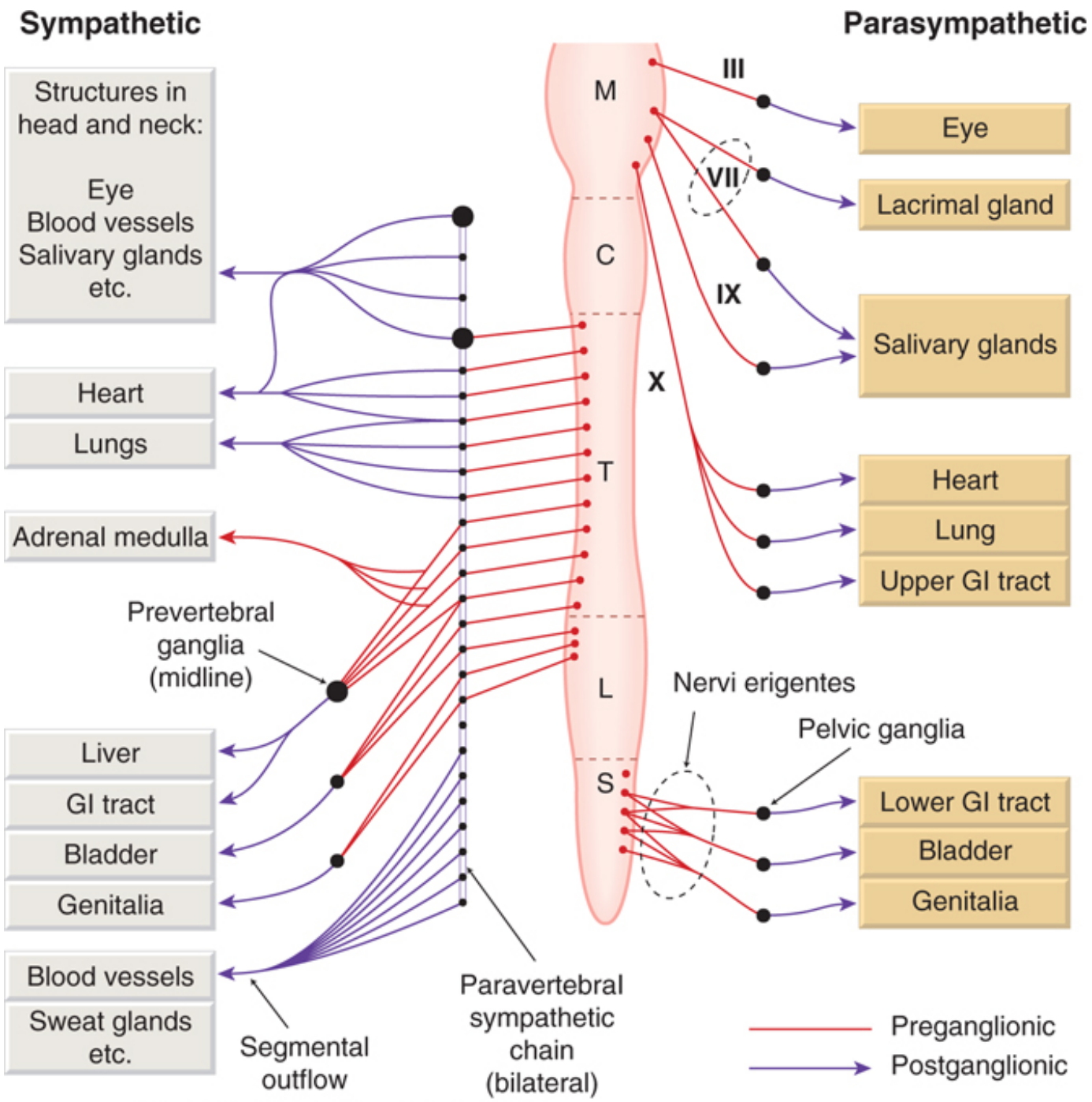
Autonomic pharmacology



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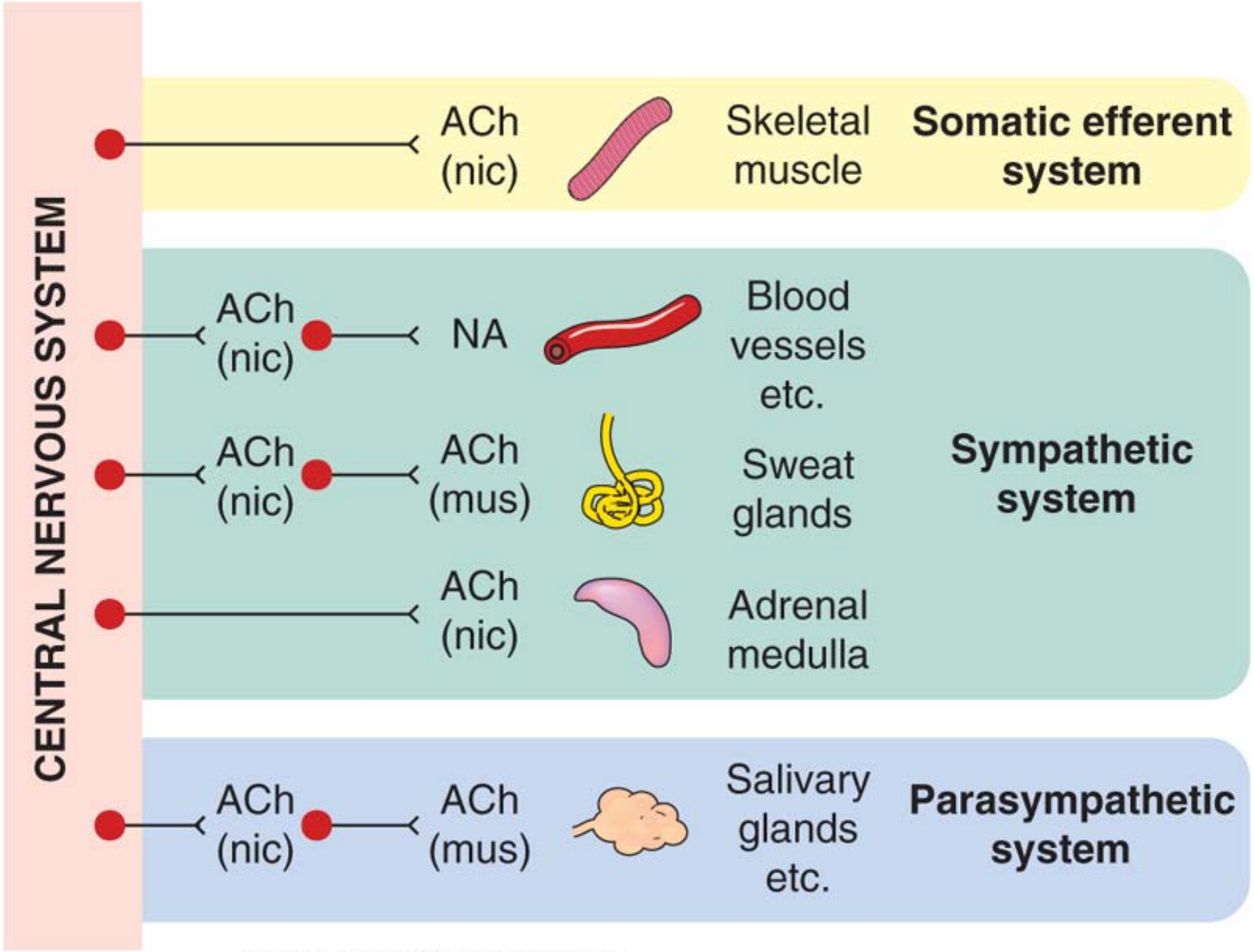

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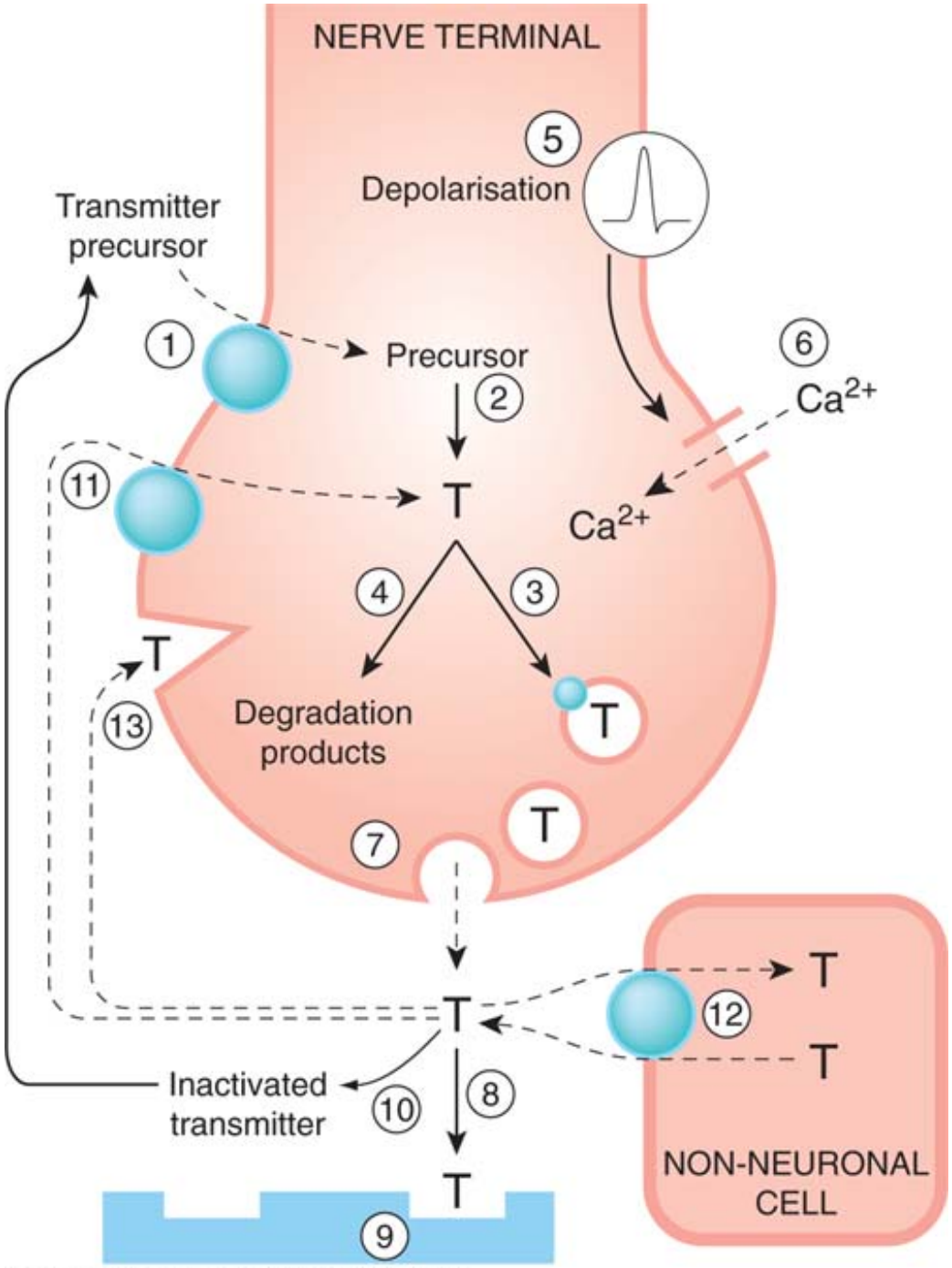

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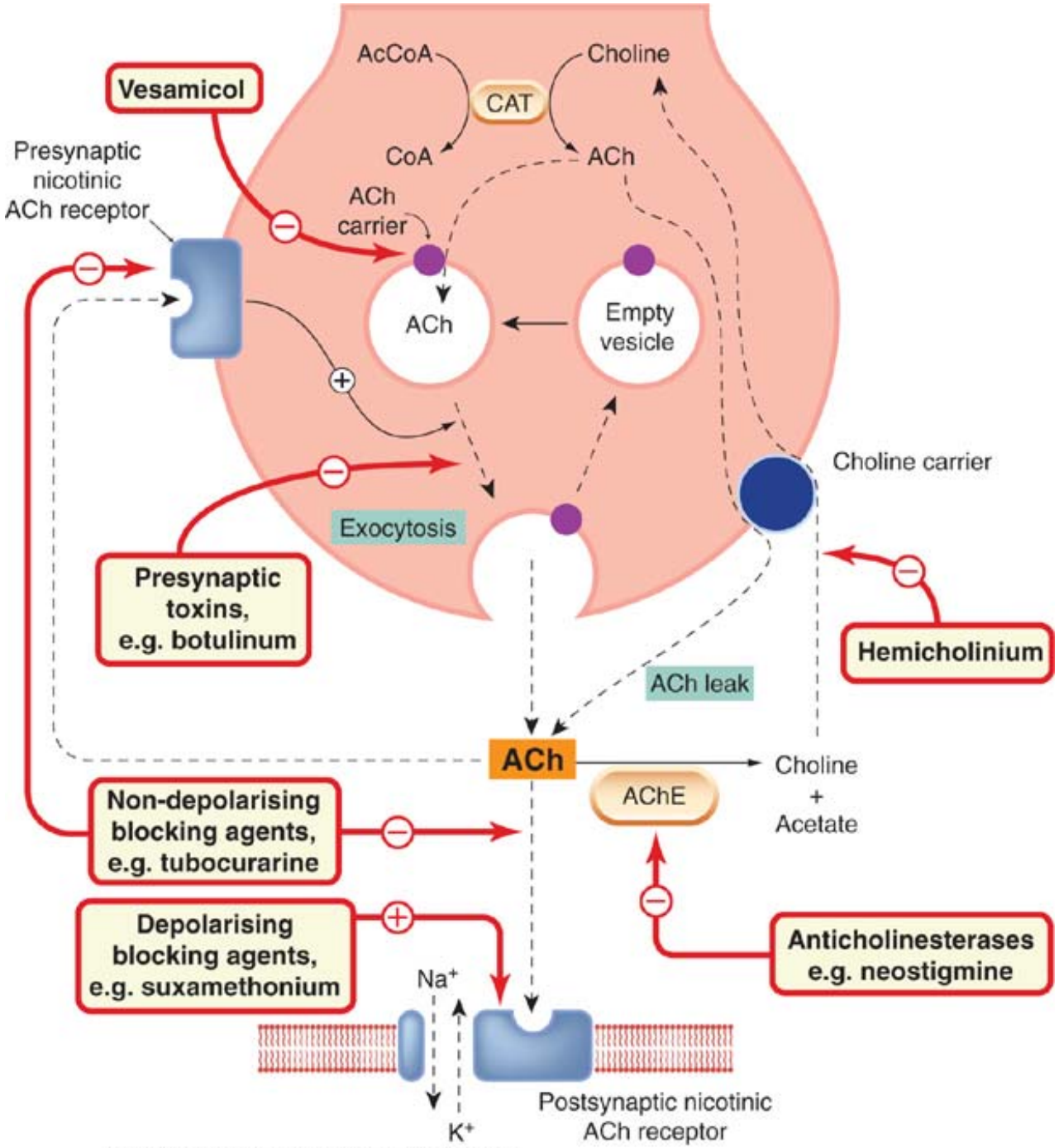

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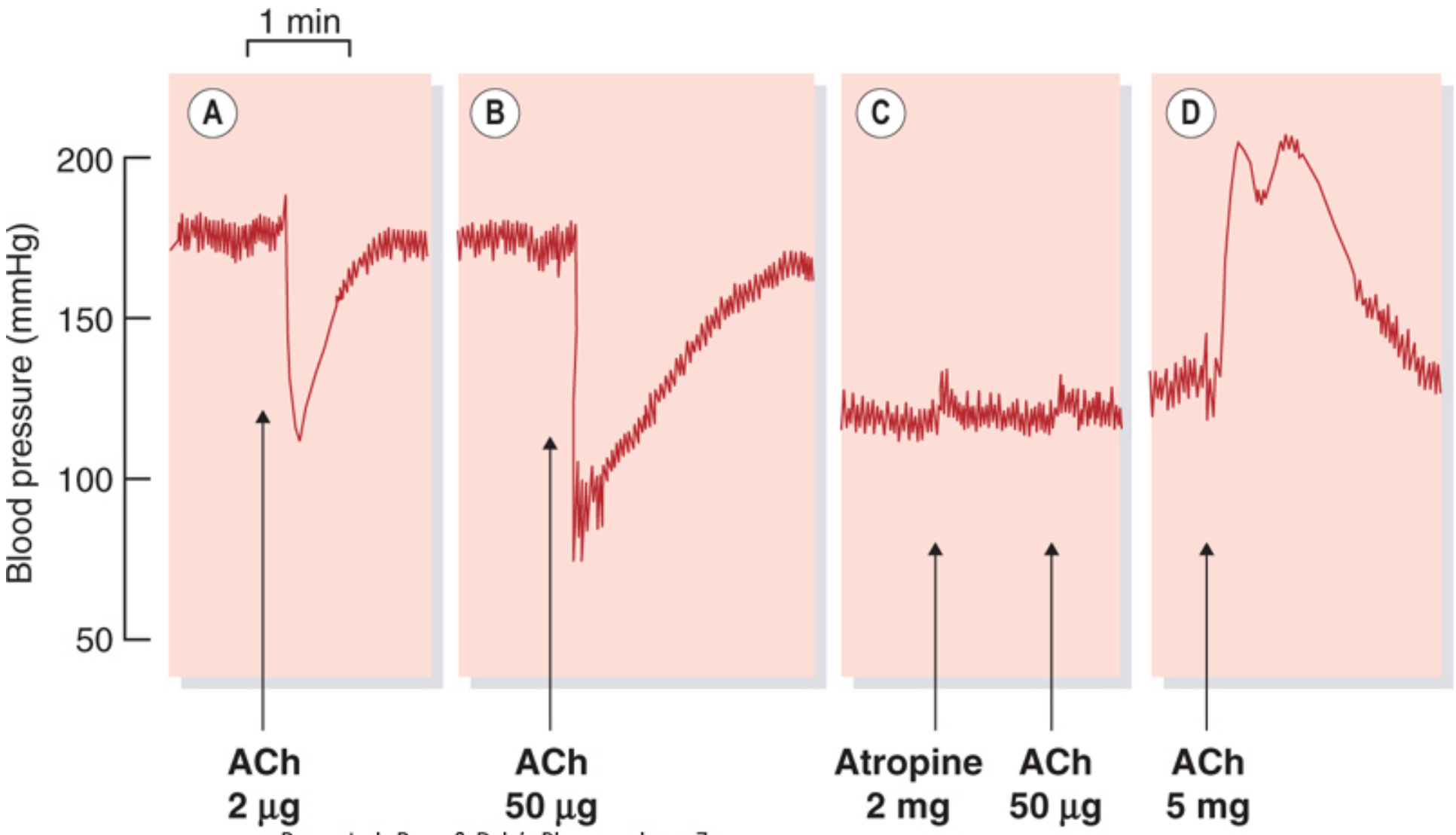
	Muscle type	Ganglion type	CNS types		Notes
Main molecular form	$(\alpha1)_2\beta1\delta\varepsilon$ (adult form)	$(\alpha3)_2(\beta2)_3$	$(\alpha4)_2(\beta2)_3$	$(\alpha7)_5$	-
Main synaptic location	Skeletal neuromuscular junction: mainly postsynaptic	Autonomic ganglia: mainly postsynaptic	Many brain regions: pre- and postsynaptic	Many brain regions: pre- and postsynaptic	-
Membrane response	Excitatory. Increased cation permeability (mainly Na^+, K^+)	Excitatory. Increased cation permeability (mainly Na^+, K^+)	Pre- and postsynaptic excitation. Increased cation permeability (mainly Na^+, K^+)	Pre- and postsynaptic excitation. Increased cation permeability	$(\alpha7)_5$ receptor produces large Ca^{2+} entry, evoking transmitter release
Agonists	Acetylcholine Carbachol Succinylcholine	Acetylcholine Carbachol Nicotine Epibatidine Dimethylphenylpiperazinium	Nicotine Epibatidine Acetylcholine Cytosine Varenicline[b]	Epibatidine Dimethylphenylpiperazinium Varenicline[b]	$(\alpha4)_2(\beta2)_3$ is main brain 'nicotine receptor' See Ch. 38
Antagonists	Tubocurarine Pancuronium Atracurium Vecuronium α-Bungarotoxin α-Conotoxin	Mecamylamine Trimetaphan Hexamethonium α-Conotoxin	Mecamylamine Methylaconitine	α-Bungarotoxin α-Conotoxin Methylaconitine	

	M_1 ('neural')	M_2 ('cardiac')	M_3 ('glandular/smooth muscle')	M_4	M_5
Main locations	Autonomic ganglia Glands: gastric, salivary, lacrimal, etc. Cerebral cortex	Heart: atria CNS: widely distributed	Exocrine glands: gastric, salivary, etc. Smooth muscle: gastrointestinal tract, eye, airways, bladder Blood vessels: endothelium	CNS	CNS: very localised expression in substantia nigra Salivary glands Iris/ciliary muscle
Cellular response	↑ IP_3, DAG Depolarisation Excitation (slow epsp) ↓ K^+ conductance	↓ cAMP Inhibition ↓ Ca^{2+} conductance ↑ K^+ conductance	↑ IP_3 Stimulation ↑ $[Ca^{2+}]_i$	↓ cAMP Inhibition	↑ IP_3 Excitation
Functional response	CNS excitation (? improved cognition) Gastric secretion	Cardiac inhibition Neural inhibition Central muscarinic effects (e.g. tremor, hypothermia)	Gastric, salivary secretion Gastrointestinal smooth muscle contraction Ocular accommodation Vasodilatation	Enhanced locomotion	Not known
Non-selective agonists (see also Table 13.3)	Acetylcholine Carbachol Oxotremorine Pilocarpine **Bethanechol**				
Selective agonists	McNA343		**Cevimeline**		
Non-selective antagonists (see also Table 13.5)	**Atropine** **Dicycloverine** **Tolterodine** **Oxybutynin** **Ipratropium**				
Selective antagonists	**Pirenzepine** Mamba toxin MT7	Gallamine (see p. 164)	**Darifenacin**	Mamba toxin MT3	



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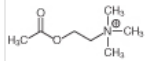
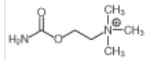
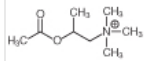
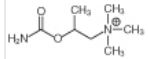
Compound	Structure	Receptor specificity		Hydrolysis by cholinesterase	Clinical uses
Muscarinic	**Nicotinic**				
Acetylcholine		+++	+++	+++	None
Carbachol		++	+++	-	None
Methacholine		+++	+	++	None
Bethanechol		+++	-	-	Treatment of bladder and gastrointestinal hypotonia[a]
Muscarine		+++	-	-	None[b]
Pilocarpine		++	-	-	Glaucoma
Oxotremorine		++	-	-	None
Cevimeline		++[c]	-	-	Sjögren's syndrome (to increase salivary and lacrimal secretion)

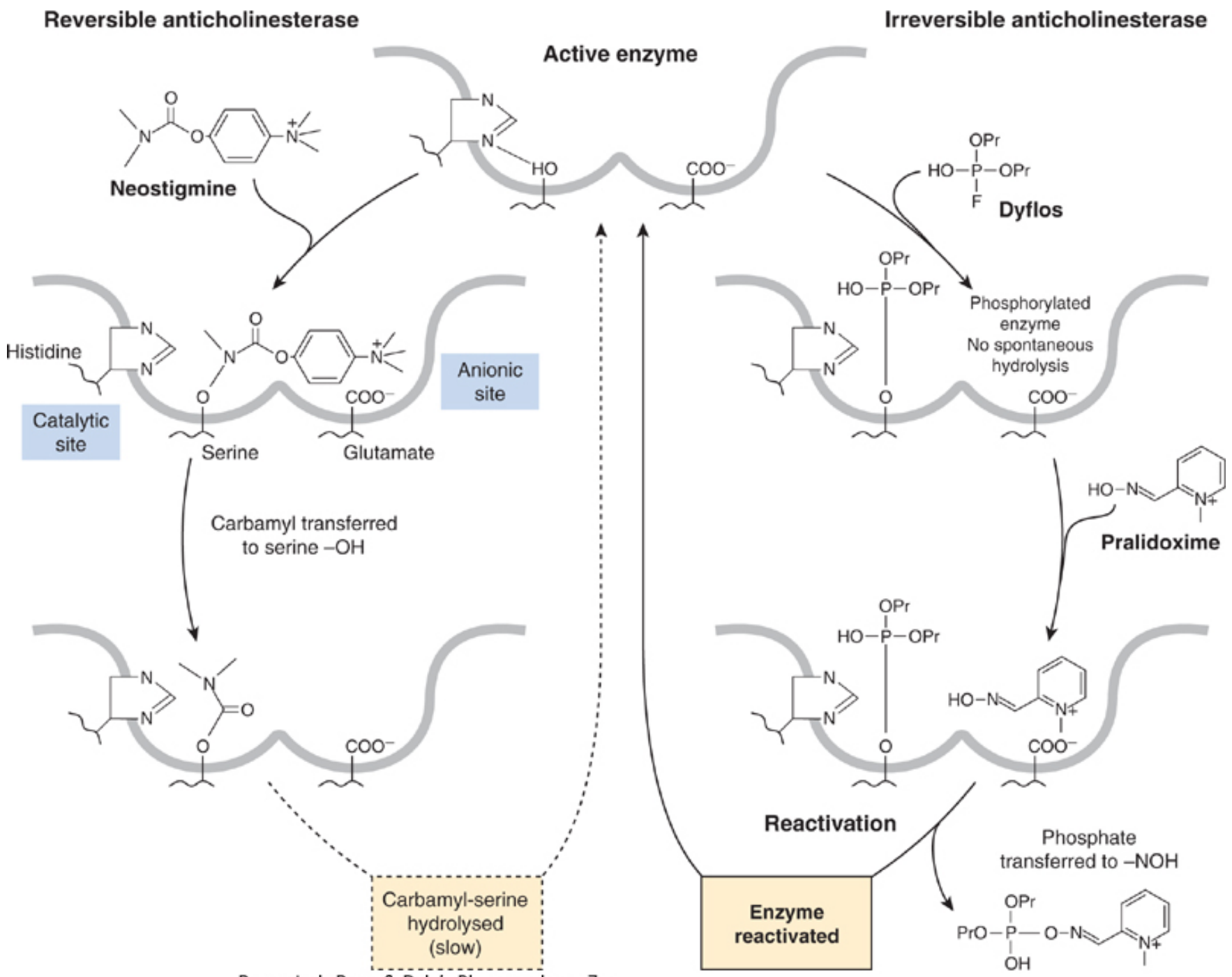
[a] Essential to check that bladder neck is not obstructed.

[b] Cause of one type of mushroom poisoning.

[c] Selective for M_3 receptors.

Drug[a]	Mechanism	Notes	See Chapter
Timolol, carteolol	β-Adrenoceptor antagonist	Given as eye drops but may still cause systemic side effects: bradycardia, bronchoconstriction	14
Acetazolamide, dorzolamide	Carbonic anhydrase inhibitor	Acetazolamide is given systemically Side effects include diuresis, loss of appetite, tingling, neutropenia Dorzolamide is used as eye drops Side effects include bitter taste and burning sensation	28
Clonidine, apraclonidine	α_2 Adrenoceptor agonist	Used as eye drops	14
Latanoprost	Prostaglandin analogue	Can alter iris pigmentation	17
Pilocarpine	Muscarinic agonist	Used as eye drops	This chapter
Ecothiophate	Anticholinesterase	Used as eye drops Can cause muscle spasm and systemic effects	This chapter
		Can cause muscle spasm and systemic effects	

[a] The most important drugs are shown in **bold**.



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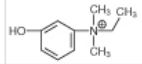
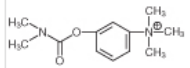
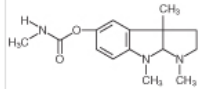
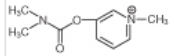
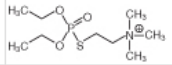
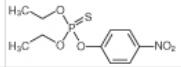
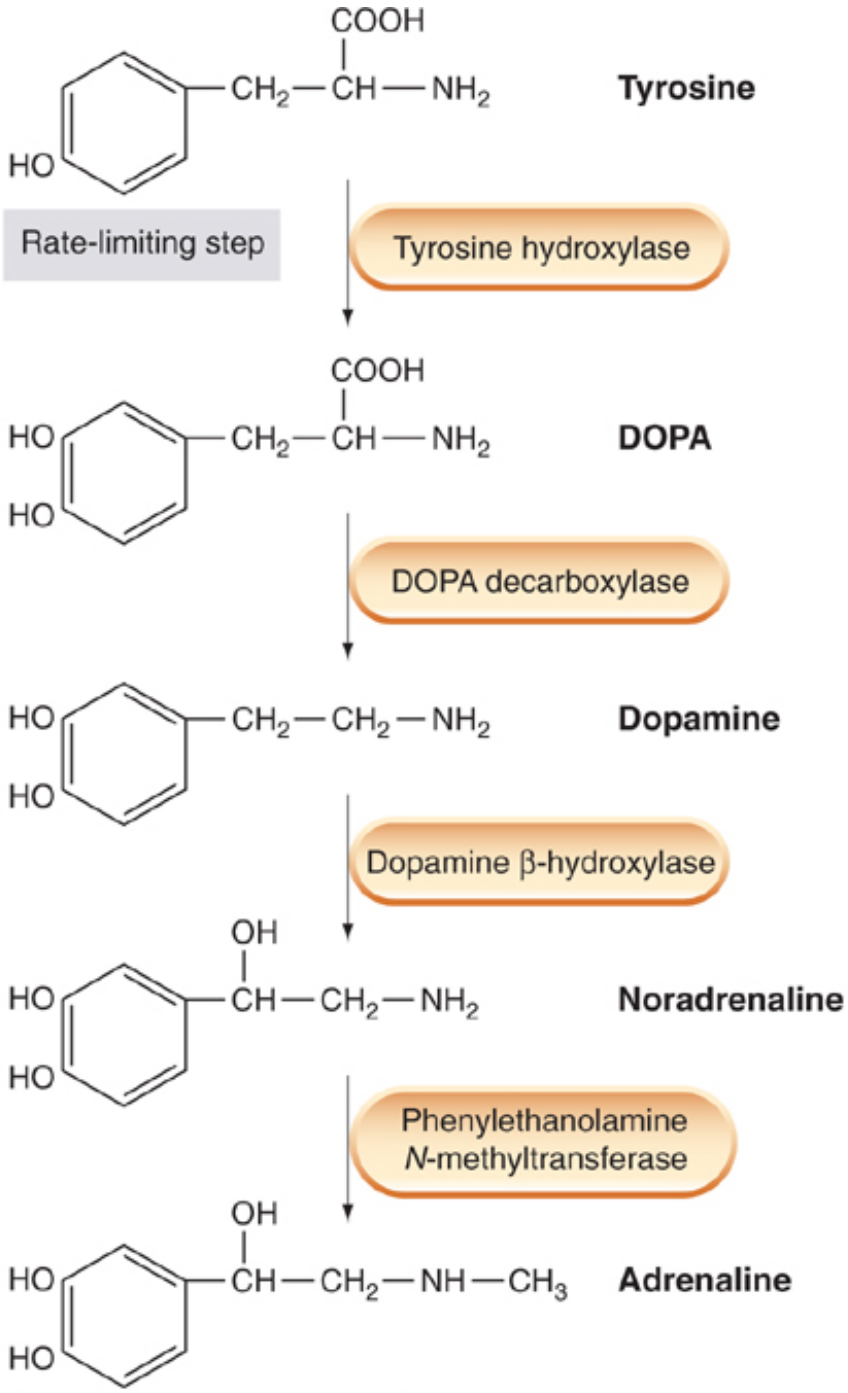
Drug	Structure	Duration of action	Main site of action	Notes
Edrophonium		Short	NMJ	Used mainly in diagnosis of myasthenia gravis Too short-acting for therapeutic use
Neostigmine		Medium	NMJ	Used intravenously to reverse competitive neuromuscular block Used orally in treatment of myasthenia gravis Visceral side effects
Physostigmine		Medium	P	Used as eye drops in treatment of glaucoma
Pyridostigmine		Medium	NMJ	Used orally in treatment of myasthenia gravis Better absorbed than neostigmine and has longer duration of action
Dyflos		Long	P	Highly toxic organophosphate, with very prolonged action Has been used as eye drops for glaucoma
Ecothiophate		Long	P	Used as eye drops in treatment of glaucoma Prolonged action; may cause systemic effects
Parathion		Long	-	Converted to active metabolite by replacement of sulfur by oxygen Used as insecticide but commonly causes poisoning in humans

Other anticholinesterase drugs developed for the treatment of dementia are described in Chapter 39.
NMJ, neuromuscular junction; P, postganglionic parasympathetic junction.

Compound	Pharmacological properties	Clinical uses	Notes
Atropine	Non-selective antagonist Well absorbed orally CNS stimulant	Adjunct for anaesthesia (reduced secretions, bronchodilatation) Anticholinesterase poisoning Bradycardia Gastrointestinal hypermotility (antispasmodic)	Belladonna alkaloid Main side effects: urinary retention, dry mouth, blurred vision Dicycloverine (dicyclomine) is similar and used mainly as antispasmodic agent
Hyoscine	Similar to atropine CNS depressant	As atropine Motion sickness	Belladonna alkaloid (also known as scopolamine) Causes sedation; other side effects as atropine
Hyoscine butylbromide	Similar to atropine but poorly absorbed and lacks CNS effects Significant ganglion-blocking activity	Mainly for gastrointestinal hypermotility	Quaternary ammonium derivative Similar drugs include atropine methonitrate, propantheline
Tiotropium	Similar to atropine methonitrate Does not inhibit mucociliary clearance from bronchi	By inhalation for asthma, bronchitis	Quaternary ammonium compound Ipratropium similar
Tropicamide	Similar to atropine May raise intraocular pressure	Ophthalmic use to produce mydriasis and cycloplegia (as eye drops) Short acting	-
Cyclopentolate	Similar to tropicamide	As tropicamide (long acting)	-
Pirenzepine	Selective for M_1 receptors Inhibits gastric secretion by action on ganglion cells Little effect on smooth muscle or CNS	Peptic ulcer	Fewer side effects than other muscarinic antagonists Largely superseded by other antiulcer drugs (see Ch. 29)
Darifenacin	Selective for M_3 receptors	Urinary incontinence	Few side effects

[a]For chemical structures, see Brunton L et al. 2006 Goodman and Gilman's pharmacological basis of therapeutics, 11th edn. McGraw-Hill, New York.
Other non-selective muscarinic antagonists in clinical use, with very similar actions and side effects, include **oxybutynin, tolterodine, fesoterodine, solifenacin** and **trospium**-an example of me-too development by pharmaceutical companies.



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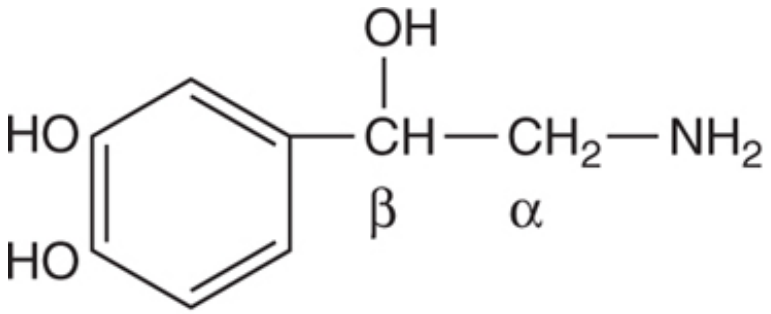
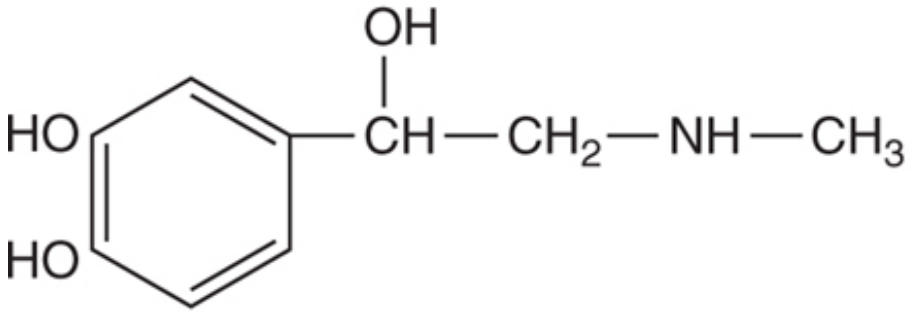
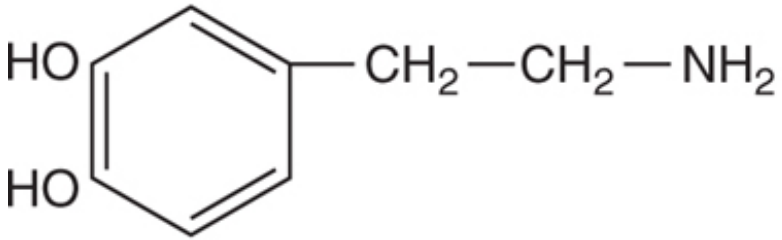


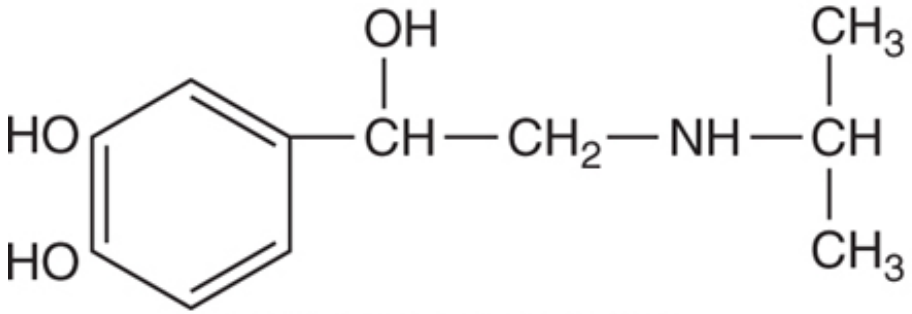
Noradrenaline



Adrenaline



Dopamine



Isoprenaline

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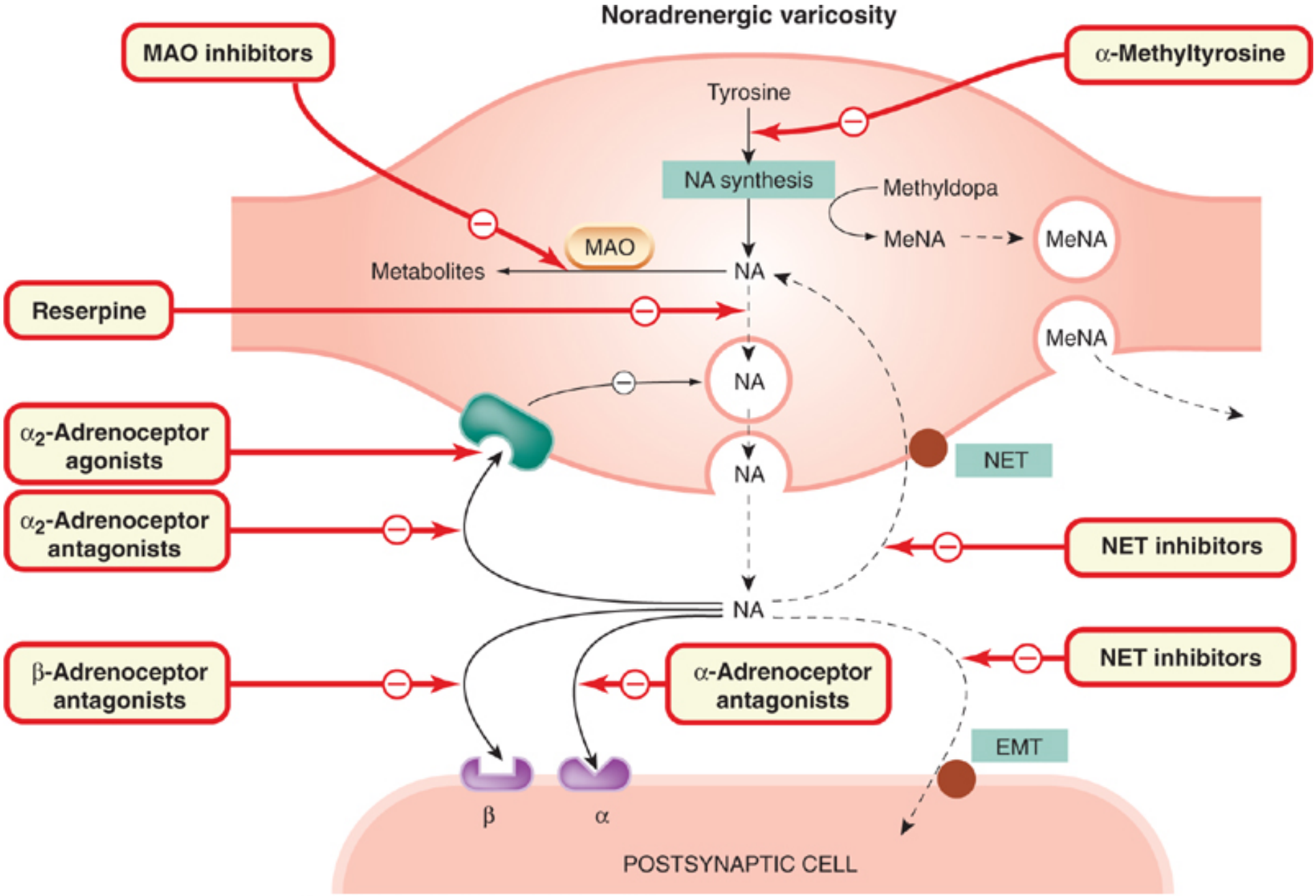

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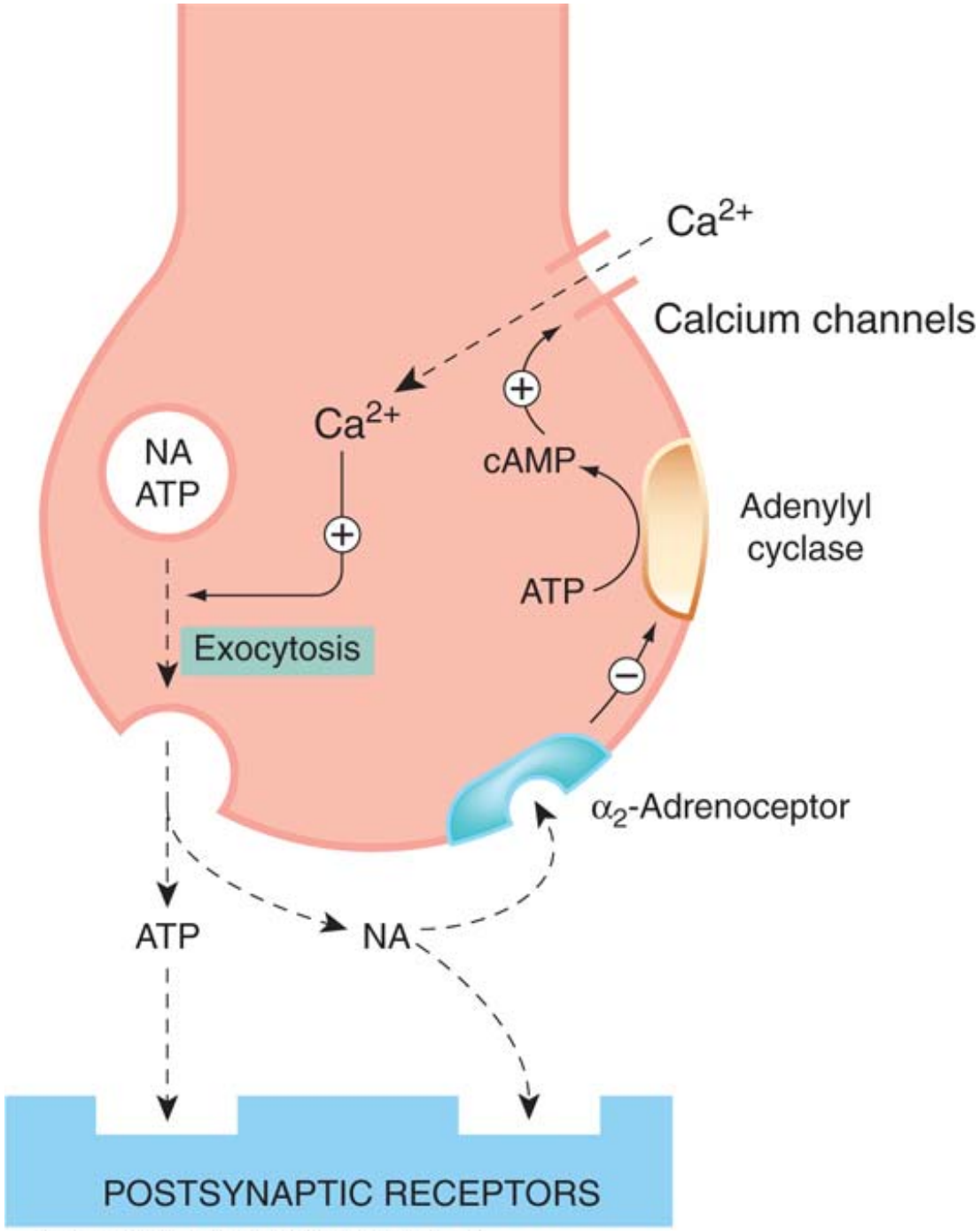
Tissues and effects	α_1	α_2	β_1	β_2	β_3
Smooth muscle					
Blood vessels	Constrict	Constrict/dilate	-	Dilate	-
Bronchi	Constrict	-	-	Dilate	-
Gastrointestinal tract	Relax	Relax (presynaptic effect)	-	Relax	-
Gastrointestinal sphincters	Contract	-	-	-	-
Uterus	Contract	-	-	Relax	-
Bladder detrusor	-	-	-	Relax	-
Bladder sphincter	Contract	-	-	-	-
Seminal tract	Contract	-	-	Relax	-
Iris (radial muscle)	Contract	-	-	-	-
Ciliary muscle	-	-	-	Relax	-
Heart					
Rate	-	-	Increase	Increase[a]	-
Force of contraction	-	-	Increase	Increase[a]	-
Skeletal muscle	-	-	-	Tremor Increased muscle mass and speed of contraction Glycogenolysis	Thermogenesis
Liver	Glycogenolysis	-	-	Glycogenolysis	-
Fat	-	-	-	-	Lipolysis Thermogenesis
Pancreatic islets	-	Decrease insulin secretion	-	-	-
Nerve terminals					
Adrenergic	-	Decrease release	-	Increase release	-
Cholinergic	-	Decrease release	-	-	-
Salivary gland	K^+ release	-	Amylase secretion	-	-
Platelets	-	Aggregation	-	-	-
Mast cells	-	-	-	Inhibition of histamine release	-
Brain stem	-	Inhibits sympathetic outflow	-	-	-
Second messengers and effectors	Phospholipase C activation ↑ Inositol trisphosphate ↑ Diacylglycerol ↑ Ca^{2+}	↓ cAMP ↓ Calcium channels ↑ Potassium channels	↑ cAMP	↑ cAMP	↑ cAMP
Agonist potency order	NA ≥ A >> ISO	A > NA >> ISO	ISO > NA > A	ISO > A > NA	ISO > NA = A
Selective agonists	Phenylephrine	Clonidine	Dobutamine	Salbutamol	BRL 37344
	Methoxamine		Xamoterol	Terbutaline	
				Salmeterol	
				Formoterol	
				Clenbuterol	
Selective antagonists	Prazosin	Yohimbine	Atenolol	Butoxamine	-
	Doxazocin	Idazoxan	Metoprolol		



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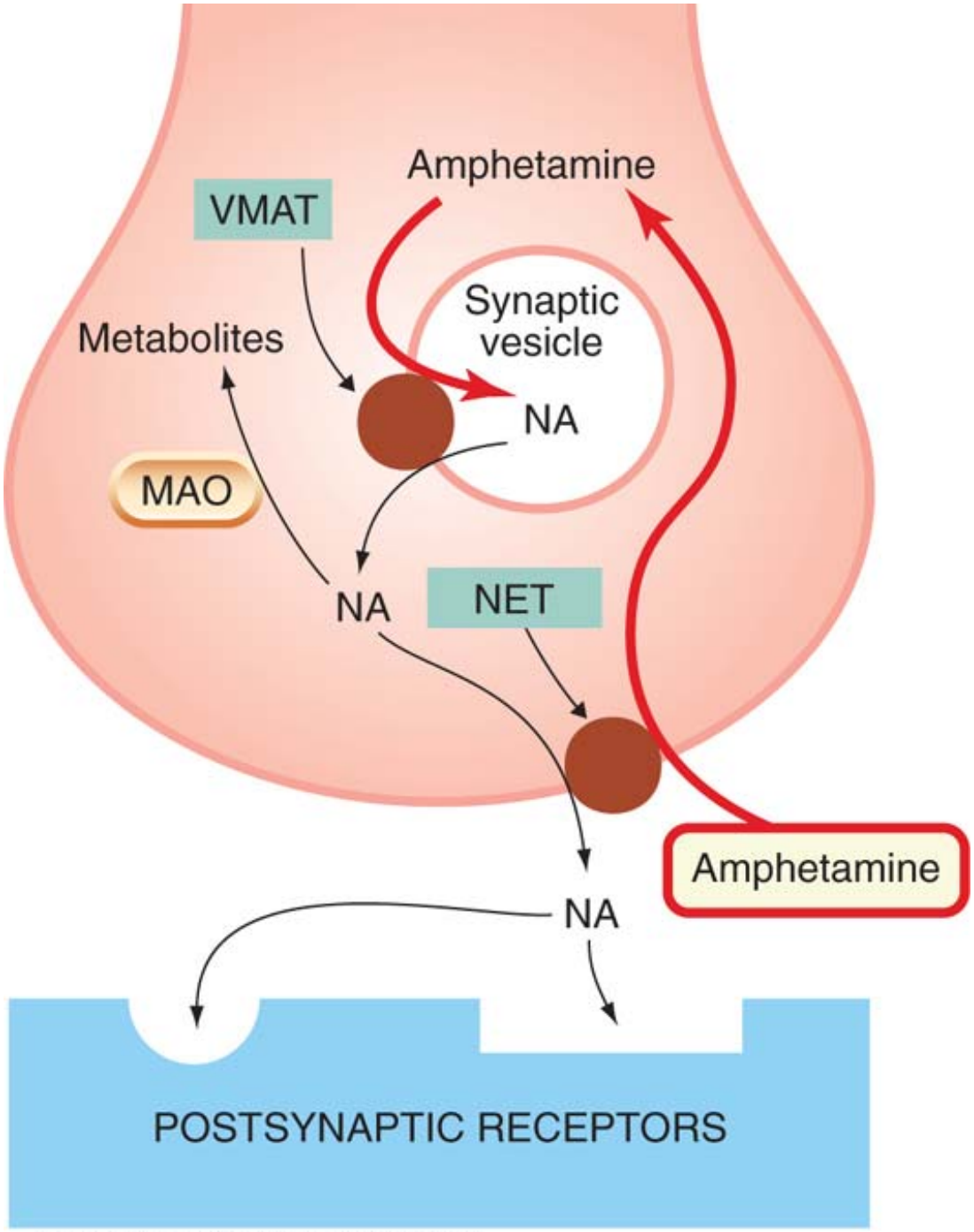

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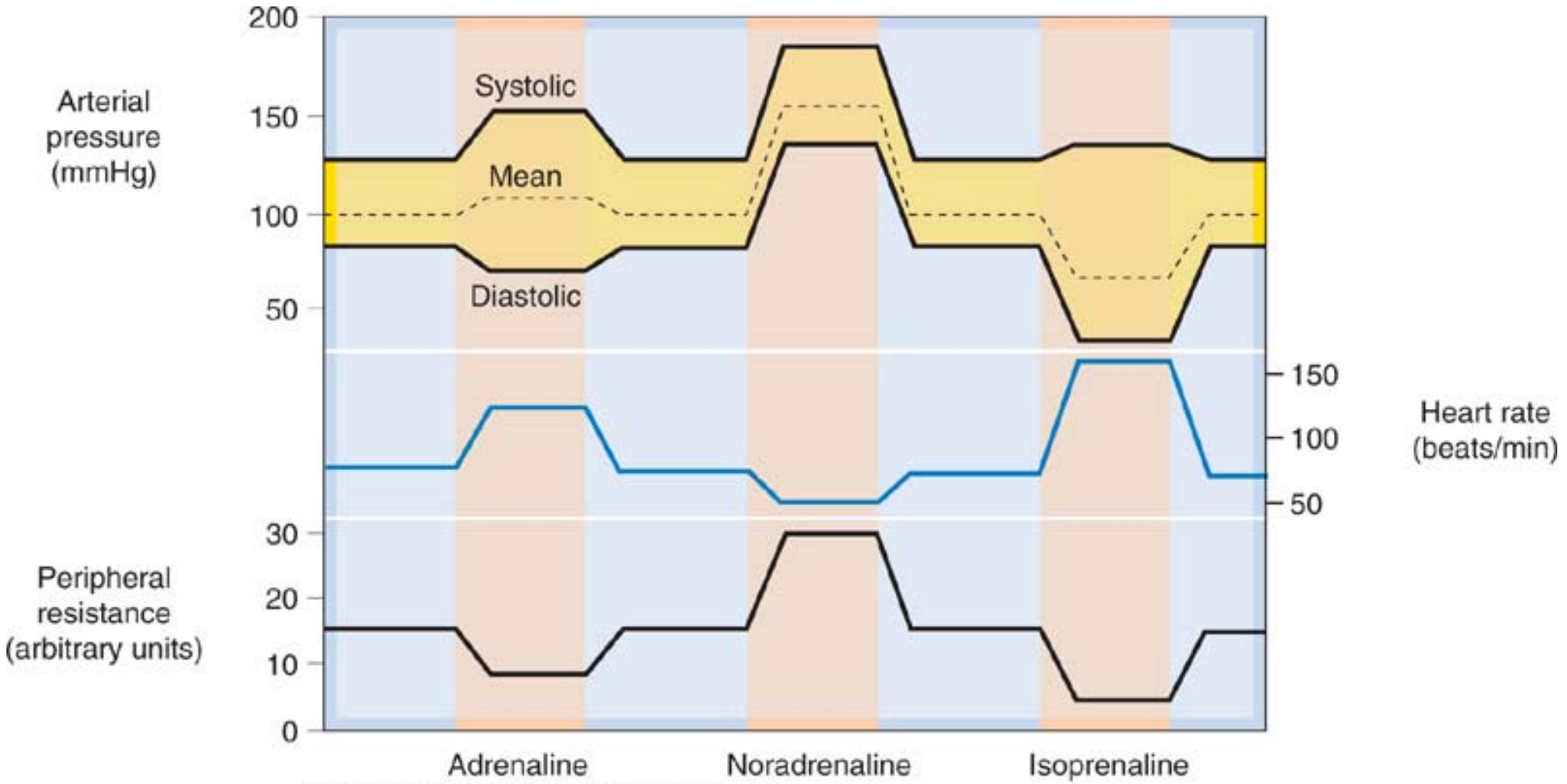
	Neuronal (NET)	Extraneuronal (EMT)	Vesicular (VMAT)
Transport of NA (rat heart)	1.2	100	-
V_{max} (nmol/g per min)			
K_m (μmol/l)	0.3	250	~0.2
Specificity	NA > A > ISO	A > NA > ISO	NA = A = ISO
Location	Neuronal membrane	Non-neuronal cell membrane (smooth muscle, cardiac muscle, endothelium)	Synaptic vesicle membrane
Other substrates	Tyramine	(+)-Noradrenaline	Dopamine
	Methylnoradrenaline	Dopamine	5-Hydroxytryptamine
	Adrenergic neuron-blocking drugs (e.g. guanethidine)	5-Hydroxytryptamine Histamine	Guanethidine MPP+ (see Ch. 37)
	Amphetamine[a]		
Inhibitors	Cocaine	Normetanephrine	Reserpine
	Tricyclic antidepressants (e.g. desipramine)	Steroid hormones (e.g. corticosterone)	Tetrabenazine
	Phenoxybenzamine	Phenoxybenzamine	
	Amphetamine[a]		

[a]Amphetamine is transported slowly, so acts both as a substrate and as an inhibitor of noradrenaline uptake. For details, see Gainetdinov & Caron (2003).
A, adrenaline; ISO, isoprenaline; NA, noradrenaline.



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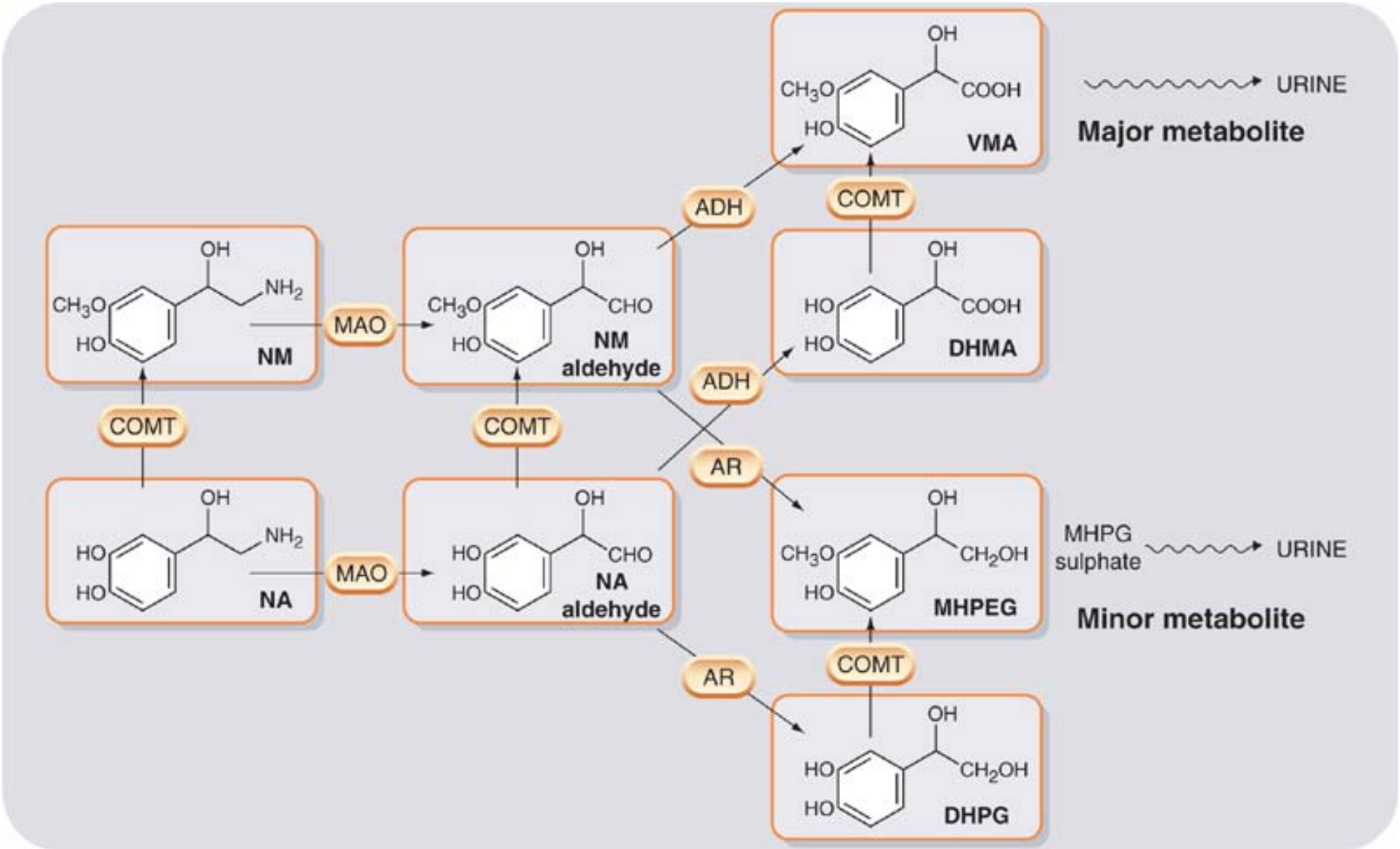

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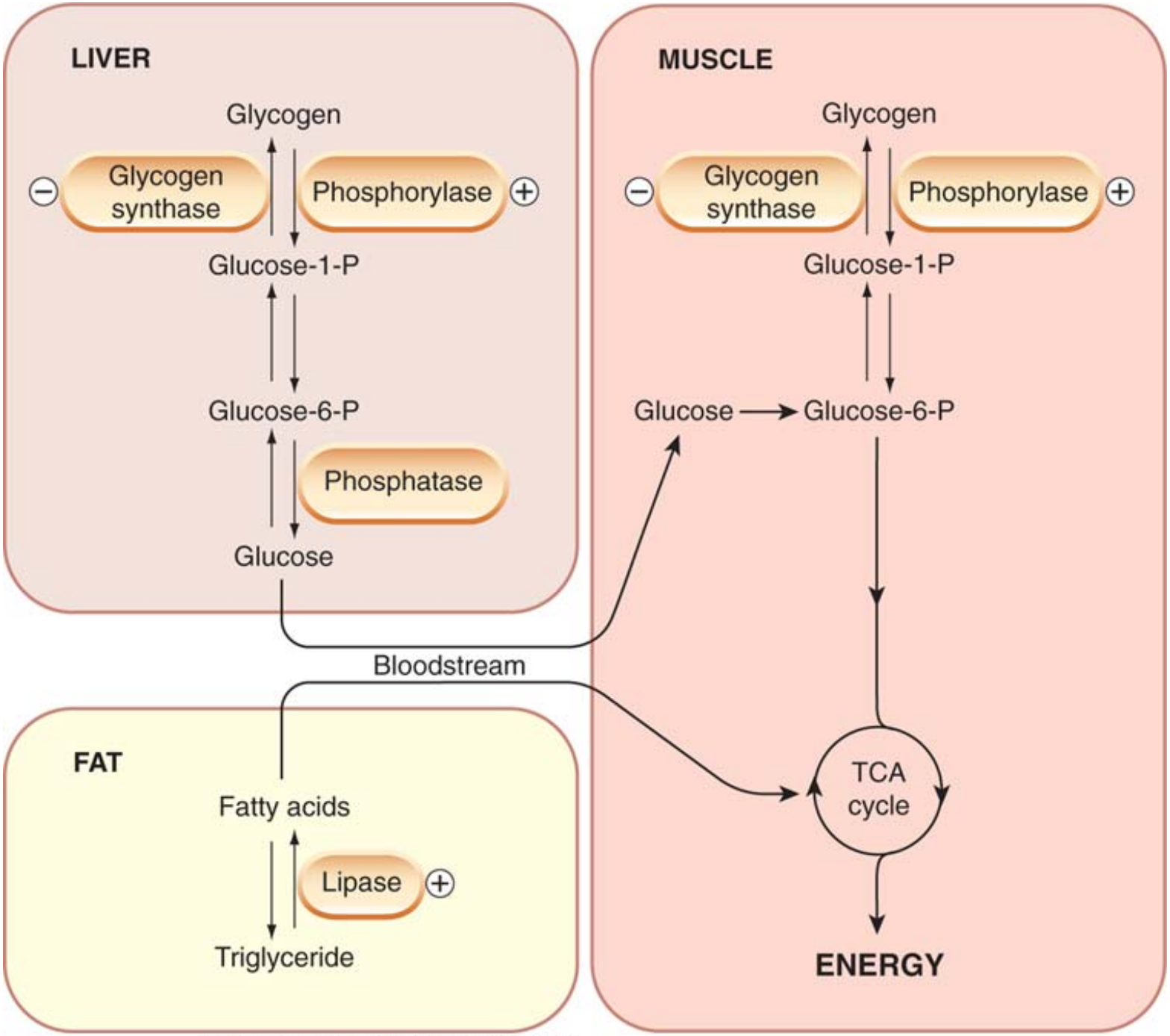

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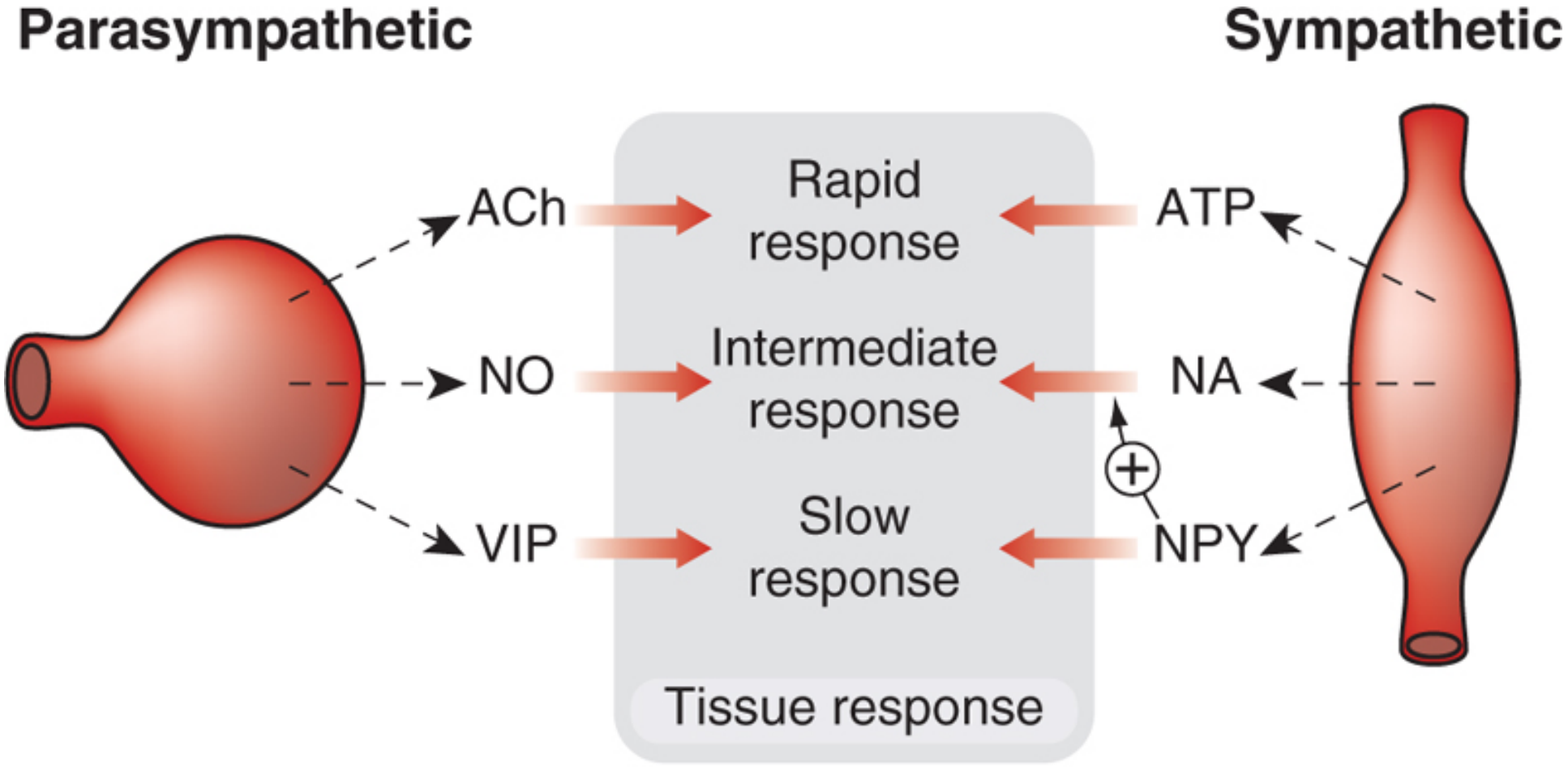

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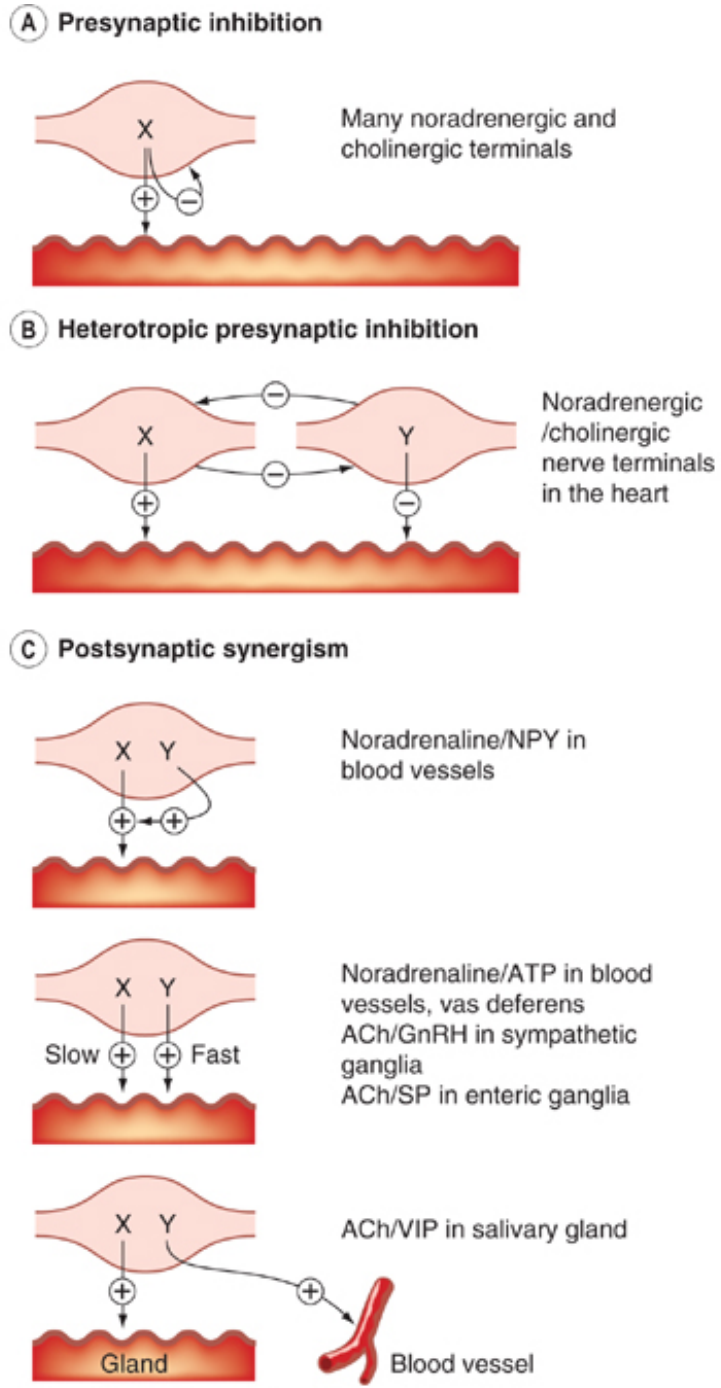

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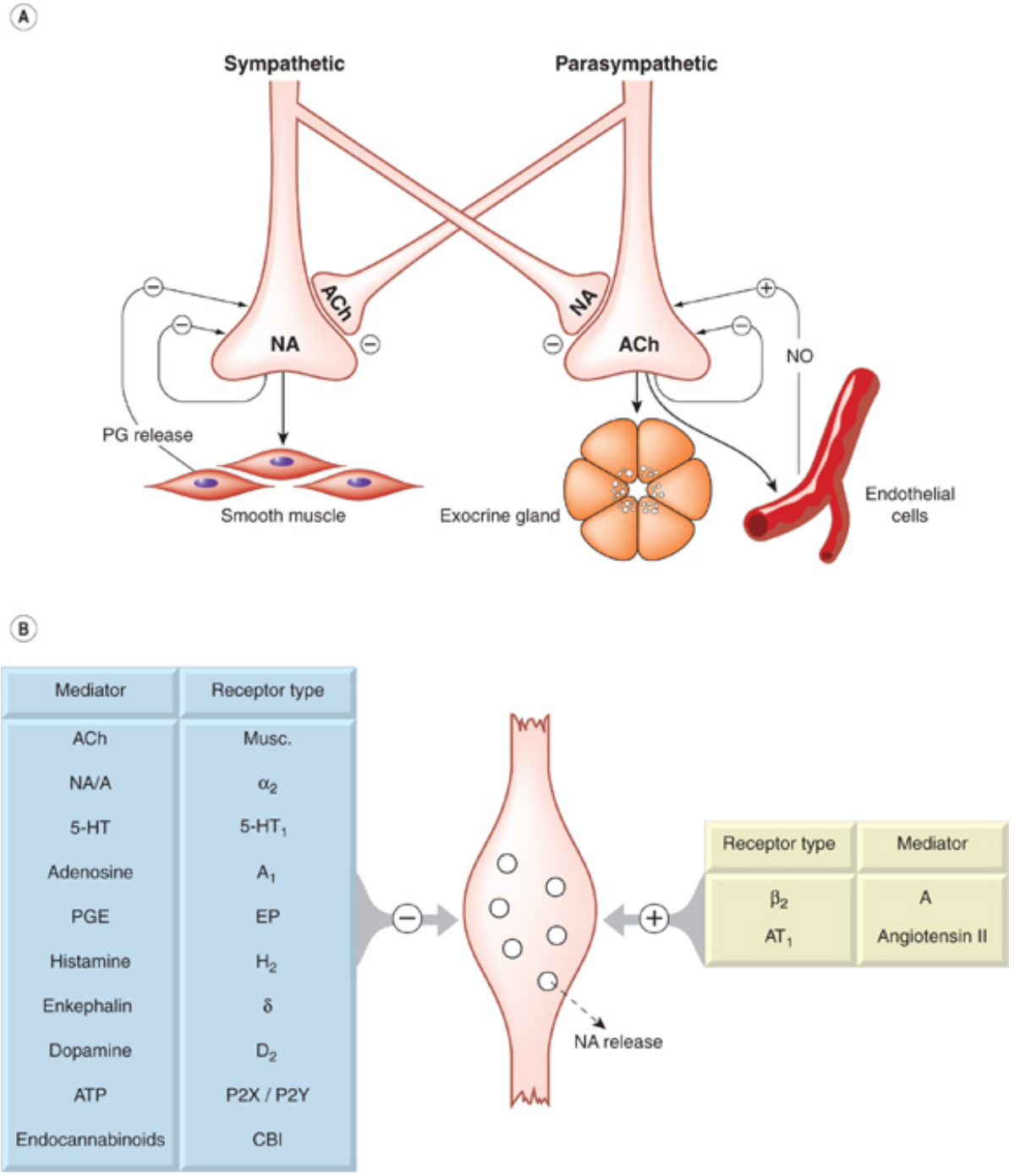

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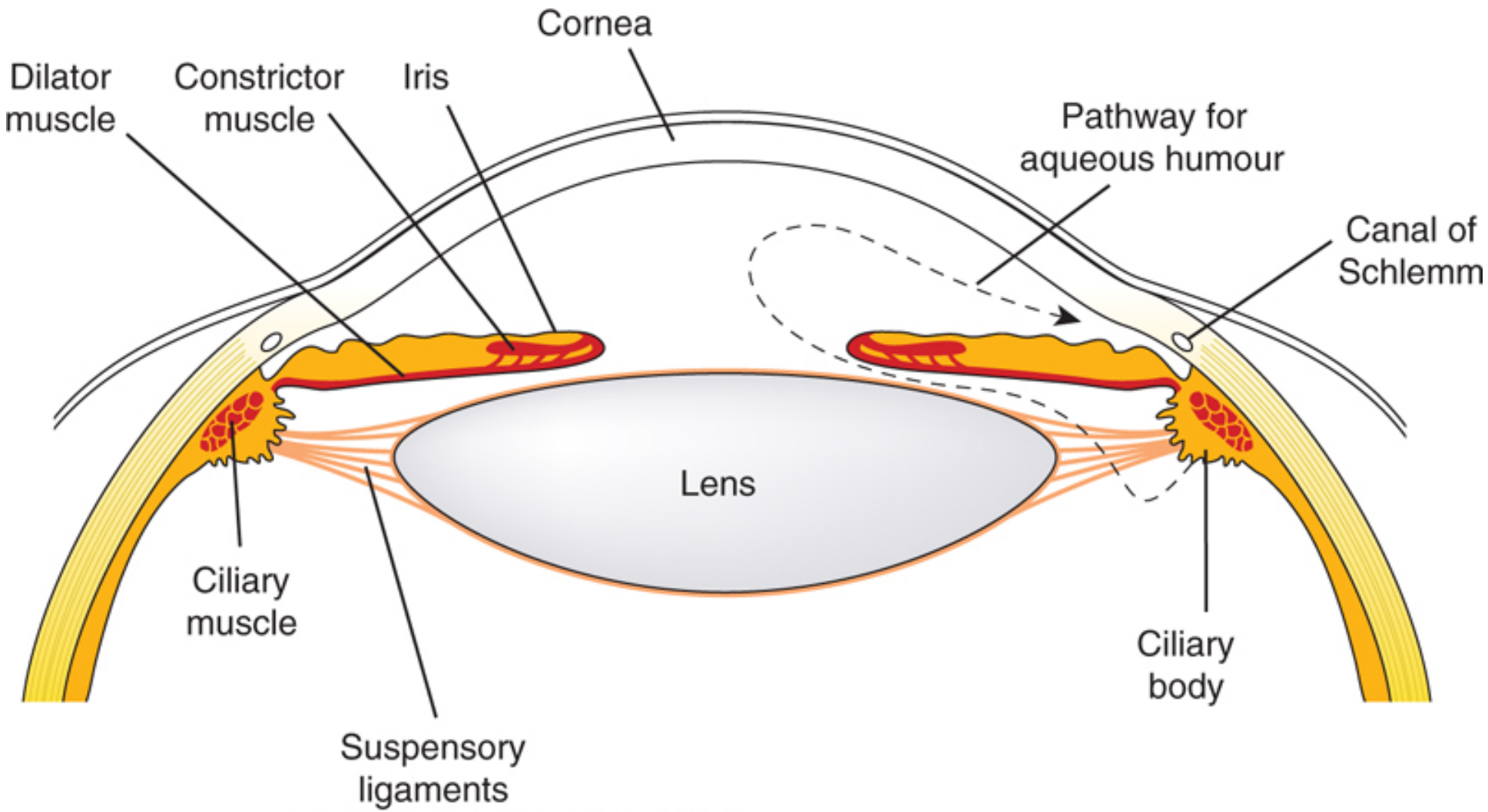

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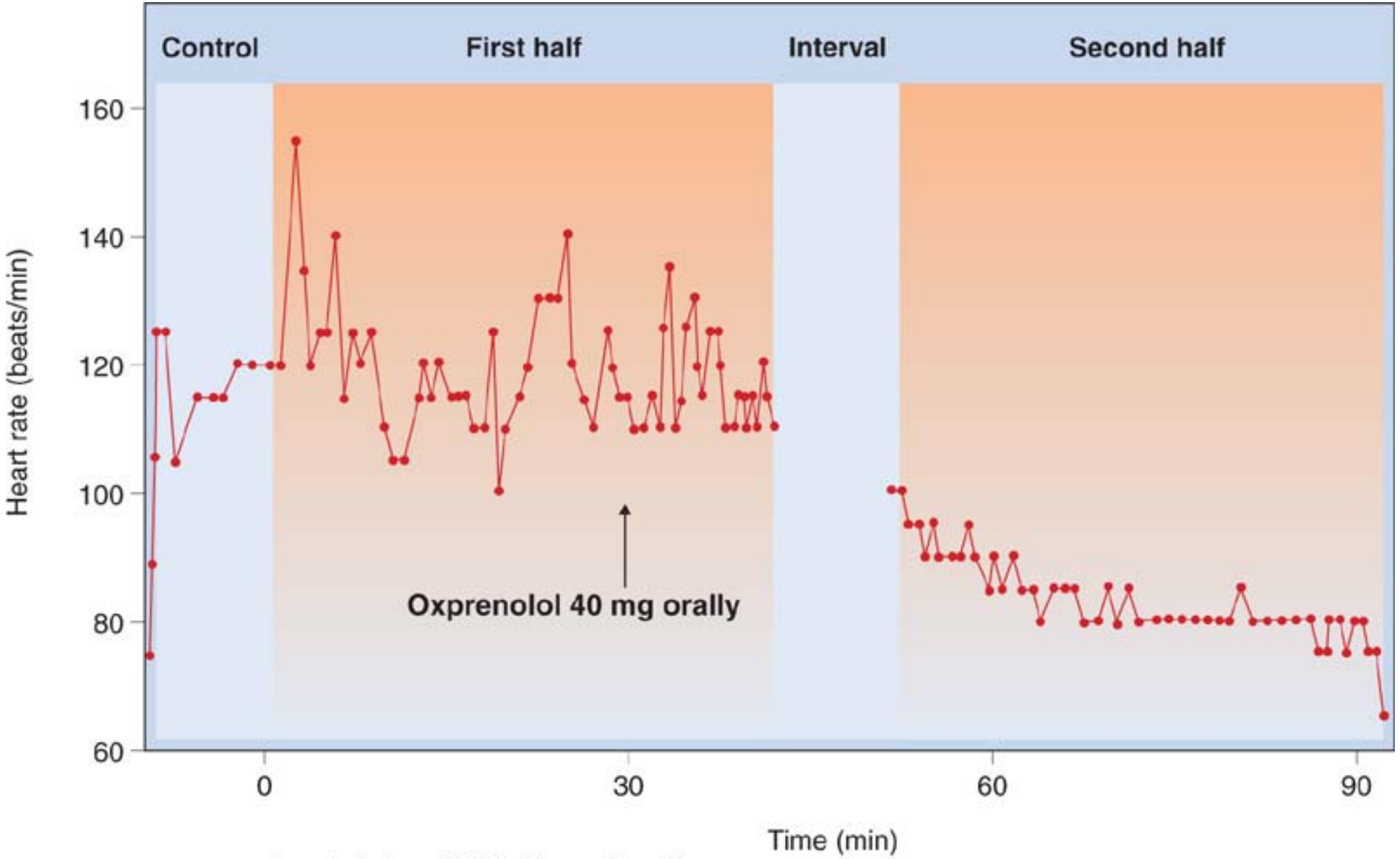

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