORS
α1
Vasoconstriction
Increased peripheral resistance
Increased blood pressure
Mydriasis
Increased closure of internal sphincter of the bladder
α2
Inhibition of norepinephrine release
Inhibition of acetylcholine release
Inhibition of insulin release
β1
Tachycardia
Increased lipolysis
Increased myocardial contractility
Increased release of renin
β2
Vasodilation
Decreased peripheral resistance
Bronchodilation
Increased muscle and liver glycogenolysis
Increased release of glucagon
Relaxed uterine smooth muscle

CLASS OF DRUG	DRUG NAMES	MECHANISM OF ACTION	SIDE EFFECTS
β-Adrenergic antagonists (topical)	*Betaxolol*, *carteolol*, *levobunolol*, *metipranolol*, *timolol*	Decrease of aqueous humor production	Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure.
α-Adrenergic agonists (topical)	*Apraclonidine*, *brimonidine*	Decrease of aqueous humor production and increase of aqueous outflow	Red eye and ocular irritation, allergic reactions, malaise, and headache.
Cholinergic agonists (topical)	*Pilocarpine*, *carbachol*	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision.
Prostaglandin-like analogues (topical)	*Latanoprost*, *travoprost*, *bimatoprost*	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.
Carbonic anhydrase inhibitors (topical and systemic)	*Dorzolamide* and *brinzolamide* (topical), *acetazolamide*, and *methazolamide* (oral)	Decrease of aqueous humor production	Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs).

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Pindolol*[1]	β_1, β_2	Hypertension
Timolol	β_1, β_2	Glaucoma, hypertension
Atenolol *Bisoprolol*[2] *Esmolol* *Metoprolol*[2]	β_1	Hypertension Angina Myocardial infarction
Acebutolol[1]	β_1	Hypertension
Nebivolol	β_1, NO ↑	Hypertension
Carvedilol[2] *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension