Farmakologija noradrenergičnega sistema

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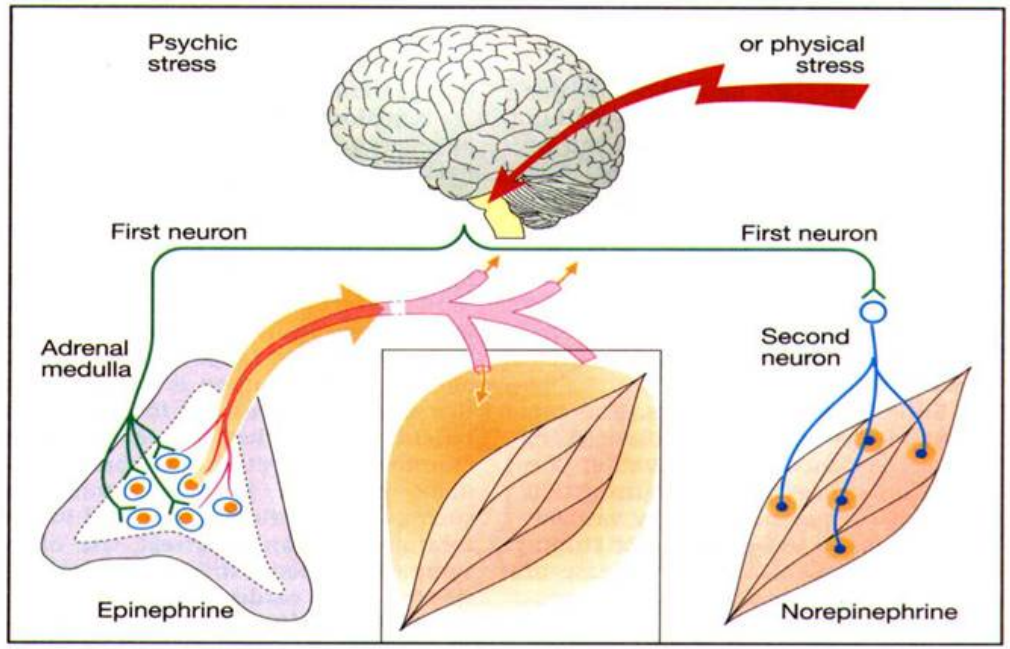
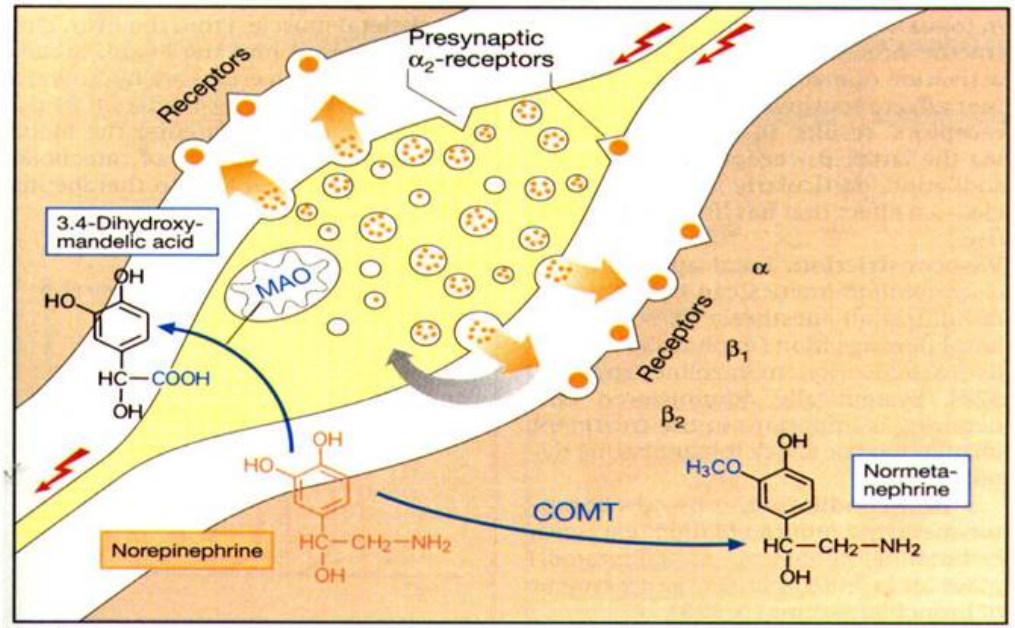
Simpatična inervacija



A. Epinephrine as hormone, norepinephrine as transmitter



B. Second neuron of sympathetic system, varicosity, norepinephrine release

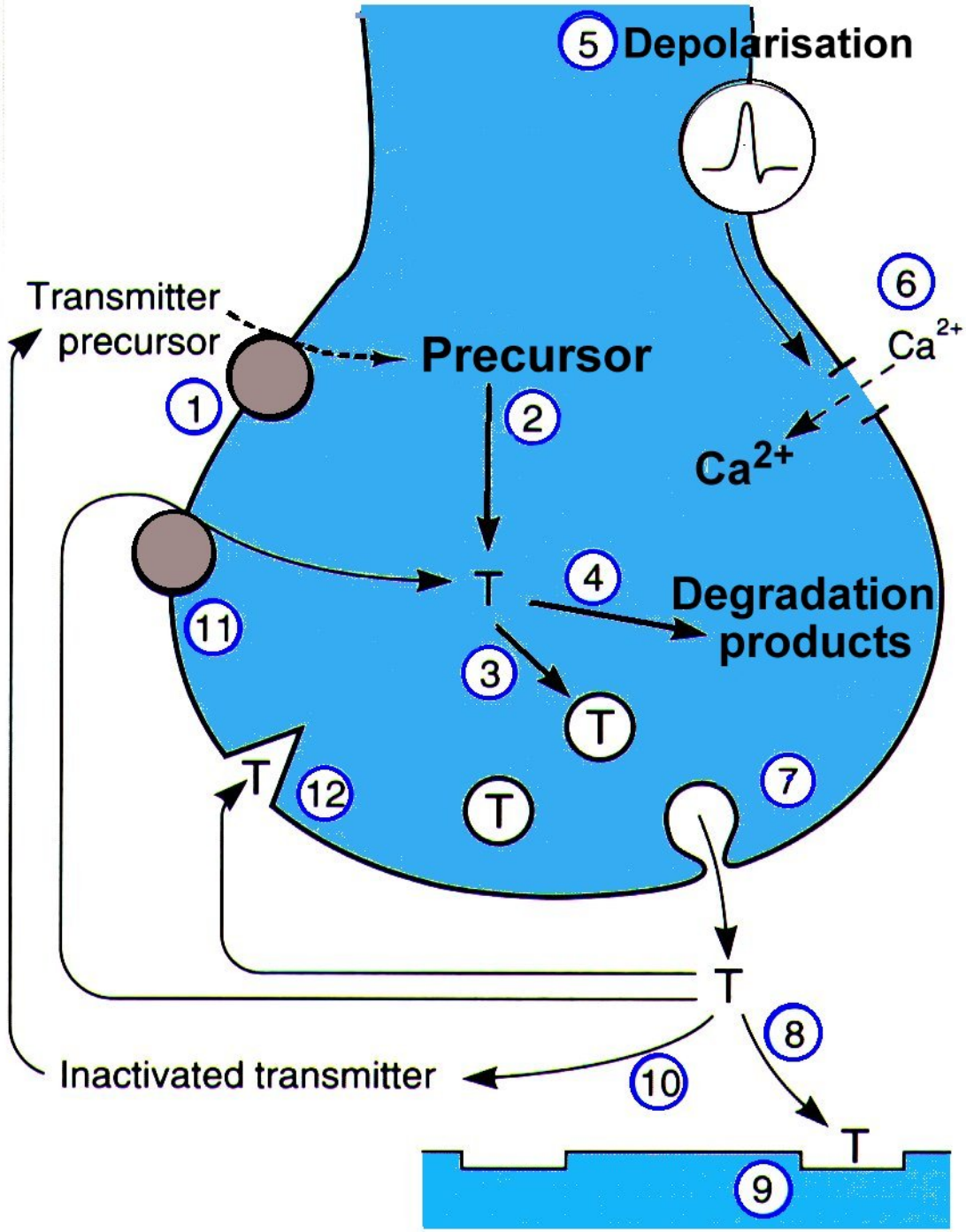
Zdravila, ki delujejo na simpatik

- Učinek podoben aktivaciji simpatika – simpatikomimetiki
- Zmanjšanje učinkov aktivacije simpatika – simpatikolitiki

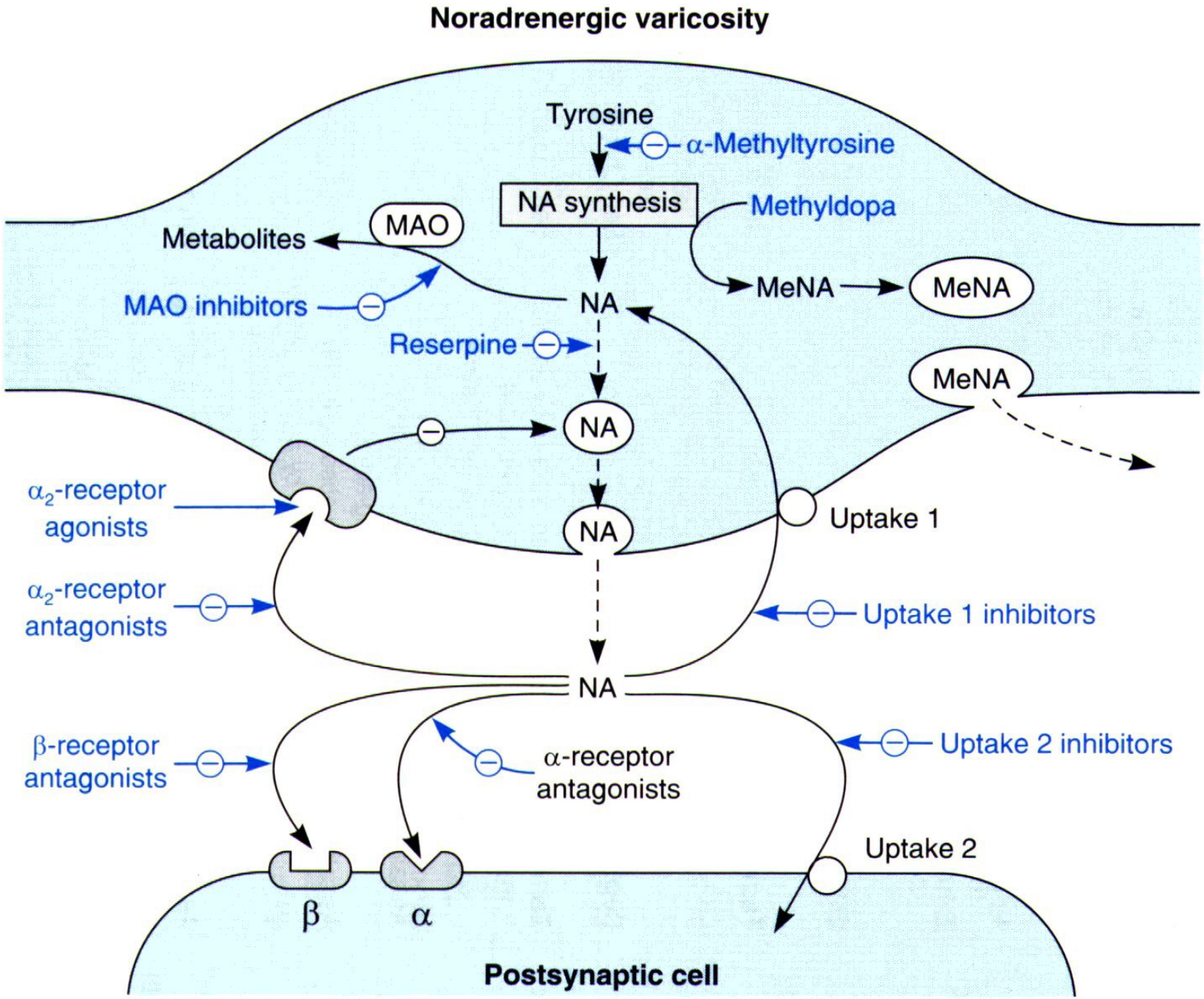
Faze sinaptičnega prenosa - kemične sinapse

- Sprejem prekurzorja v živčni končič
- Sinteza mediatorja
- Shranjevanje (skladiščenje) mediatorja
- Razgradnja znotraj živčnega končiča
- Depolarizacija ob akcijskem potencialu (AP)
- Vdor Ca^{++} ob AP
- Sproščanje mediatorja
- Difuzija do receptorjev
- Kombinacija z receptorji (pre-in post-sinapt.)
- Aktivacija R → → E
- Inaktivacija mediatorja

Faze sinaptičnega prenosa

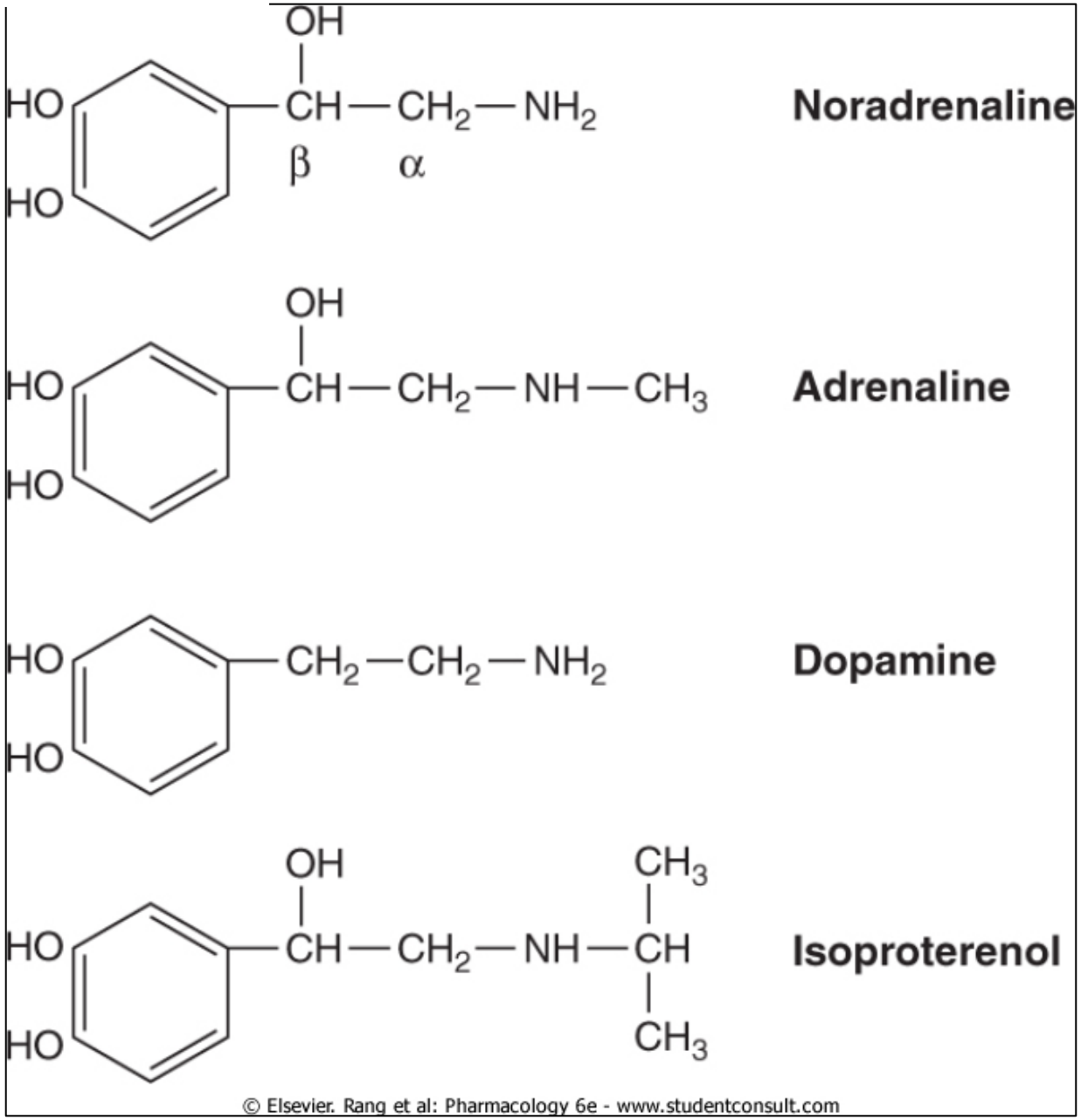


NA sinapsa


Noradrenergic varicosity
Tyrosine
α-Methyltyrosine
NA synthesis
Methyldopa
Metabolites
MAO
MAO inhibitors
NA
MeNA
MeNA
Reserpine
MeNA
NA
NA
α2-receptor agonists
Uptake 1
α2-receptor antagonists
Uptake 1 inhibitors
NA
β-receptor antagonists
α-receptor antagonists
Uptake 2 inhibitors
Uptake 2
β
α
Postsynaptic cell

Sinteza mediatorja

- Poteka v aksoplazmi
- Sledi prenos v vezikle ali zrnca
- Aksonski transport encimov za sintezo
- Pogosta povratna inhibicija (feed back)
- Možnost blokade encimov



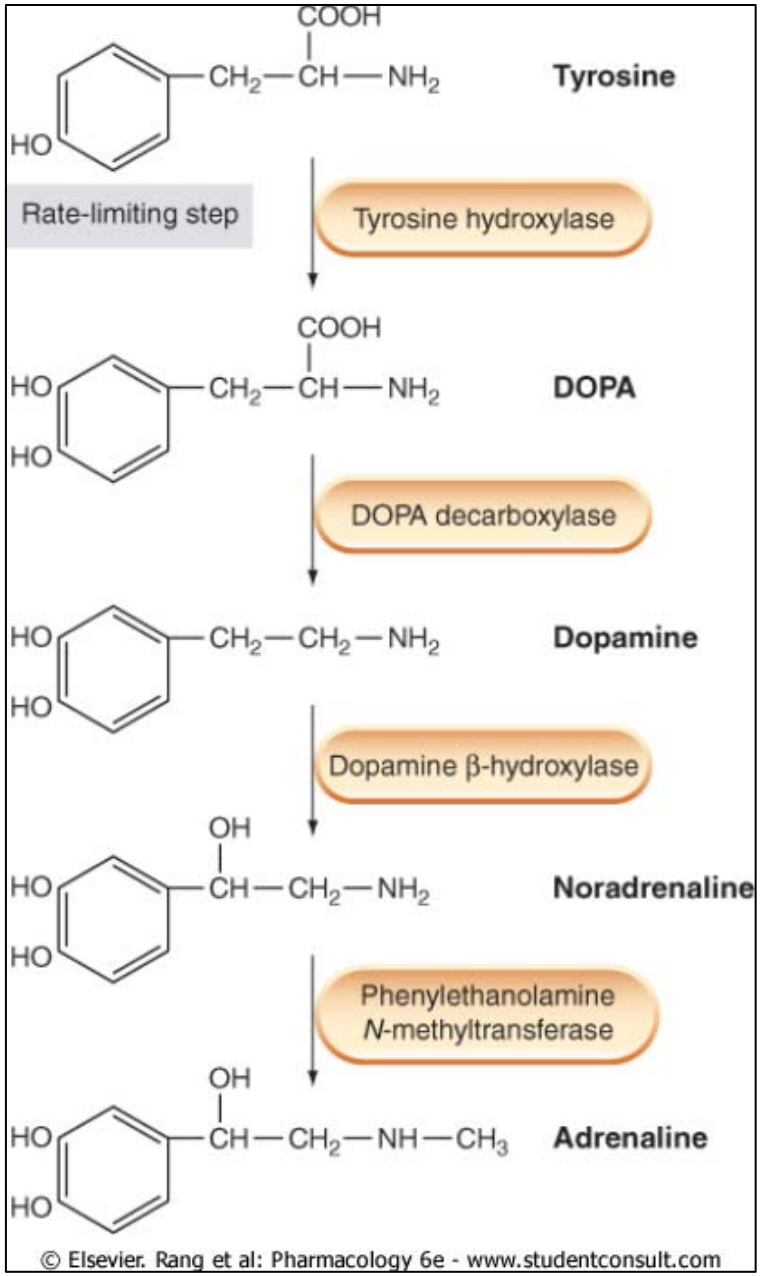


Figure 11-2 Biosynthesis of catecholamines. DOPA, dihydroxyphenylalanine.

Table 6–4 Enzymes for Synthesis of Catecholamines

ENZYME	OCCURRENCE	SUBCELLULAR DISTRIBUTION	COFACTOR REQUIREMENT	SUBSTRATE SPECIFICITY	COMMENTS
Tyrosine hydroxylase	Widespread; sympathetic nerves	Cytoplasmic	Tetrahydrobiopterin, O_2, Fe^{2+}	Specific for L-tyrosine	Rate-limiting step. Inhibition can lead to depletion of NE
Aromatic L-amino acid decarboxylase	Widespread; sympathetic nerves	Cytoplasmic	Pyridoxal phosphate	Nonspecific	Inhibition does not alter tissue NE and Epi appreciably
β-hydroxylase	Widespread; sympathetic nerves	Synaptic vesicles	Ascorbic acid, O_2 (contains copper)	Nonspecific	Inhibition can decrease NE and Epi levels
Phenylethanolamine *N*-methyltransferase	Largely in adrenal gland	Cytoplasmic	*S*-Adenosyl methionine (CH_3 donor)	Nonspecific	Inhibition leads to decrease in adrenal catecholamines; under control of glucocorticoids

Prenos v mesto skladiščenja

- Že pred zadnjo stopnjo v sintezi (često)
- Poseben transportni sistem
- Možnost kompeticije za mesto na transporterju
- Inhibicija transporta
- Izrivanje z mest vezave v granulih (veziklih)

Characteristics of noradrenaline transport systems

	Uptake 1	Uptake 2	Vesicular
Transport of noradrenaline (rat heart)			
V_{max} (nmol/g per min)	1.2	100	
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	Methylnoradrenaline	(+)-noradrenaline	Dopamine
	Dopamine	Dopamine	5-HT
	5-hydroxytryptamine	Serotonin	Guanethidine
	Tyramine	Histamine	MPP^+ (see Ch. 31)
	Adrenergic neuron blocking drugs (e.g. guanethidine)		
Inhibitors	Cocaine	Normetanephrine	Reserpine
	Tricyclic antidepressants (e.g. desipramine)	Steroid hormones (e.g. corticosterone)	Tetrabenazine
	Phenoxybenzamine	Phenoxybenzamine	
	Amphetamine		

Sproščanje mediatorja

- kontinuirno (počasno) sproščanje → → mepp → vzdrževanje fiziol. odzivnosti efektorja – udeleženi prenašalci
- proces eksocitoze
  - pomen Ca^{++} - Ca kanali v bližini mesta 'pristanka' vezikla
  - poleg osnovnega mediatorja se sproščajo tudi encimi, ATP – kotransmitor
  - modifikacija sproščanja - presinaptični R
    - za mediator, ki se sprošča - avto R
    - za druge mediatorje (heteroreceptorji)
    - v spl. → zavora sproščanja

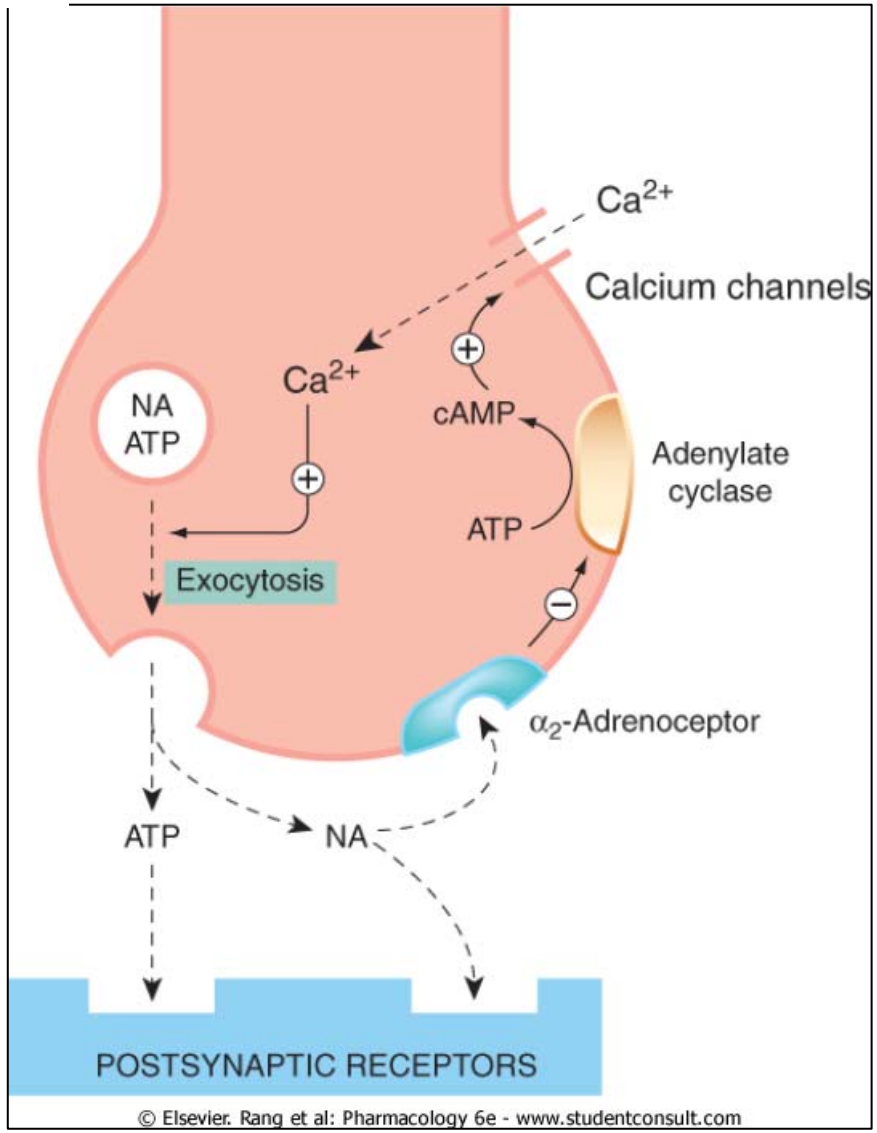


Figure 11-3 Feedback control of noradrenaline release. The presynaptic α2 receptor inhibits adenylate cyclase, thereby reducing intracellular cAMP. cAMP acts to promote Ca2+ influx in response to membrane depolarisation, and hence to promote the release of noradrenaline and ATP.

Delovanje NA na presinaptične receptorje

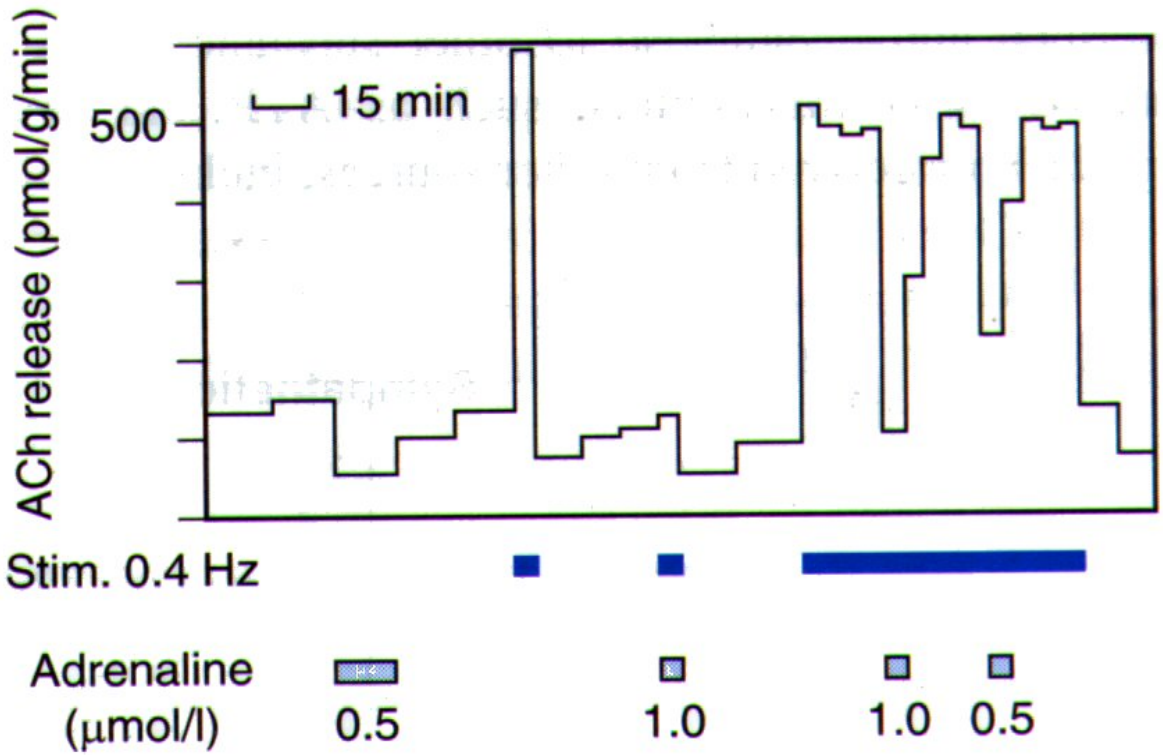


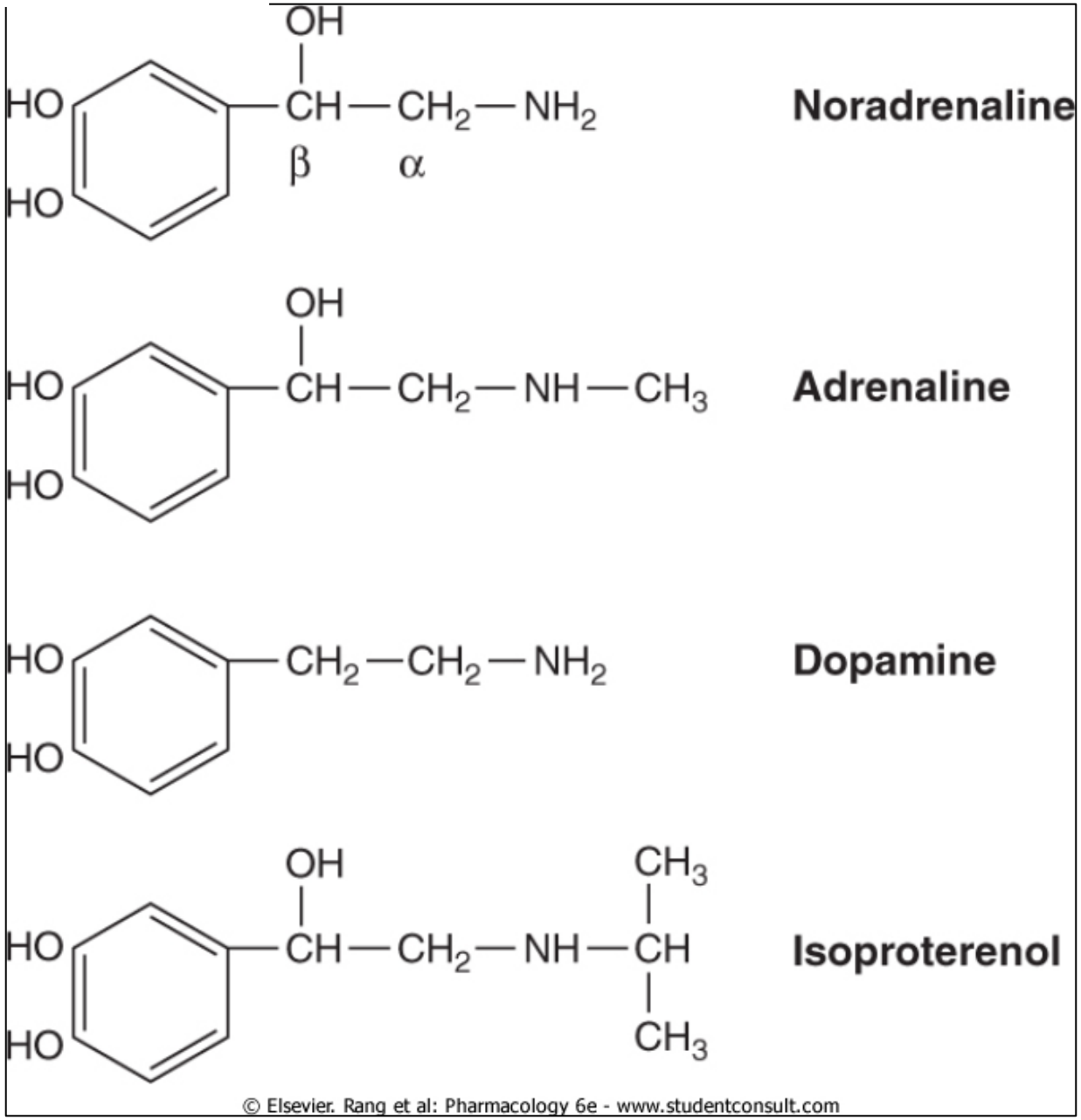
Fig. 6.3 Inhibitory effect of adrenaline on acetylcholine release from postganglionic parasympathetic nerves in the guinea-pig ileum. The intramural nerves were stimulated electrically where indicated, and the acetylcholine released into the bathing fluid determined by bioassay. Adrenaline strongly inhibits acetylcholine release. (From: Vizi E S 1979 Prog Neurobiol 12: 181)

Vezava na receptor (R)

- Različne vrste receptorjev glede na:
- Transdukcijske mehanizme
  - Receptorji, sklopljeni s proteinom G (metabotropni R)
- Lokalizacijo
  - Postsinaptični R
  - Presinaptični R

Funkcija receptorjev (R) glede na njihovo lokalizacijo

- Postsinaptični R:
  - Efektorni organi – kontrakcija, sekrecija
  - Drugi nevroni – depolarizacija, hiperpolarizacija
- Presinaptični R (hetero R, avto R):
  - Zmanjšanje sproščanja (sekrecije) mediatorja
  - Povečanje sproščanja mediatorja



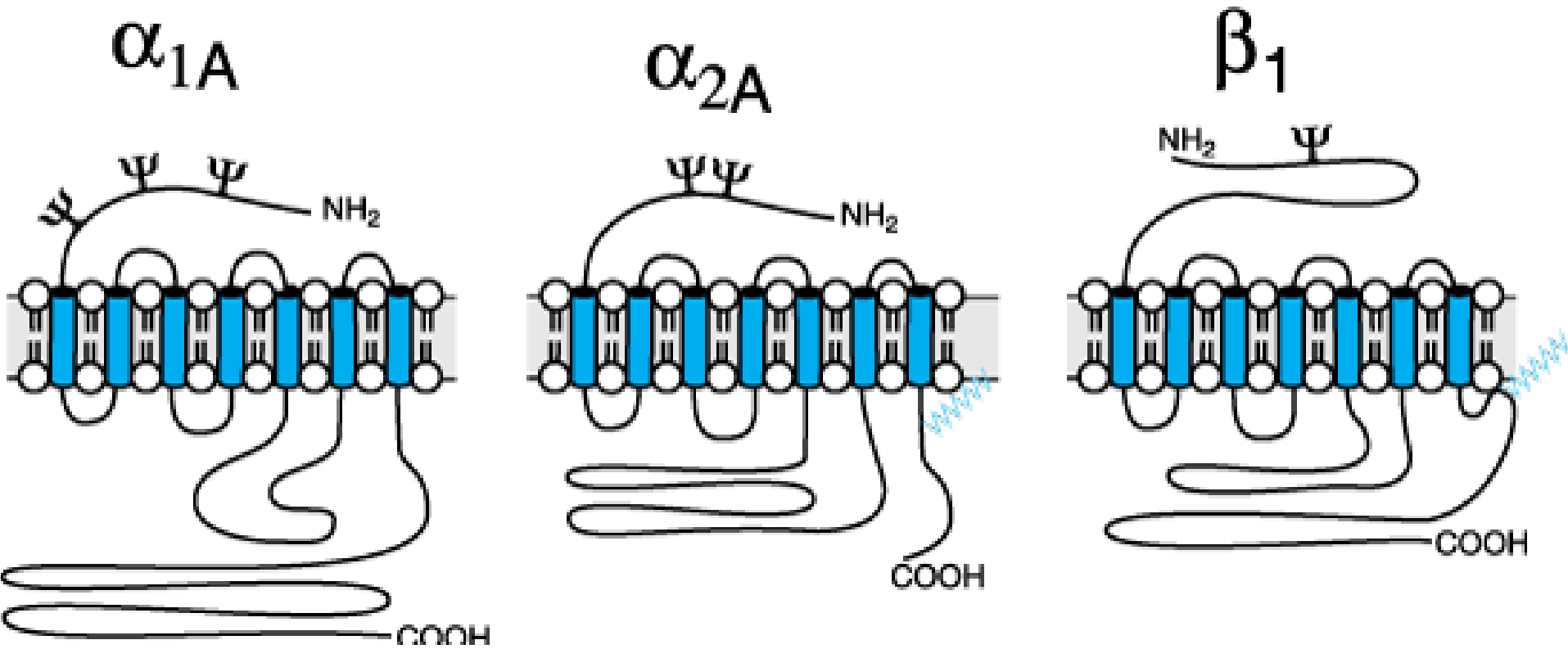
Noradrenergic receptor subtypes: α

RECEPTOR	AGONISTS	ANTAGONISTS	TISSUE	RESPONSES
α_1	Epi ≥ NE >> Iso	Prazosin	Vascular smooth muscle	Contraction
	Phenylephrine		GU smooth muscle	Contraction
			Liver‡	Glycogenolysis; gluconeogenesis
			Intestinal smooth muscle	Hyperpolarization and relaxation
			Heart	Increased contractile force; arrhythmias
α_2	Epi ≥ NE >> Iso	Yohimbine	Pancreatic islets (β cells)	Decreased insulin secretion
	Clonidine		Platelets	Aggregation
			Nerve terminals	Decreased release of NE
			Vascular smooth muscle	Contraction

Noradrenergic receptor subtypes: β

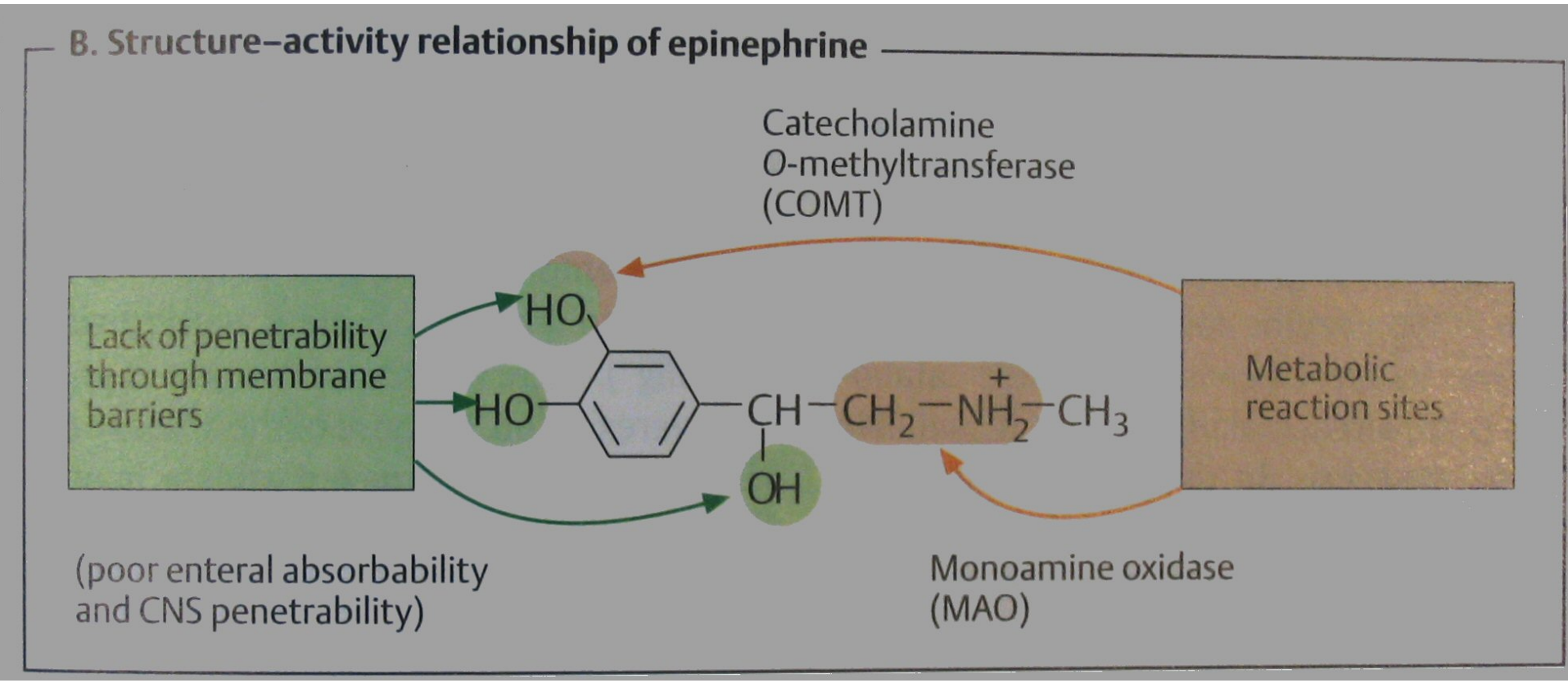
RECEPTOR	AGONISTS	ANTAGONISTS	TISSUE	RESPONSES
β_1	Iso > Epi = NE	Metoprolol	Juxtaglomerular cells	Increased renin secretion
	Dobutamine	CGP 20712A	Heart	Increased force and rate of contraction and AV nodal conduction velocity
β_2	Iso > Epi >> NE	ICI 118551	Smooth muscle (vascular, bronchial, GI, and GU)	Relaxation
	Terbutaline		Skeletal muscle	Glycogenolysis; uptake of K+
			Liver‡	Glycogenolysis; gluconeogenesis
β_3	Iso = NE > Epi	ICI 118551	Adipose tissue	Lipolysis
	BRL 37344	CGP 20712A		

Struktura NA receptorjev

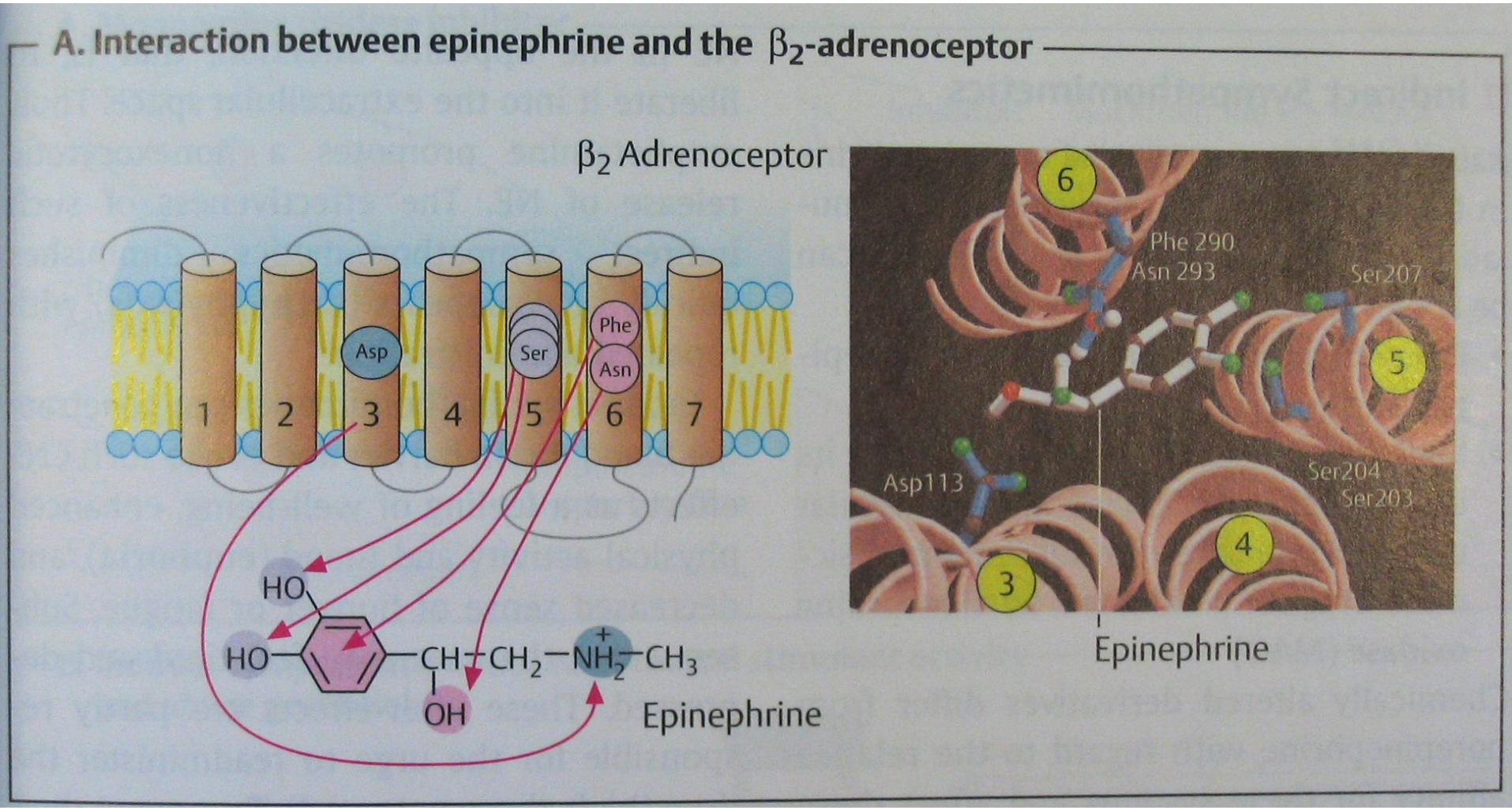


Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

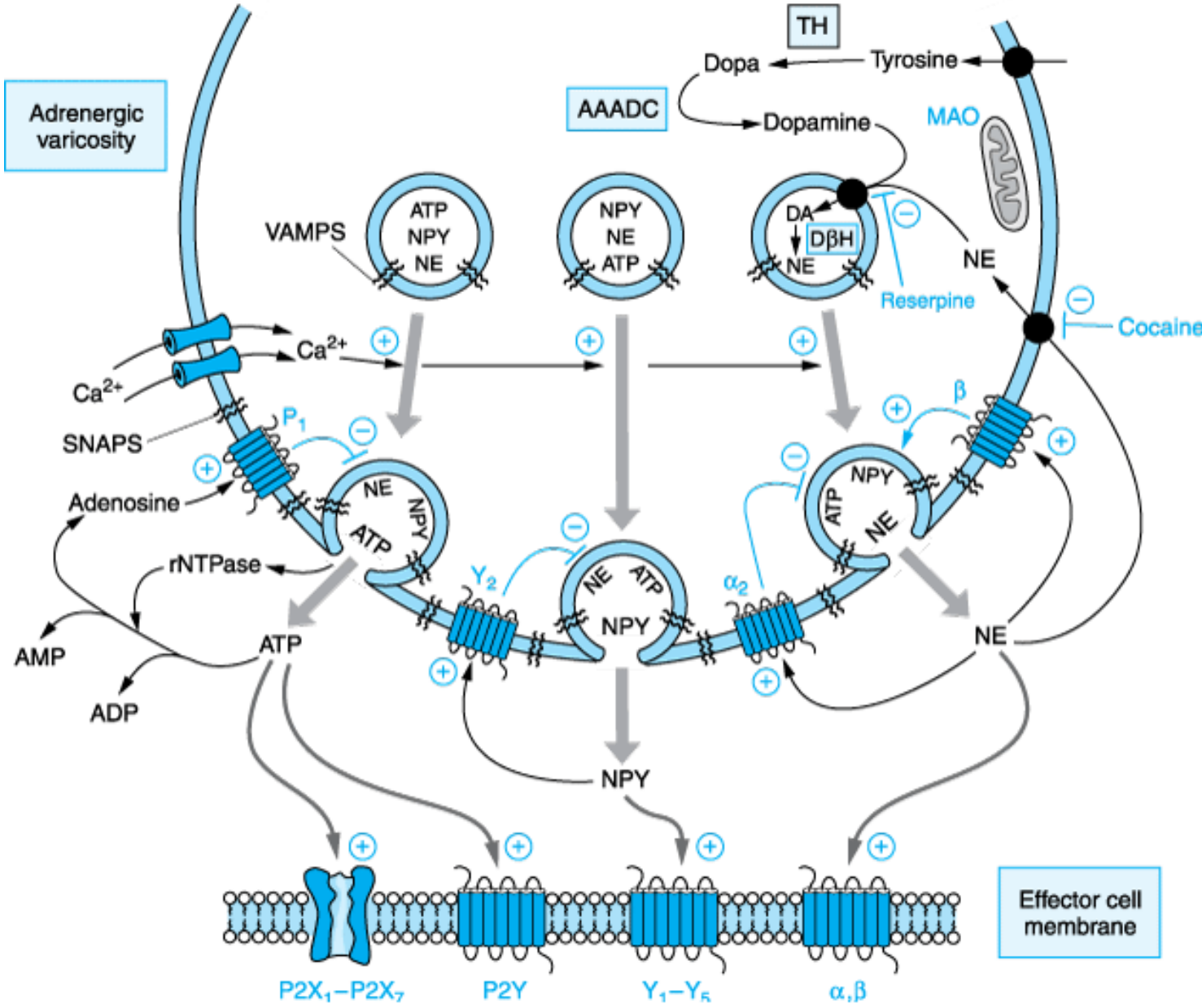
Odnos med strukturo in aktivnostjo adrenalina



Interakcija A z receptorji β



Dogajanja v noradrenergični sinapsi

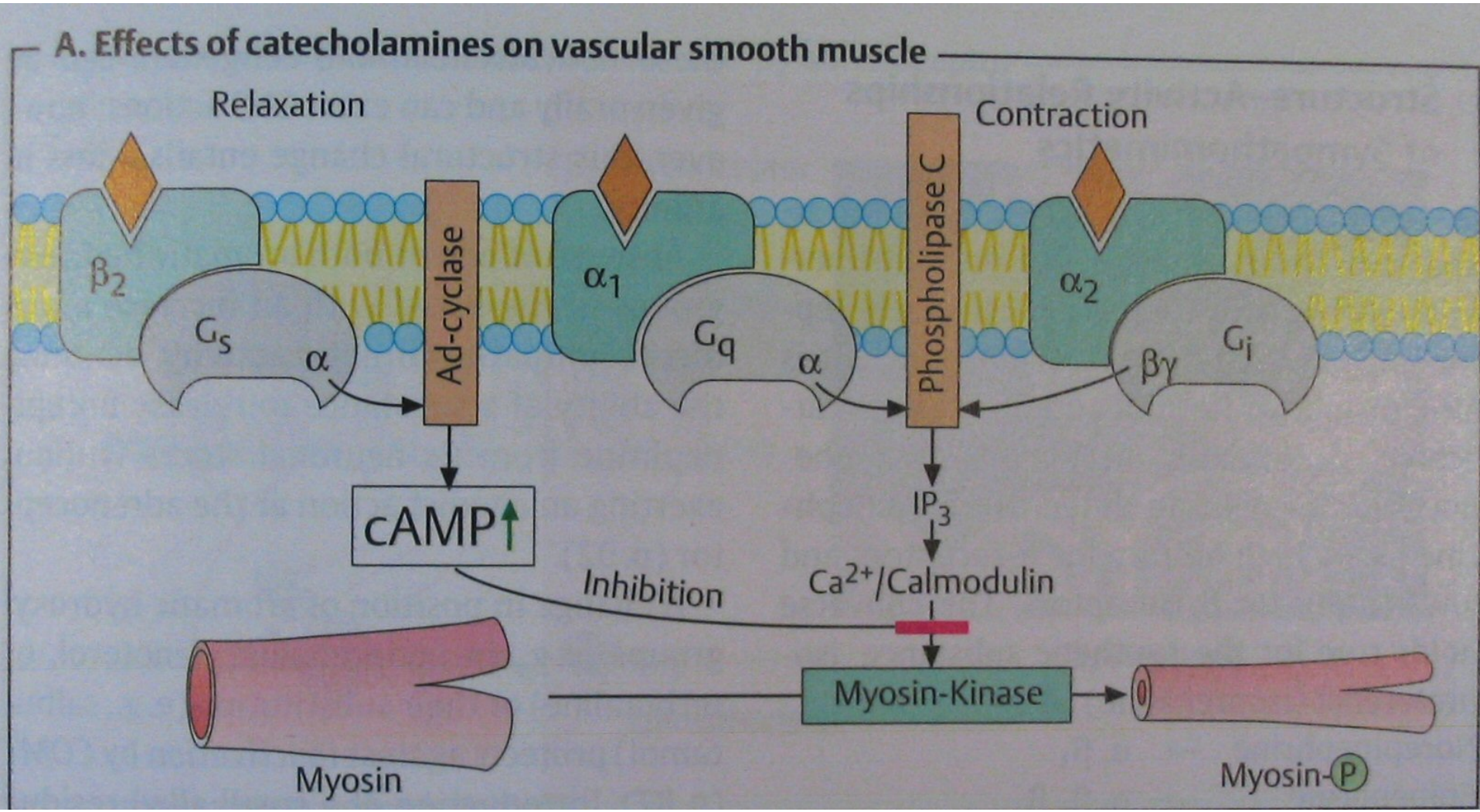


Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

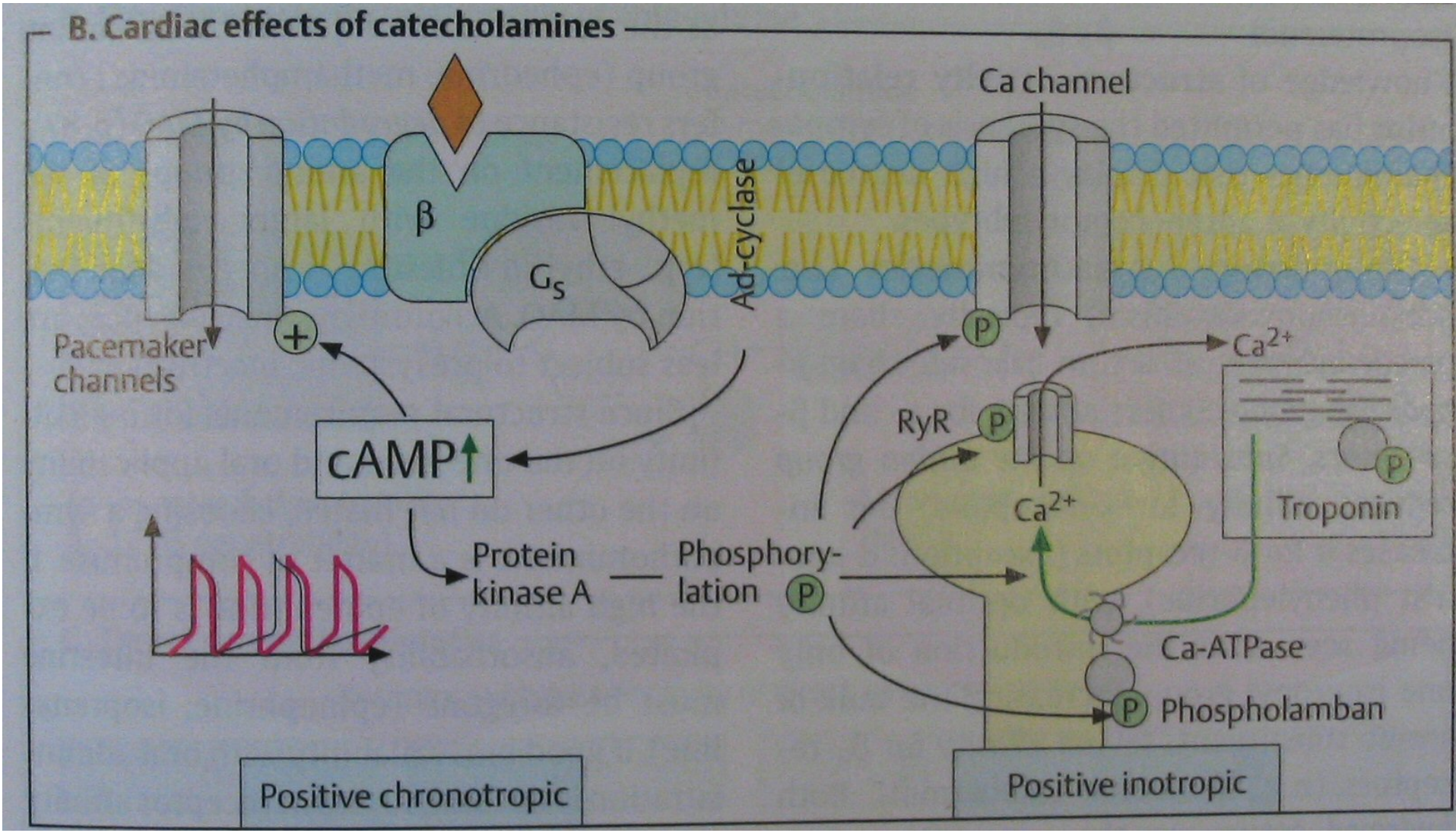
Denervacijska preobčutljivost

- Povečana odzivnost postsinaptične celice na eksogeni mediator (agonist)
- Vzroki:
  - spremenjen mehanizem inaktivacije mediatorja
  - proliferacija R
  - ↑ občutljivost iz drugih vzrokov (depolarizacija postsinaptične membrane iz neznanega vzroka)

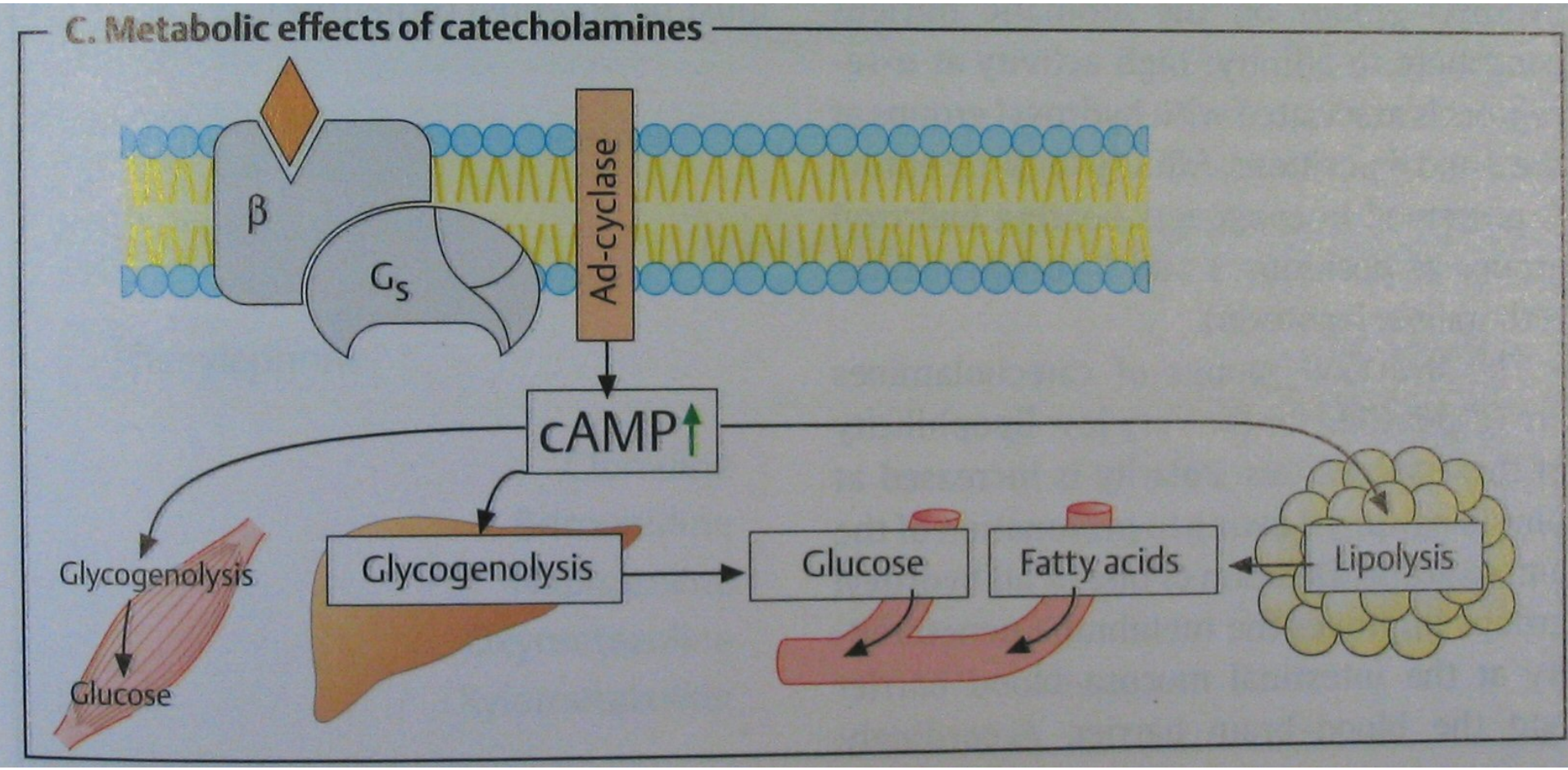
Učinki kateholaminov na žilje



Kardialni učinki kateholaminov



Metabolni učinki kateholaminov



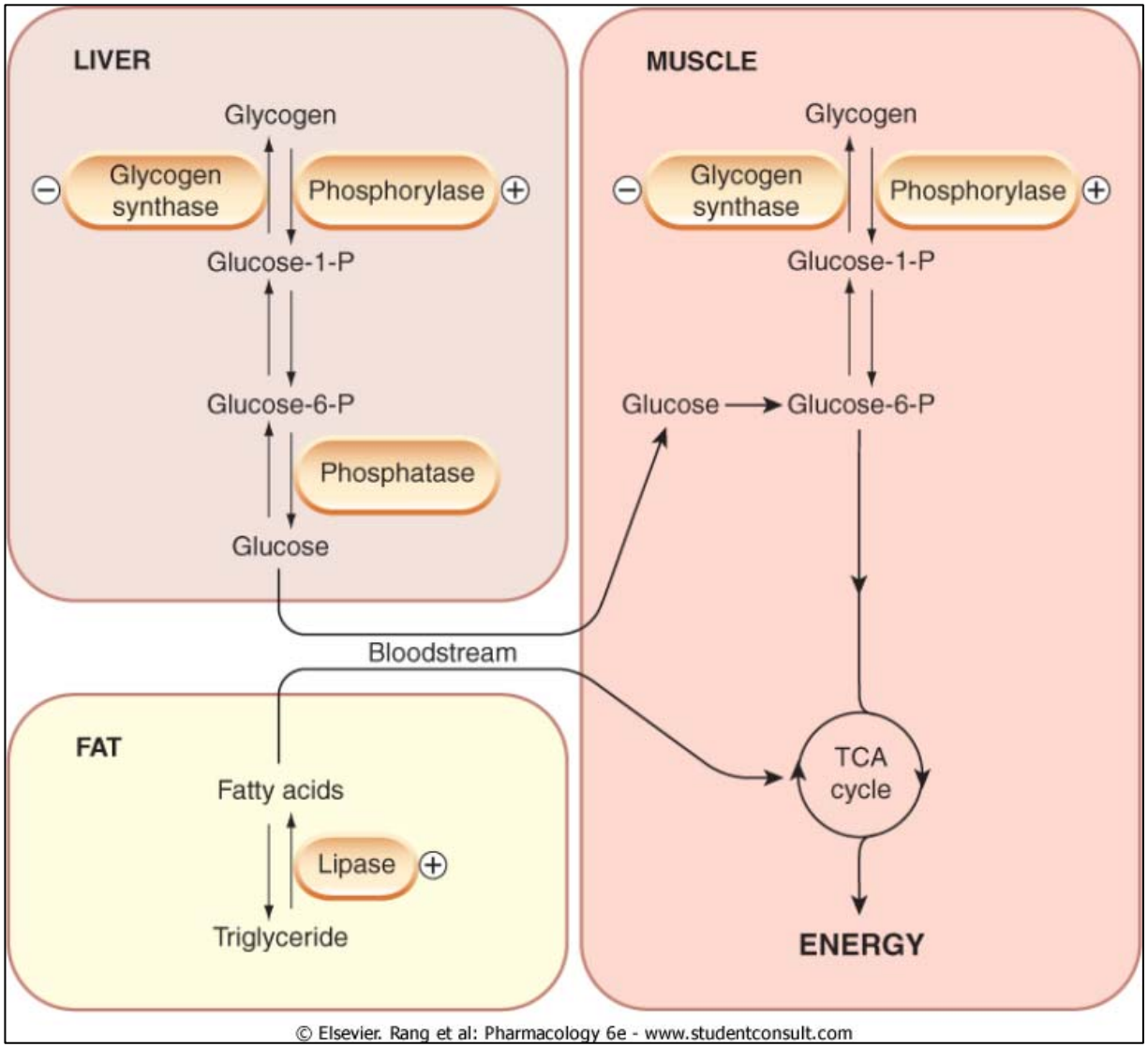


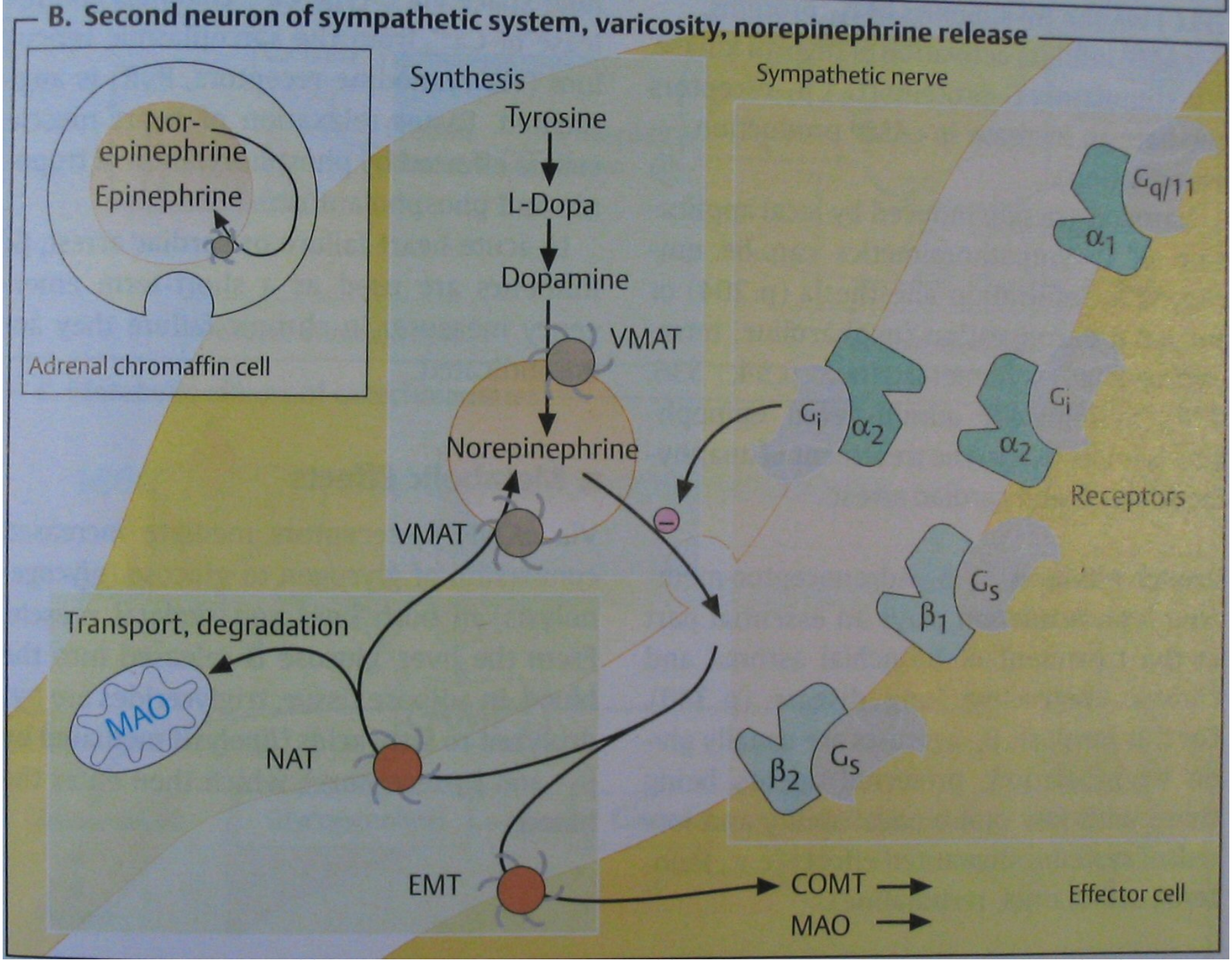
Figure 11-6 Regulation of energy metabolism by catecholamines. The main enzymic steps that are affected by β-adrenoceptor activation are indicated by + and - signs, denoting stimulation and inhibition, respectively. The overall effect is to mobilise glycogen and fat stores to meet energy demands.

Inaktivacija mediatorja

- Privzem (ponovni) ((re)uptake) – noradrenergična, dopaminergična.... sinapsa:
  - nevronski (privzem 1) – NET
  - ekstranevronski (privzem 2) – OCT3
- Difuzija iz sinaptične reže
- Možnosti farmakološkega vpliva na prva dva procesa

Characteristics of noradrenaline transport systems

	Uptake 1	Uptake 2	Vesicular
Transport of noradrenaline (rat heart)		OCT 3	
V_{max} (nmol/g per min)	1.2	100	
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	Methylnoradrenaline Dopamine 5-hydroxytryptamine Tyramine Adrenergic neuron blocking drugs (e.g. guanethidine)	(+)-noradrenaline Dopamine Serotonin Histamine	Dopamine 5-HT Guanethidine MPP^+ (see Ch. 31)
Inhibitors	Cocaine Tricyclic antidepressants (e.g. desipramine) Phenoxybenzamine Amphetamine	Normetanephrine Steroid hormones (e.g. corticosterone) Phenoxybenzamine	Reserpine Tetrabenazine


B. Second neuron of sympathetic system, varicosity, norepinephrine release
Nor-
epinephrine
Epinephrine
Adrenal chromaffin cell
Synthesis
Tyrosine
L-Dopa
Dopamine
VMAT
Norepinephrine
VMAT
Transport, degradation
MAO
NAT
EMT
COMT
MAO
Sympathetic nerve
$G_{q/11}$
α_1
G_i
α_2
G_i
α_2
Receptors
G_s
β_1
G_s
β_2
Effector cell

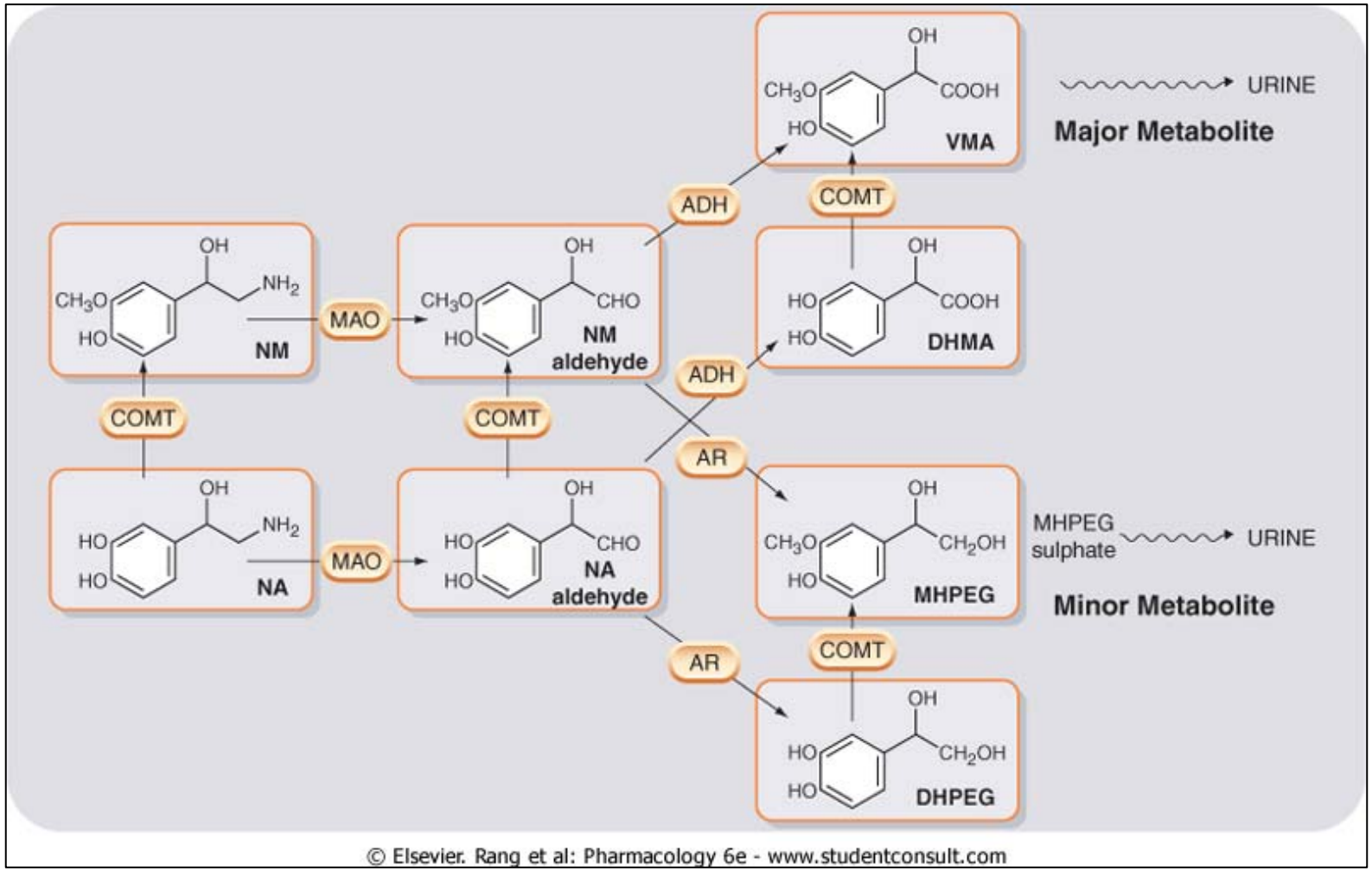


Figure 11-4 The main pathways of noradrenaline metabolism. The oxidative branch (catalysed by ADH) predominates, giving VMA as the main urinary metabolite. The reductive branch (catalysed by AR) produces the less abundant metabolite, MHPEG, which is conjugated to MHPEG sulfate before being excreted. ADH, aldehyde dehydrogenase; AR, aldehyde reductase; CNS, central nervous system; COMT, catechol-O-methyl transferase; DHMA, 3,4-dihydroxymandelic acid; DHPEG, 3,4-dihydroxyphenylglycol; MAO, monoamine oxidase; MHPEG, 3-methoxy, 4-hydroxyphenylglycol; NA, noradrenaline; NM, normetanephrine; VMA, vanillylmandelic acid.

Razlike med učinki A in NA pri človeku I

Comparison of the Effects of Intravenous Infusion of Epinephrine and Norepinephrine in Human Beings*

EFFECT	EPINEPHRINE	NOREPINEPHRINE
Cardiac		
Heart rate	+	−†
Stroke volume	++	++
Cardiac output	+++	0,−
Arrhythmias	++++	++++
Coronary blood flow	++	++
Blood pressure		
Systolic arterial	+++	+++
Mean arterial	+	++
Diastolic arterial	+,0,−	++
Mean pulmonary	++	++

*0.1 to 0.4 μg/kg/min

Abbreviations: + = increase; 0 = no change; − = decrease; † = after atropine, +

SOURCE: After Goldenberg *et al.*, **1950**. Courtesy of *Archives of Internal Medicine.*

Razlike med učinki A in NA pri človeku II

Comparison of the Effects of Intravenous Infusion of Epinephrine and Norepinephrine in Human Beings*

EFFECT	EPINEPHRINE	NOREPINEPHRINE
Peripheral circulation		
Total peripheral resistance	−	++
Cerebral blood flow	+	0,−
Muscle blood flow	+++	0,−
Cutaneous blood flow	−−	−−
Renal blood flow	−	−
Splanchnic blood flow	+++	0,+
Metabolic effects		
Oxygen consumption	++	0,+
Blood glucose	+++	0,+
Blood lactic acid	+++	0,+
Eosinopenic response	+	0
Central nervous system		
Respiration	+	+
Subjective sensations	+	+

*0.1 to 0.4 μg/kg/min

Abbreviations: + = increase; 0 = no change; − = decrease; † = after atropine, +

SOURCE: After Goldenberg *et al.*, **1950**. Courtesy of *Archives of Internal Medicine.*

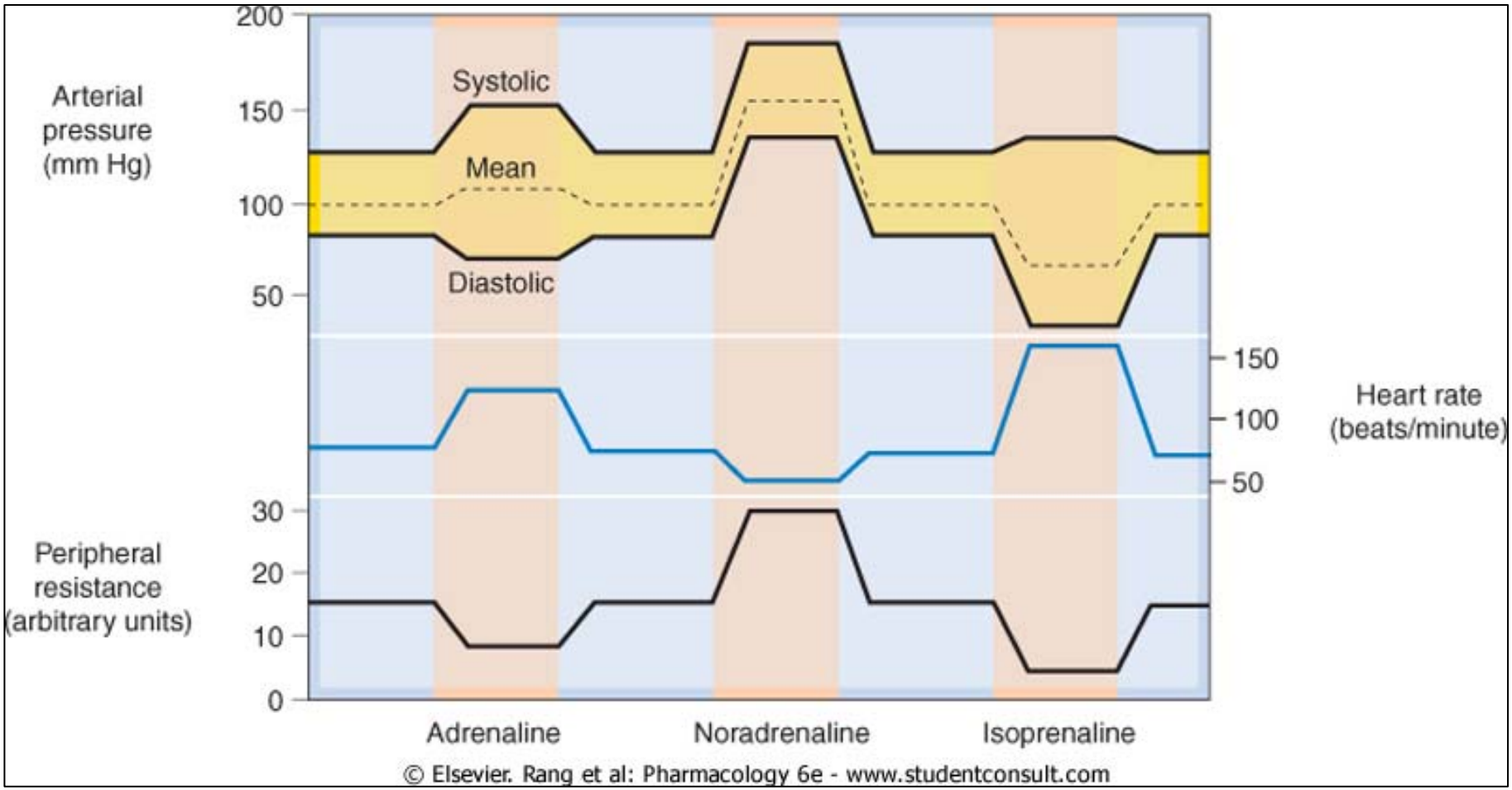
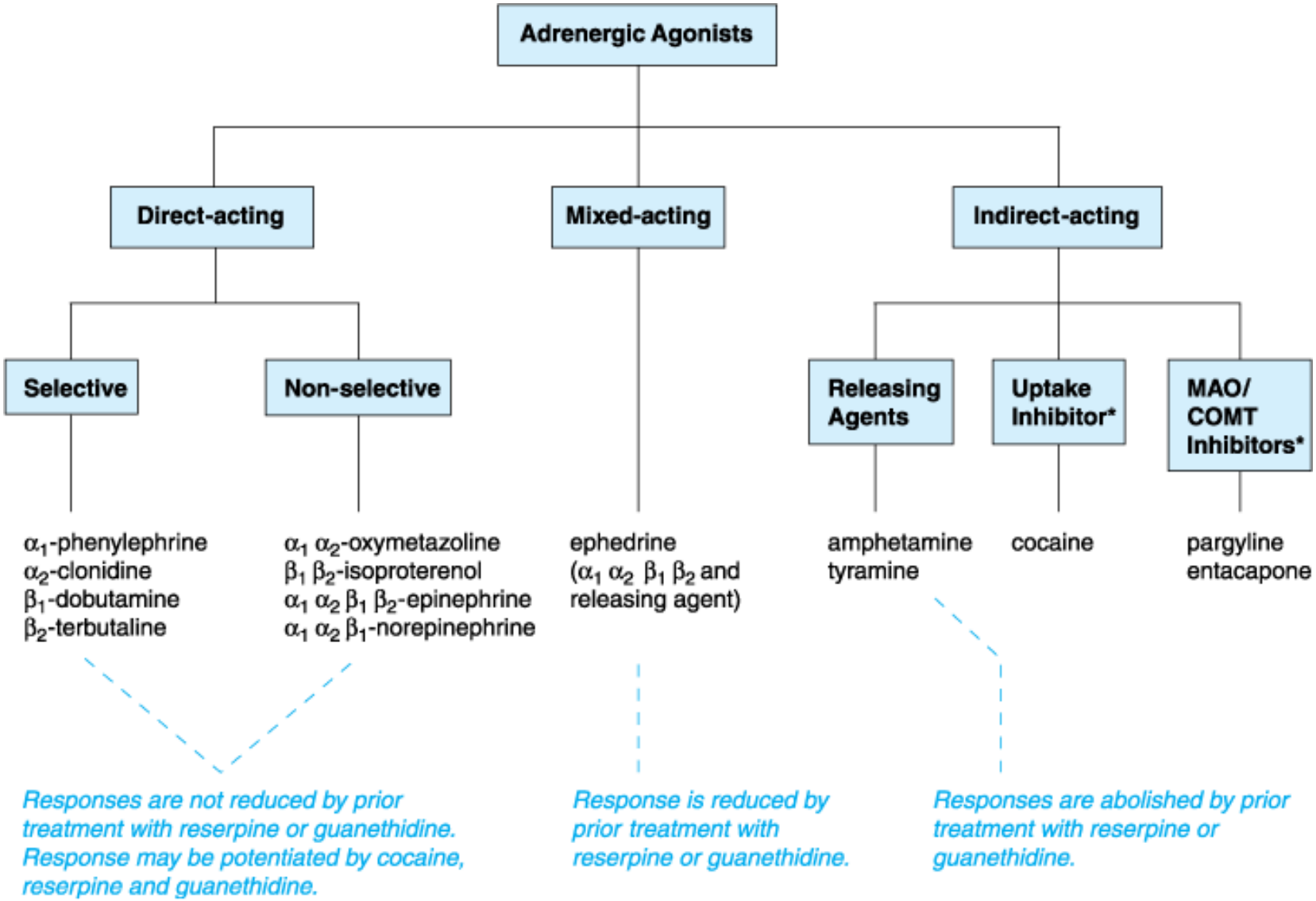


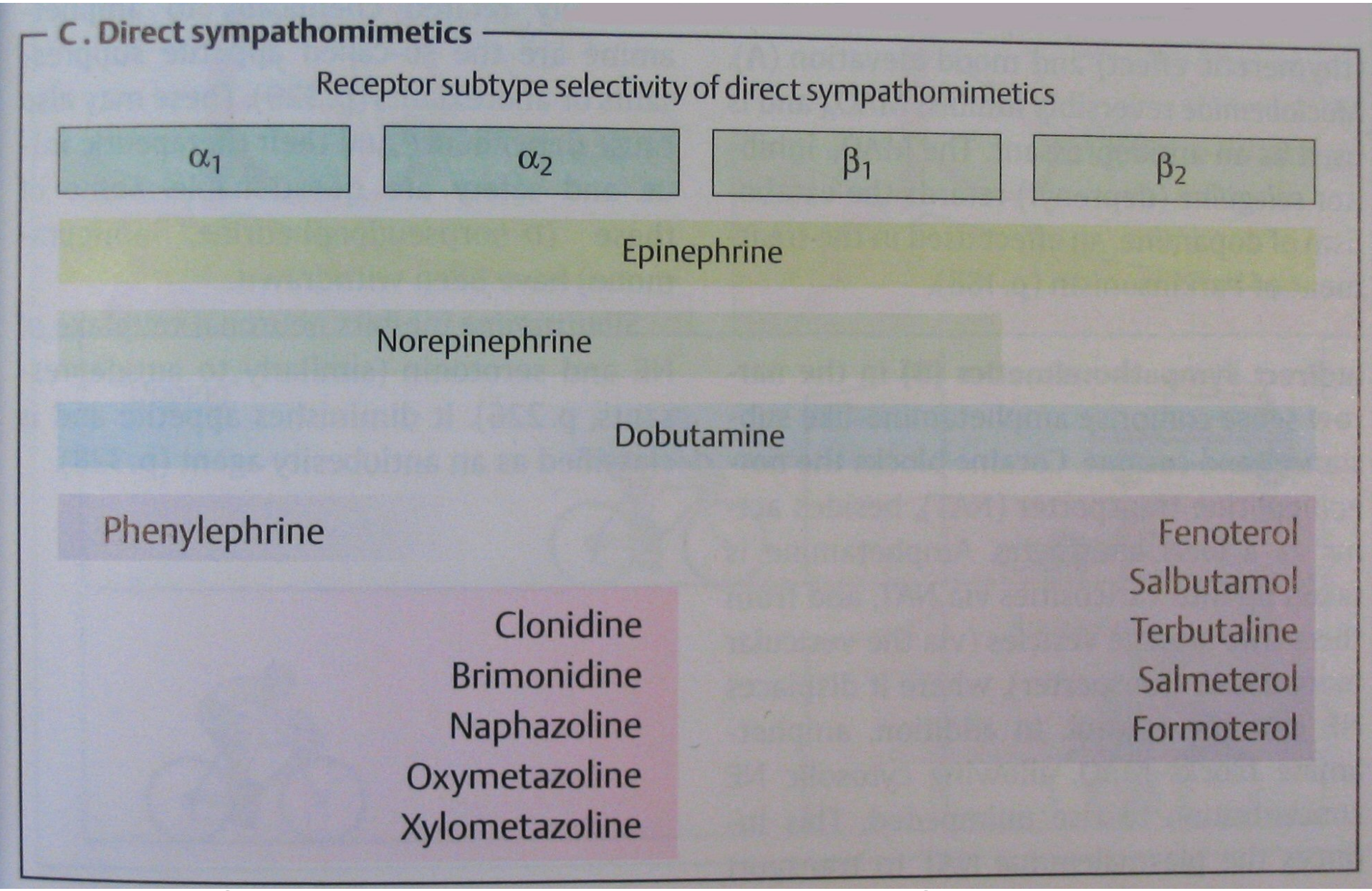
Figure 11-5 Schematic representation of the cardiovascular effects of intravenous infusions of adrenaline, noradrenaline and isoproterenol in humans. Noradrenaline (predominantly α agonist) causes vasoconstriction and increased systolic and diastolic pressure, with a reflex bradycardia. Isoproterenol (β agonist) is a vasodilator, but strongly increases cardiac force and rate. Mean arterial pressure falls. Adrenaline combines both actions.

Pregled adrenergičnih agonistov



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

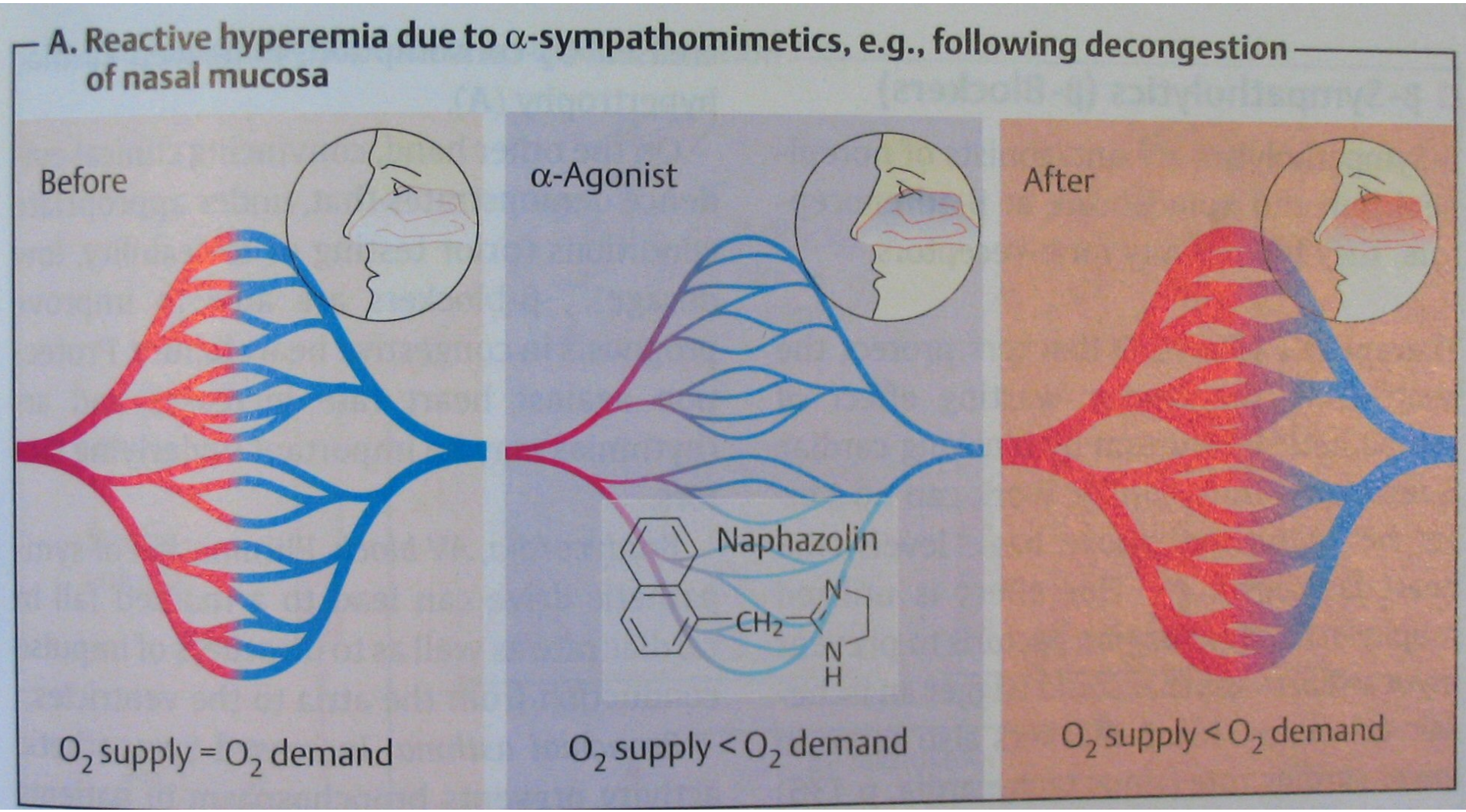
Razdelitev direktnih simpatikomimetikov



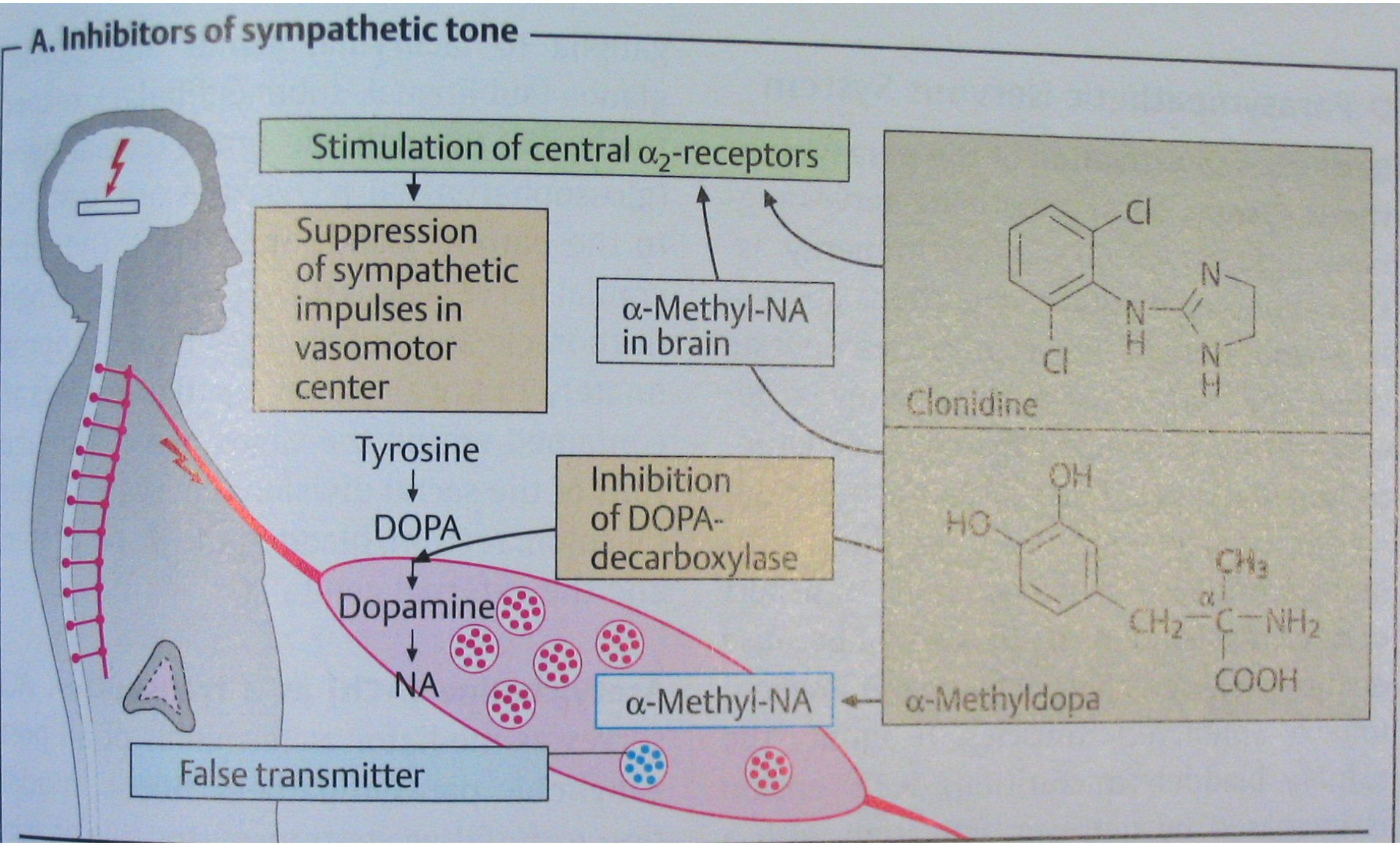
Uporaba agonistov α

- Neselektivni: adrenalin
  - Srčni zastoj
- α_1 : fenilefrin (efedrin)
  - dekongestija nosne sluznice
  - arterijska hipotenzija
- α_2 : klonidin, …..
  - arterijska hipertenzija
  - abstinenčni pojavi
  - prevencija migrene
  - postmenopavzalne težave

Agonisti α - vpliv na kongestijo nosne sluznice



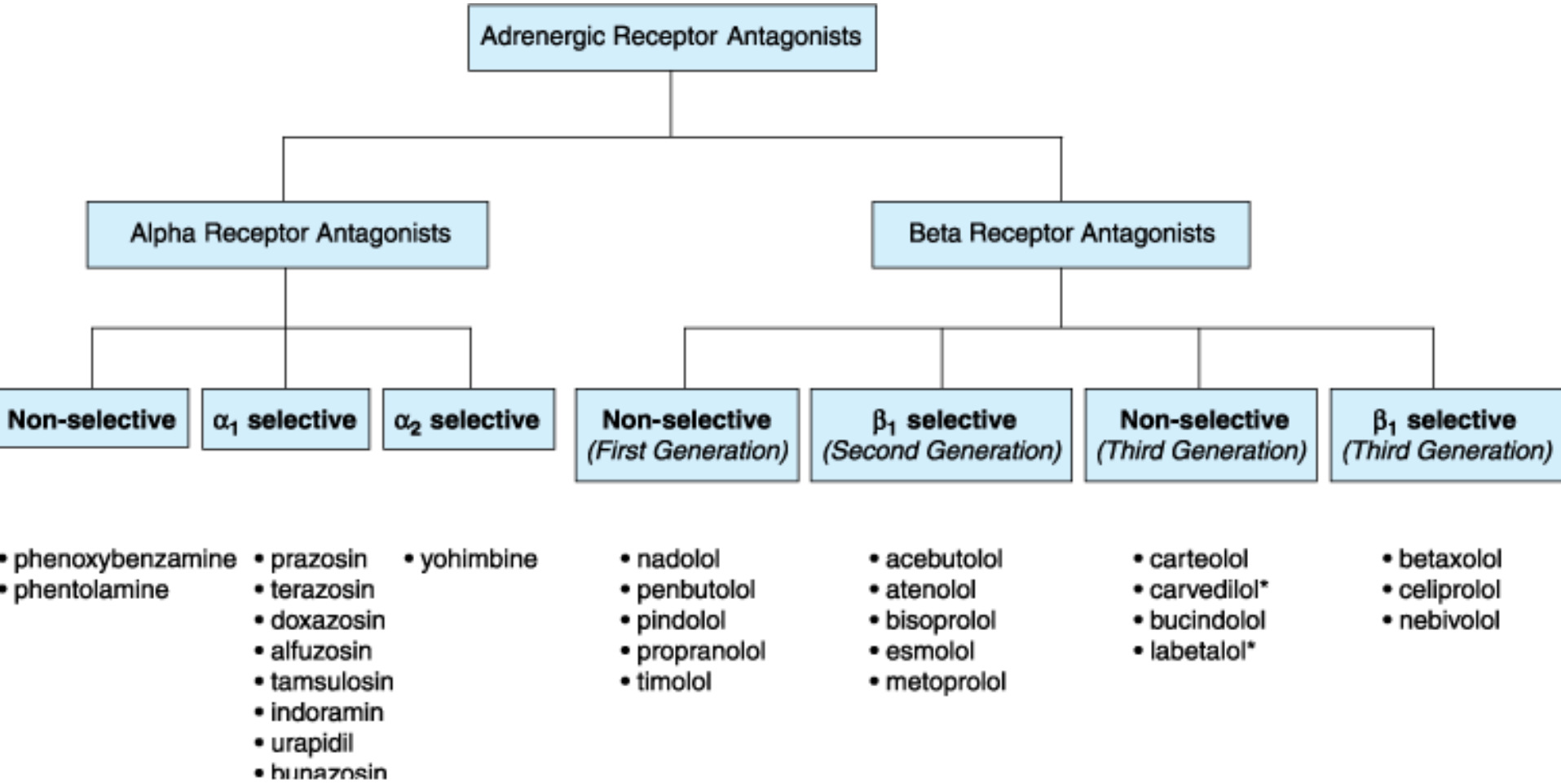
Inhibicija tonusa simpatika I



Uporaba agonistov β

- β_1: dobutamin – kardiogeni šok
- β_2: salbutamol,… -
  - astma
  - prezgodnji porod

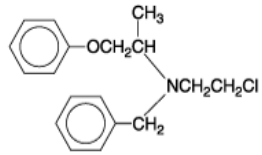
Pregled adrenergičnih antagonistov



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

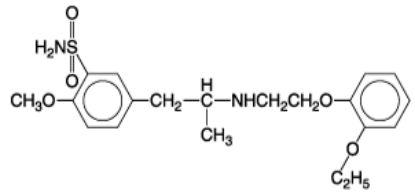
Struktura antagonistov α

Alkylating agent



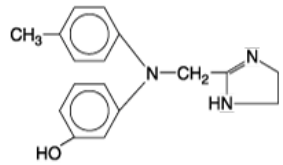
PHENOXYBENZAMINE

Benzenesulfonamide

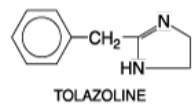


TAMSULOSIN

Imidazolines

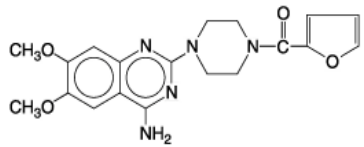


PHENTOLAMINE

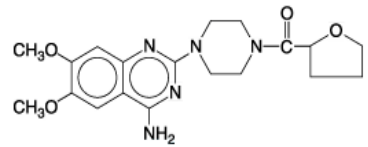


TOLAZOLINE

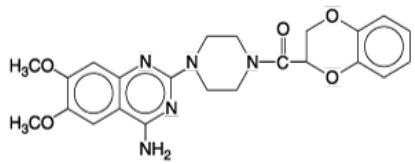
Piperazinyl quinazolines



PRAZOSIN

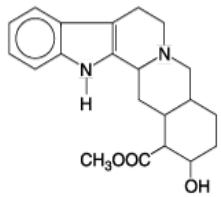


TERAZOSIN

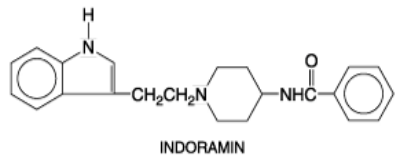


DOXAZOSIN

Indoles

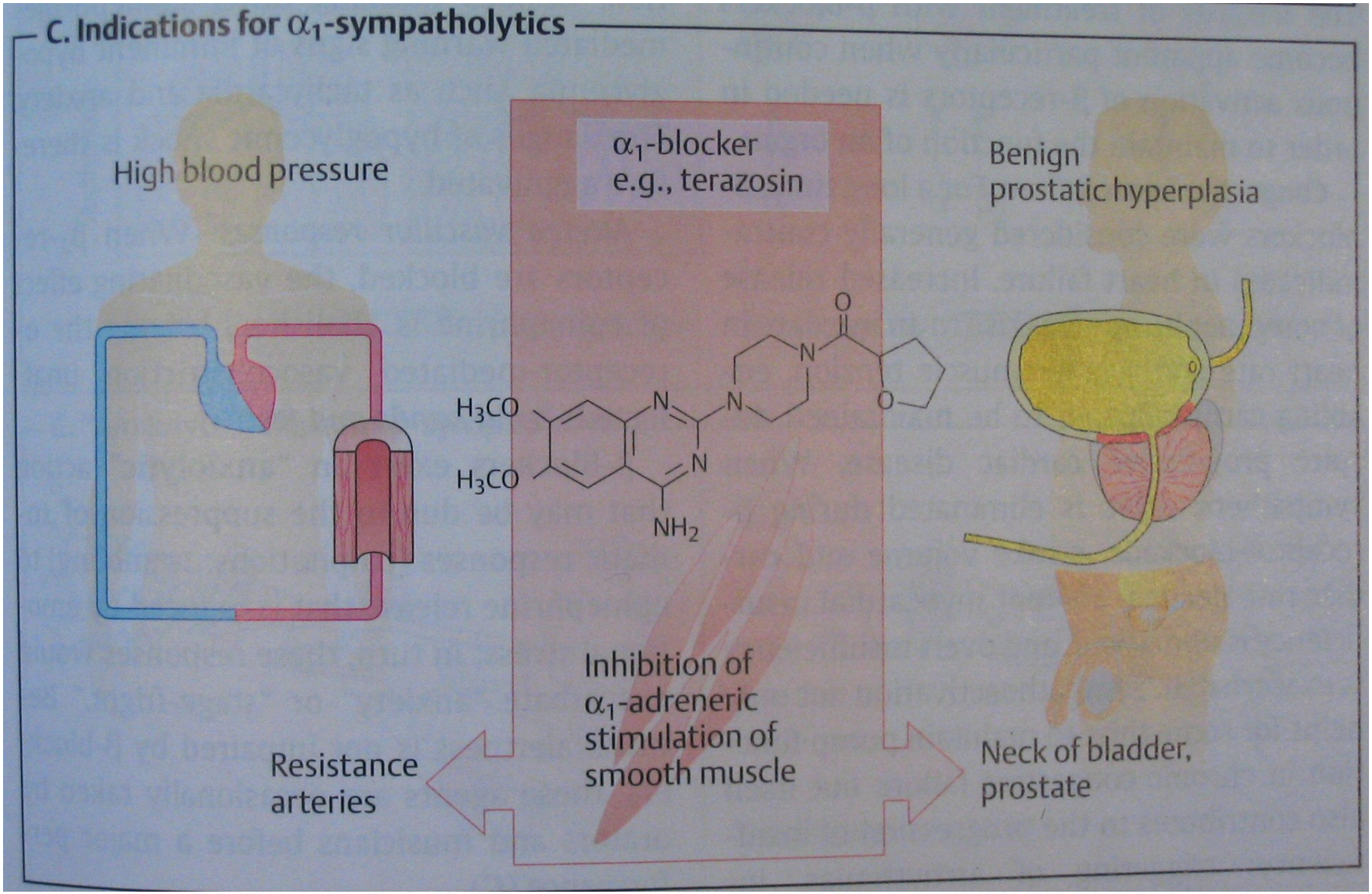


YOHIMBINE

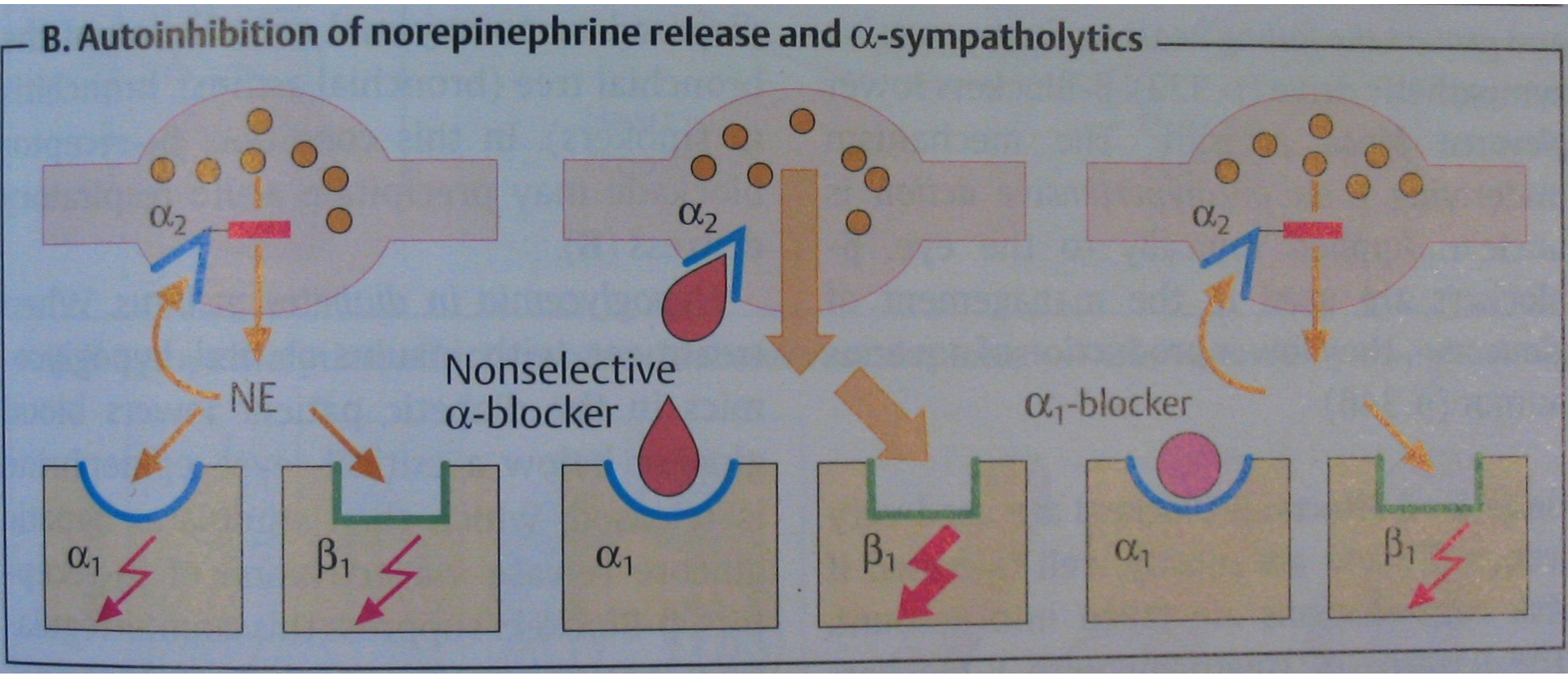


INDORAMIN

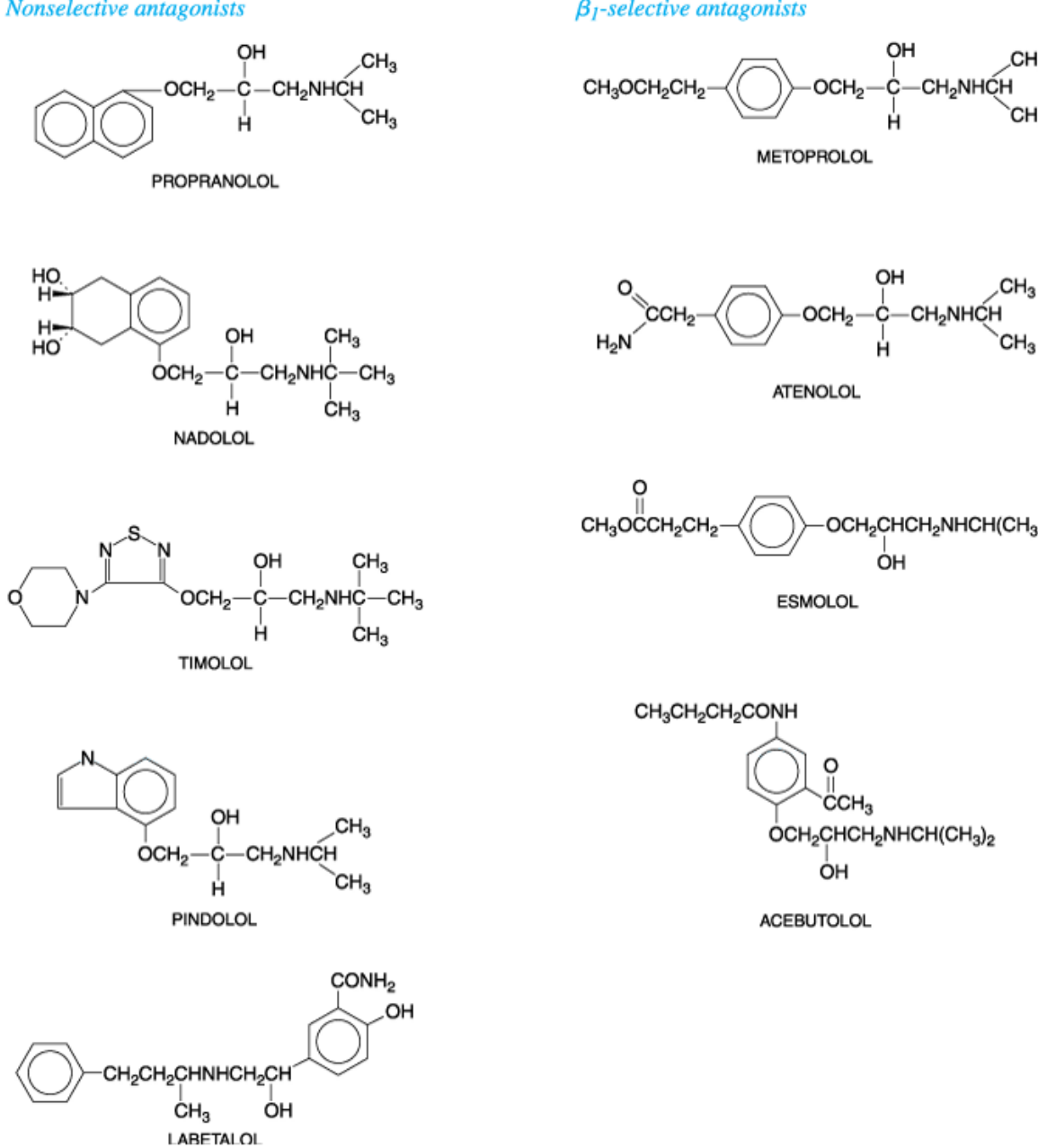
Indikacije za blokatorje α_1



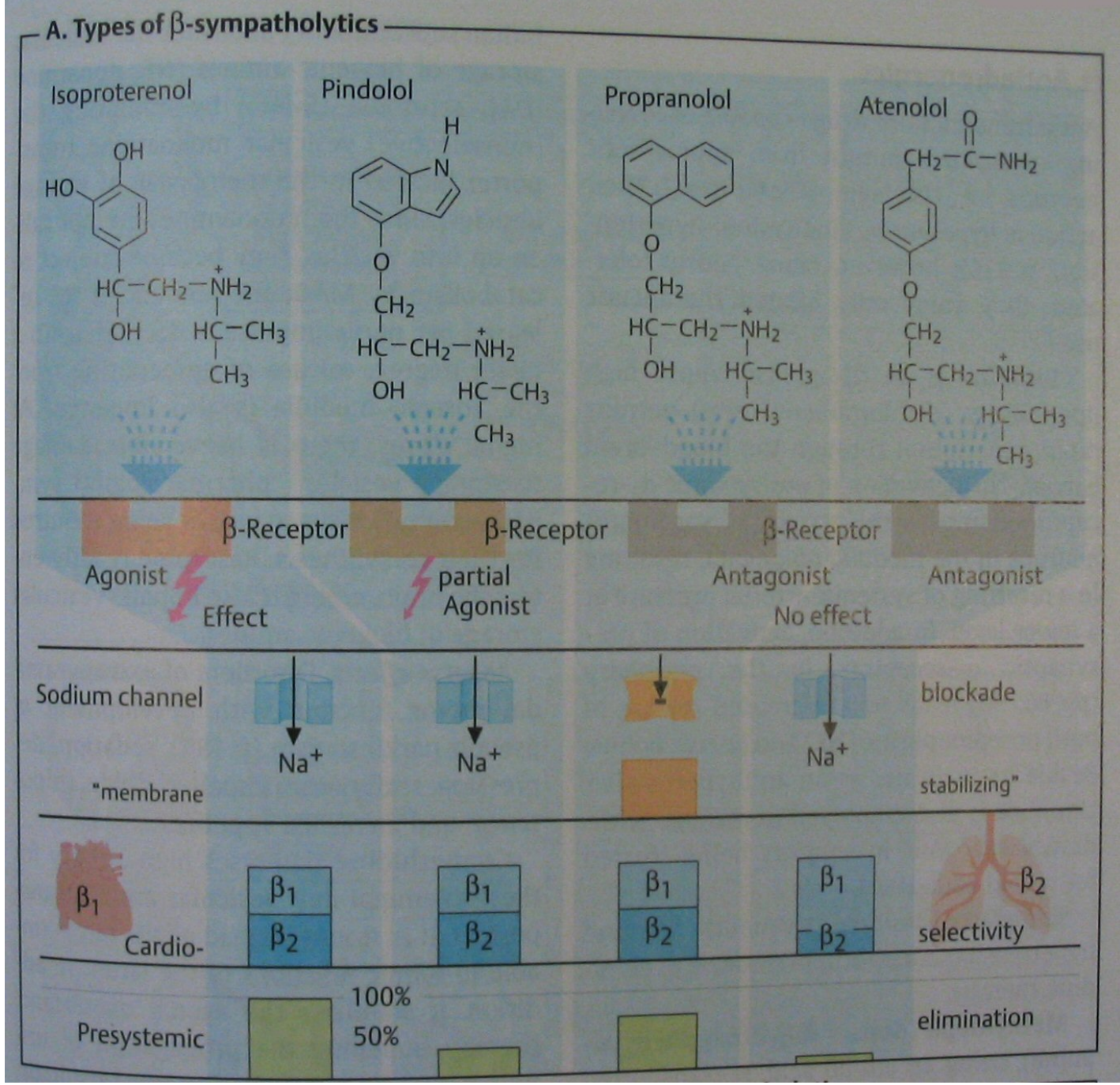
Vpliv blokatorjev α na na sproščanje NA



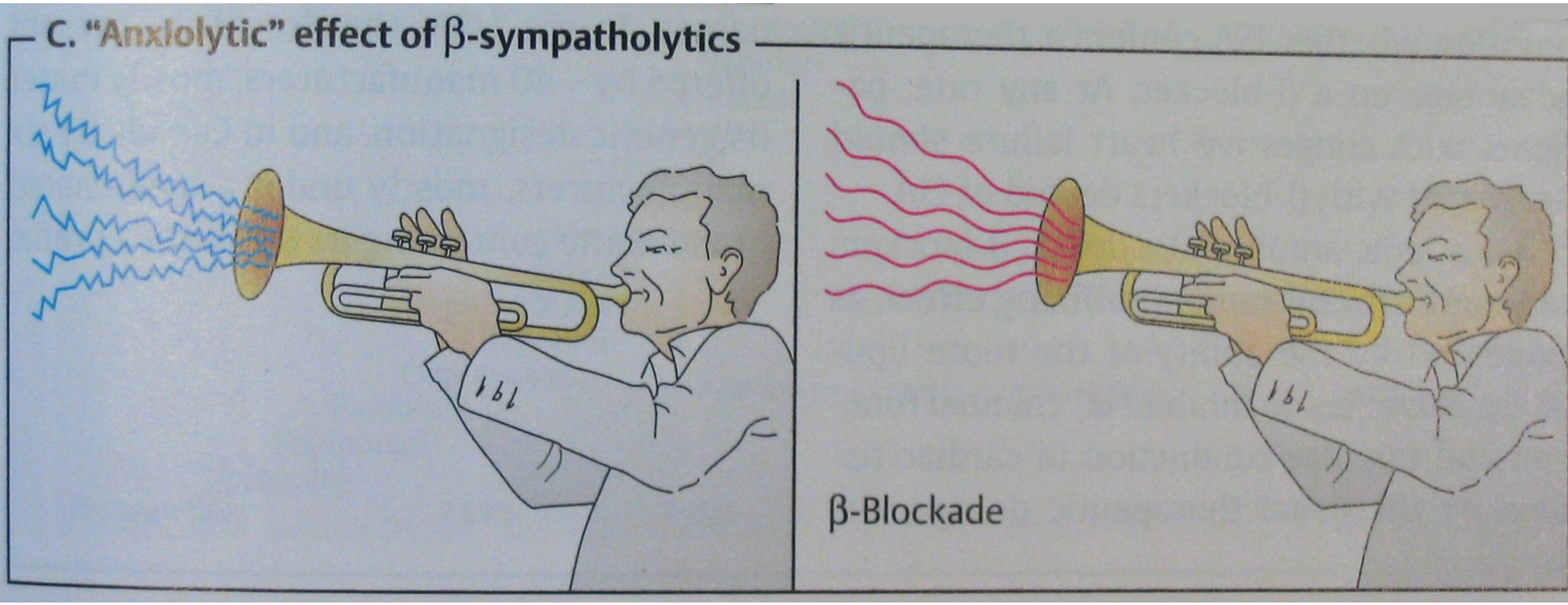
Struktura antagonistov β



Tipi antagonistov β



Anksiolitično delovanje antagonistov β



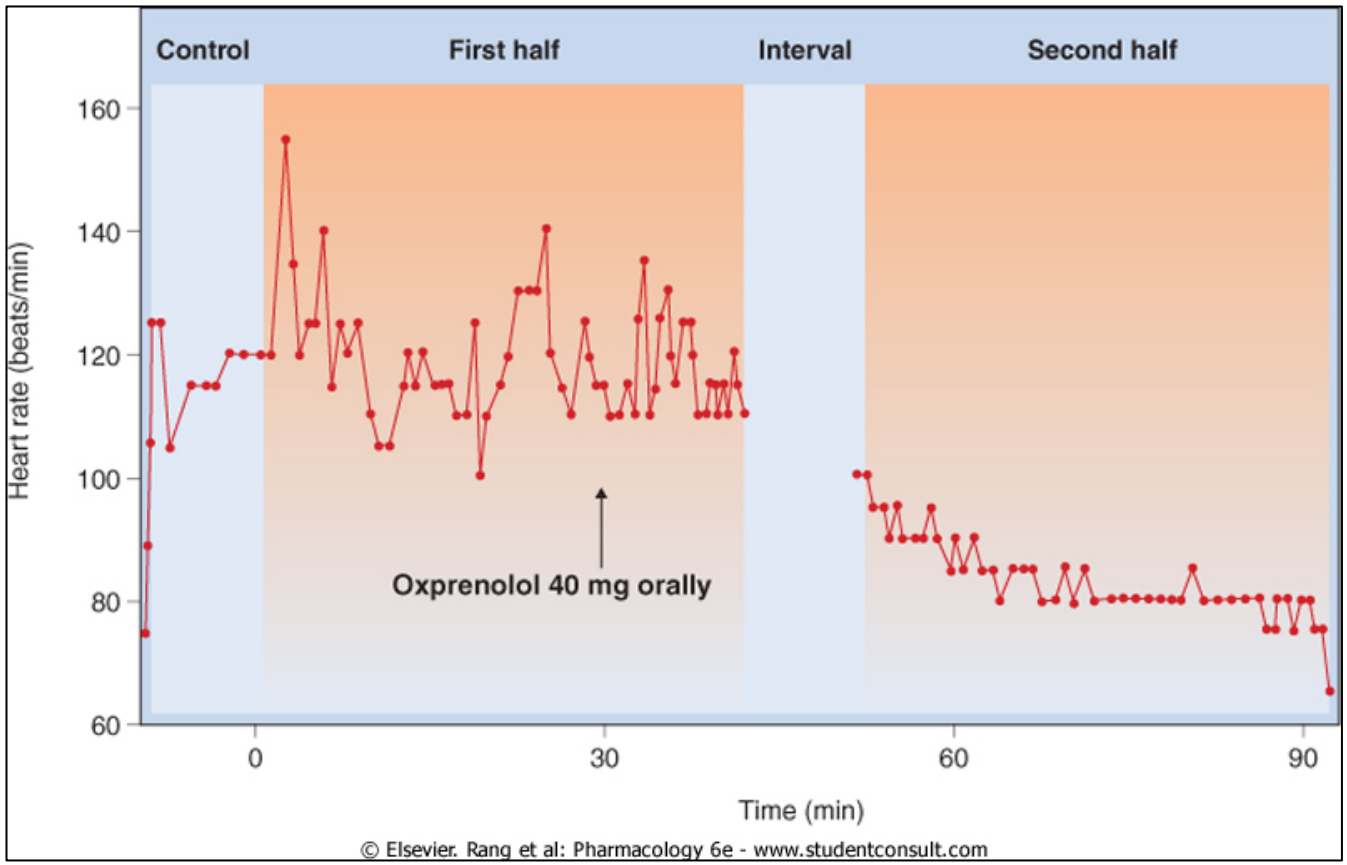
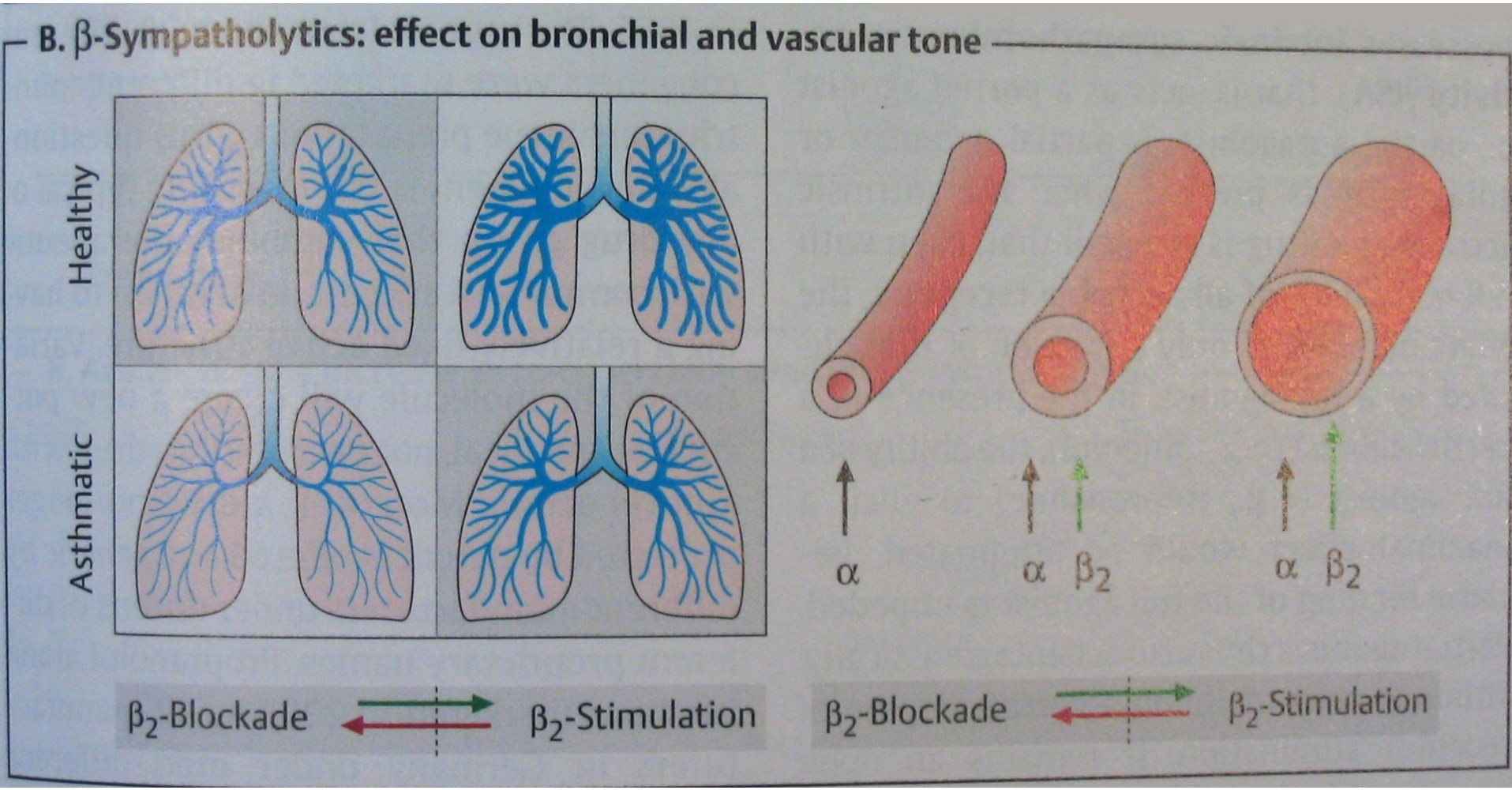
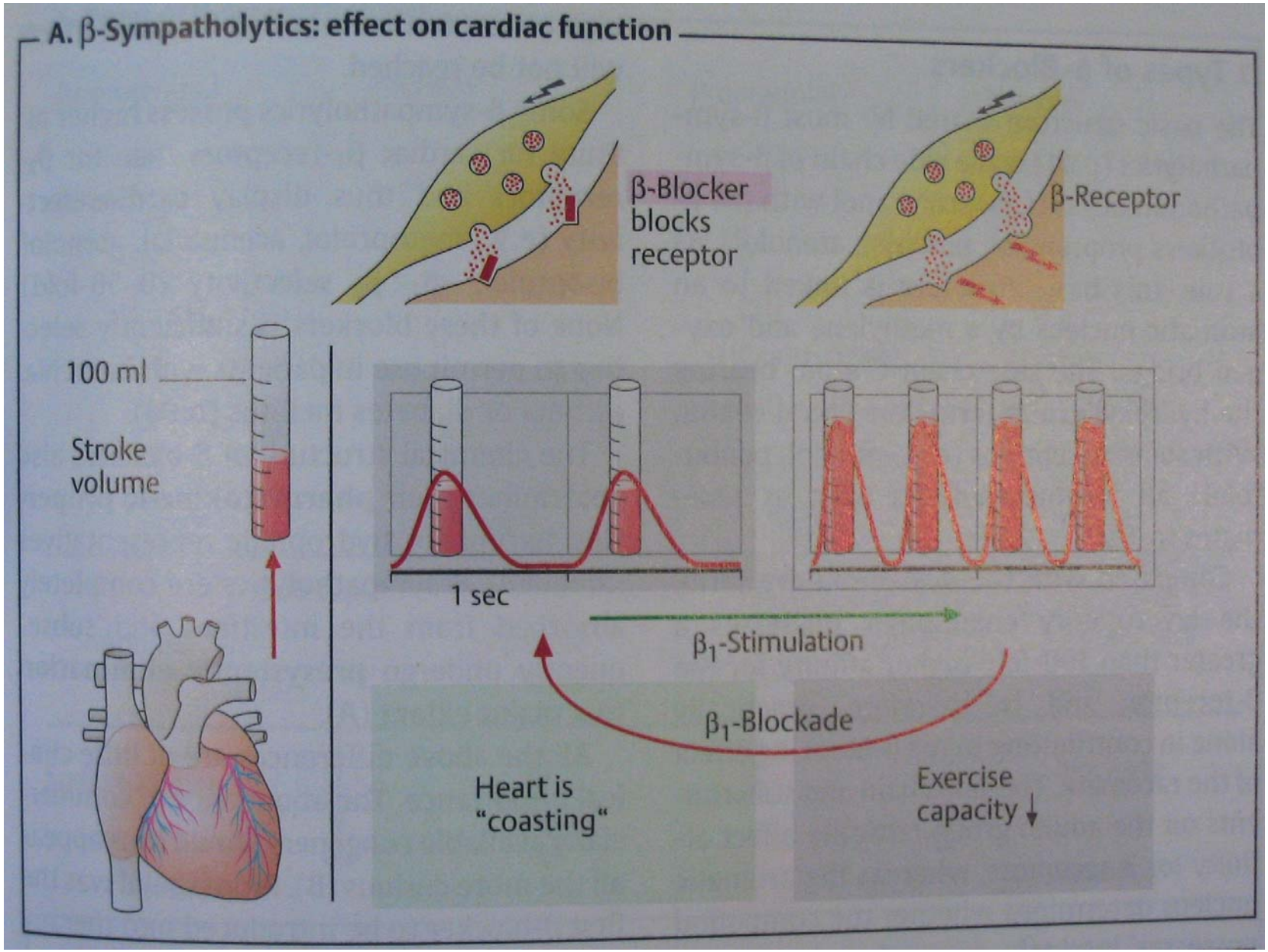


Figure 11-7 Heart rate recorded continuously in a spectator watching a live football match, showing the effect of the β-adrenoceptor antagonist oxprenolol. (From Taylor S H, Meeran M K 1973 In: Burley et al. (eds) New perspectives in beta-blockade. CIBA Laboratories, Horsham.)

Vpliv agonistov in antagonistov β na bronhialni sistem in na žilje



Vpliv blokatorjev β na srce



Pharmacological/Pharmacokinetic Properties of Receptor Blocking Agents I

DRUG	MEMBR. STAB. ACTIVITY	INTRINSIC AGONIST ACTIVITY	LIPID SOLUBILITY	EXTENT OF ABSORPTION (%)	ORAL BIOAVAIL. (%)	PLASMA t½ (hours)	PROTEIN BINDING (%)
Classical non-selective blockers: First generation							
Nadolol	0	0	Low	30	30-50	20-24	30
Penbutolol	0	+	High	100	100	5	80-98
Pindolol	+	+++	Low	>95	100	3-4	40
Propranolol	++	0	High	<90	30	3-5	90
Timolol	0	0	Low to Moderate	90	75	4	<10
β_1-Selective blockers: Second generation							
Acebutolol	+	+	Low	90	20-60	3-4	26
Atenolol	0	0	Low	90	50-60	6-7	6-16
Bisoprolol	0	0	Low	90	80	9-12	30
Esmolol	0	0	Low	NA		0.15	55
Metoprolol	+*	0	Moderate	100	40-50	3-7	12

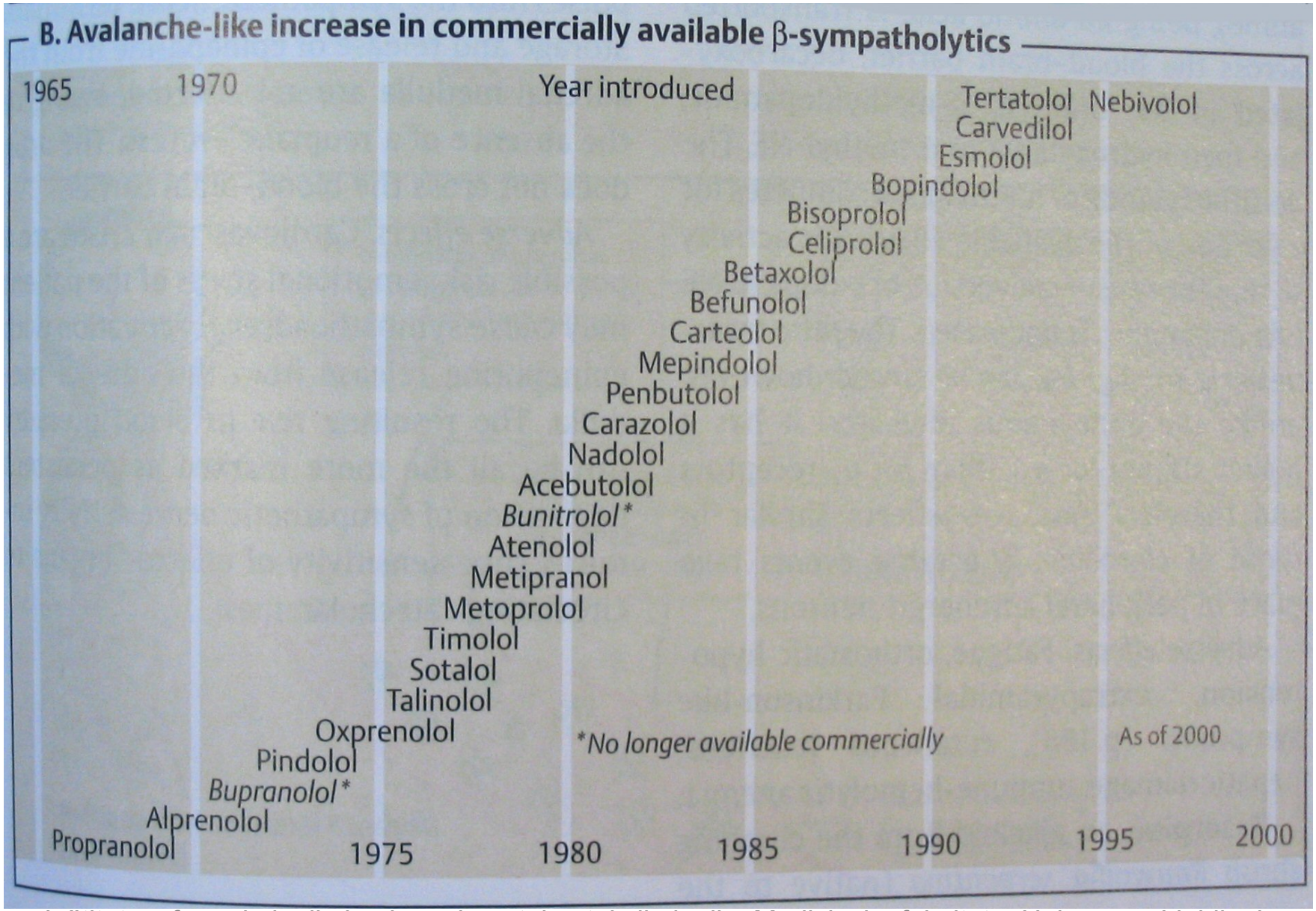
Pharmacological/Pharmacokinetic Properties of Receptor Blocking Agents II

DRUG	MEMBR. STAB. ACT.	INTRINSIC AGONIST ACTIVITY	LIPID SOL.	EXTENT OF ABSORPTION (%)	ORAL BIOAVAIL. (%)	PLASMA t½ (hours)	PROTEIN BINDING (%)
Non-selective blockers with additional actions: Third generation							
Carteolol	0	++	Low	85	85	6	23-30
Carvedilol	++	0	Moderate	>90	~30	7-10	98
Labetalol	+	+	Low	>90	~33	3-4	50
β_1-selective blockers with additional actions: Third generation							
Betaxolol	+	0	Moderate	>90	~80	15	50
Celiprolol	0	+	Low	~74	30-70	5	4-5

Third-Generation β Receptor Antagonists with Additional Cardiovascular Actions: Proposed Mechanisms Contributing to Vasodilation

NITRIC OXIDE PRODUCTION	β_2 - R AGONISM	α_1 - R ANTAGONISM	Ca^{2+} ENTRY BLOCKADE	K^+ CHANNEL OPENING	ANTIOXIDANT ACTIVITY
Celiprolol*	Celiprolol*	Carvedilol	Carvedilol	Tilisolol*	Carvedilol
Nebivolol*	Carteolol	Bucindolol*	Betaxolol		
Carteolol	Bopindolol*	Bevantolol*	Bevantolol*		
Bopindolol*		Nipradilol*			
Nipradilol*		Labetalol			

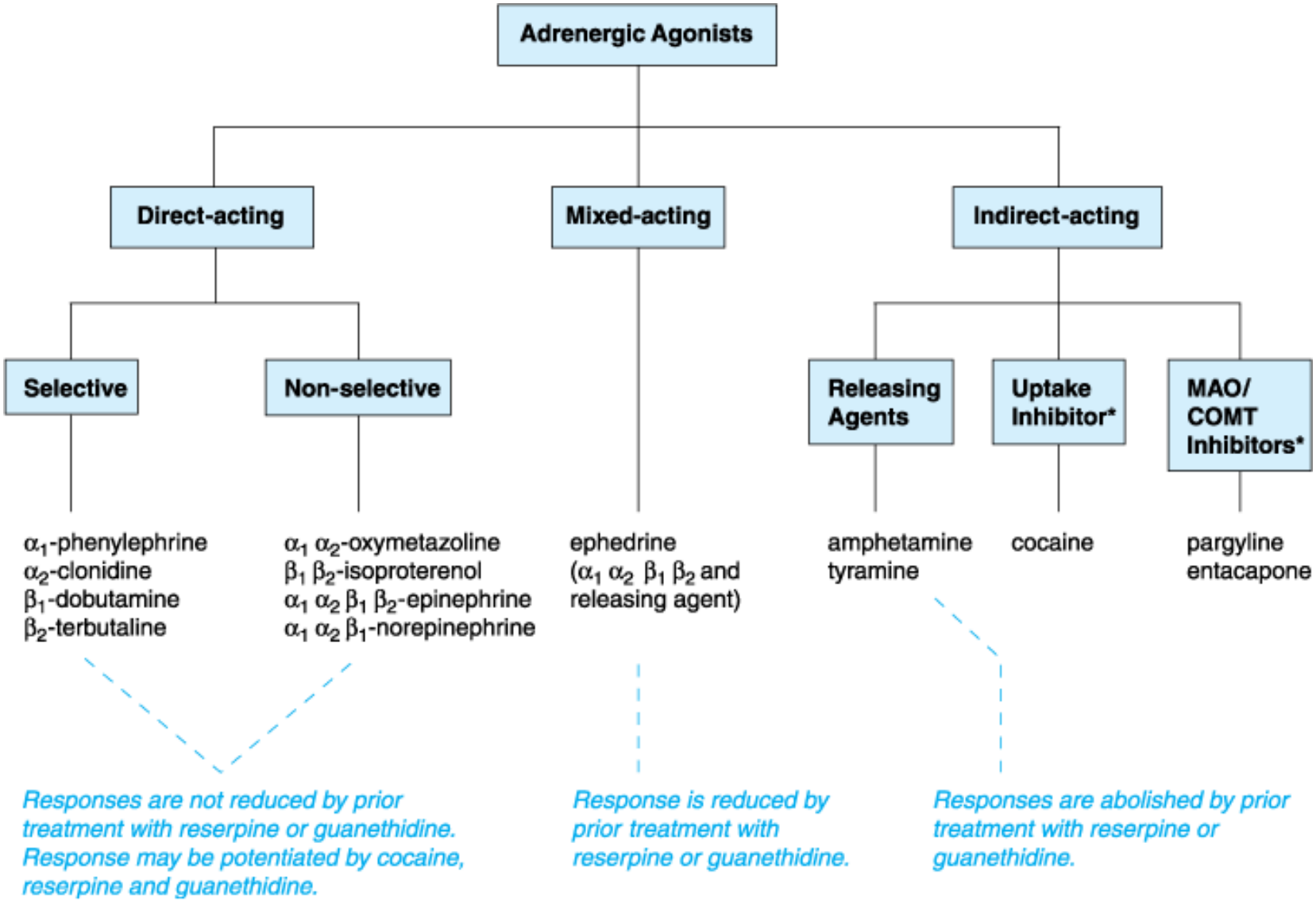
Naraščanje števila blokatorjev β



Indikacije za uporabo antagonistov β

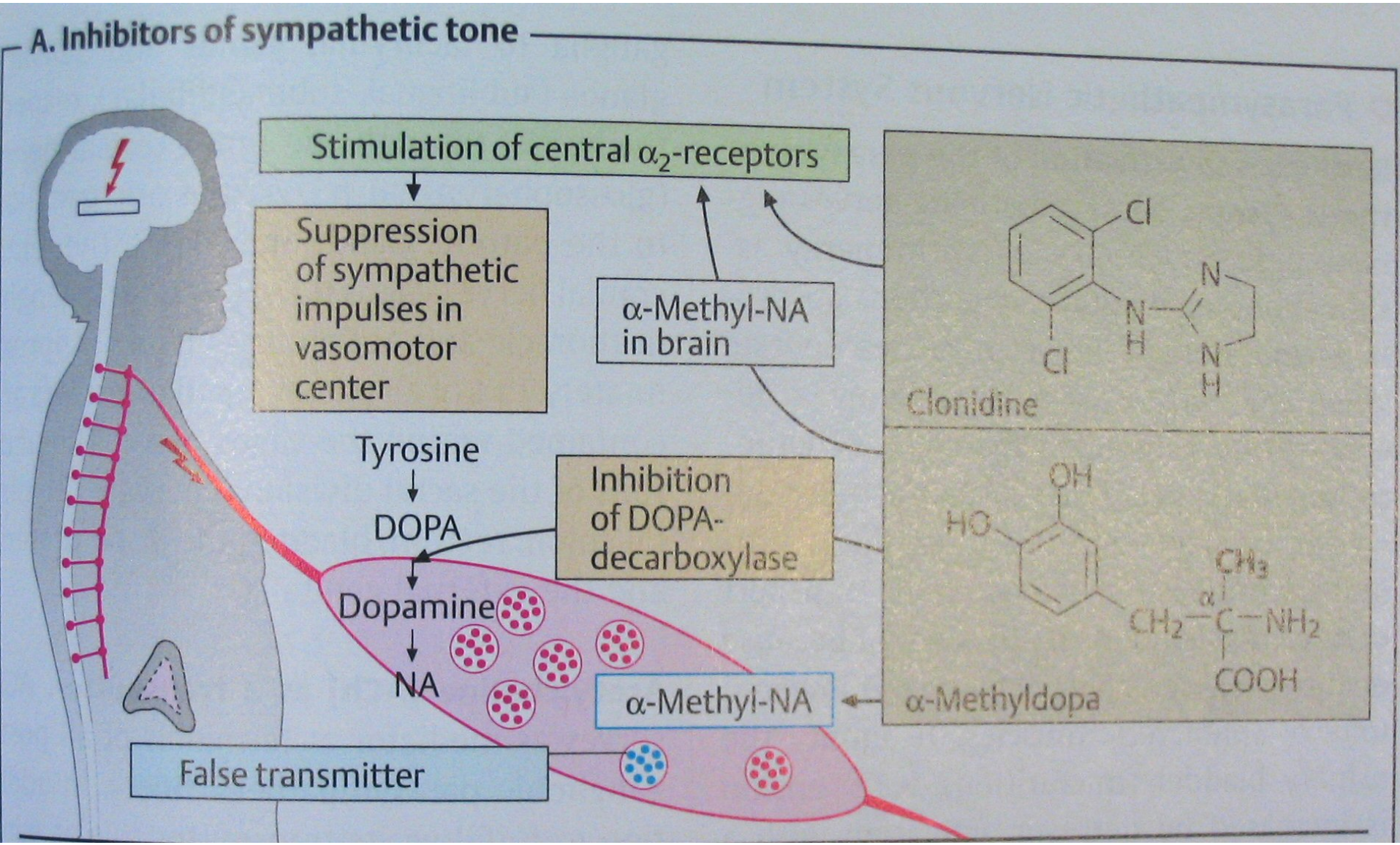
- Kardiovaskularni sistem:
  - angina pectoris
  - miokardni infarkt
  - motnje srčnega ritma (disritmije)
  - pešanje srca
  - arterijska hipertenzija
- Druge indikacije:
  - glavkom
  - tireotoksikoza
  - anksioznost
  - profilaksa migrene
  - benigni esencialni tremor

Pregled adrenergičnih agonistov

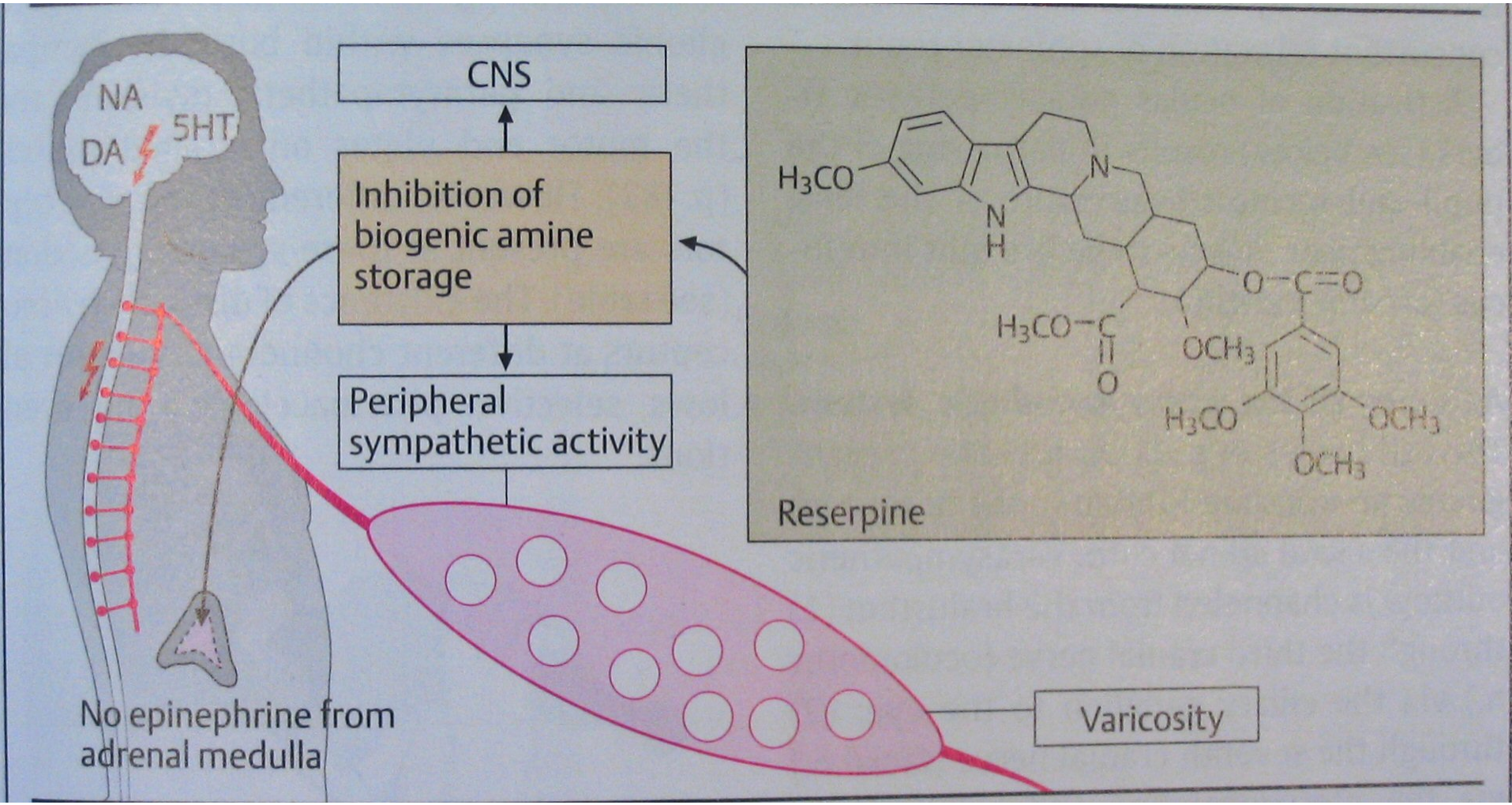


Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Inhibicija tonusa simpatika I



Inhibicija tonusa simpatika II



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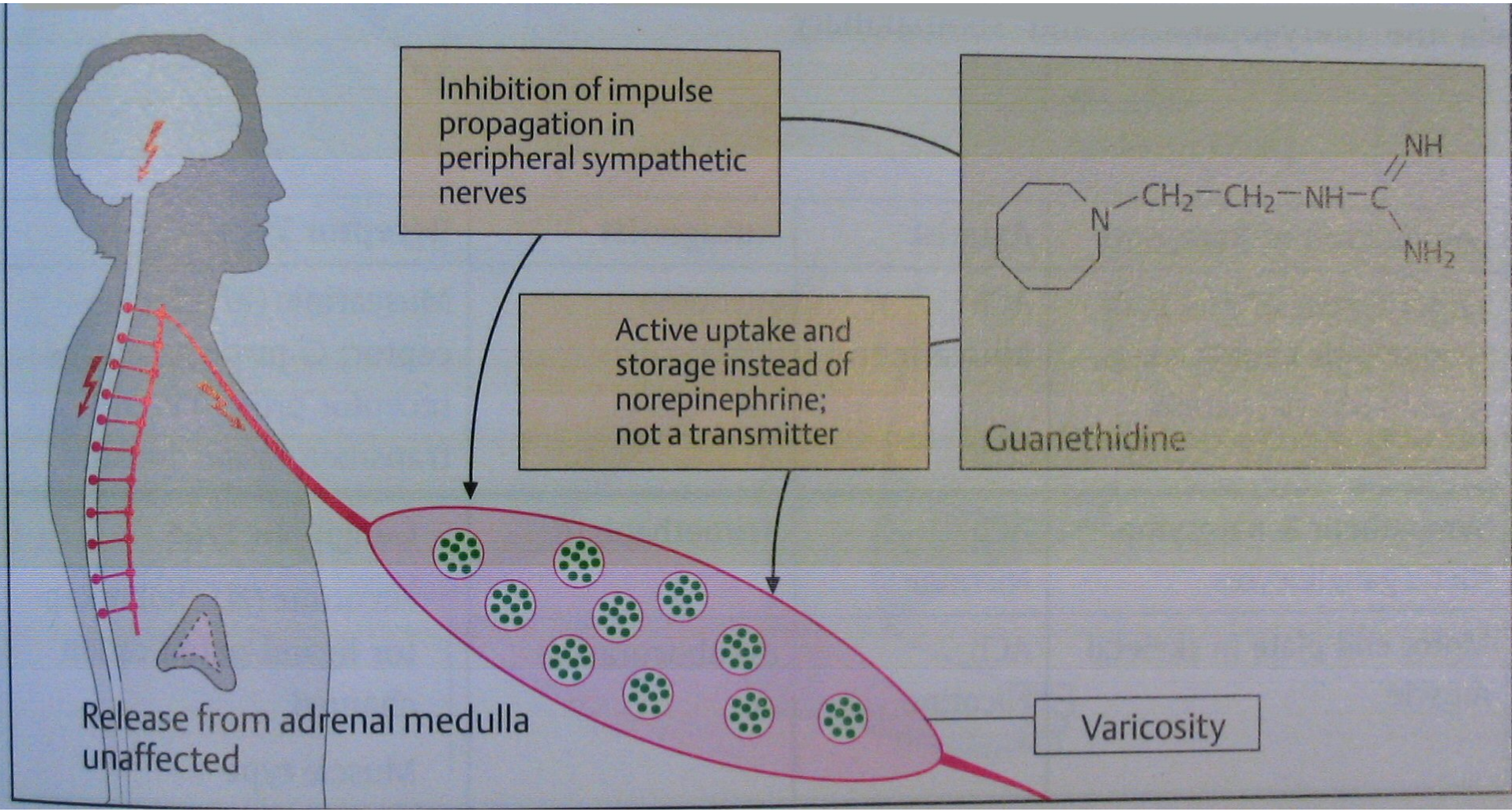
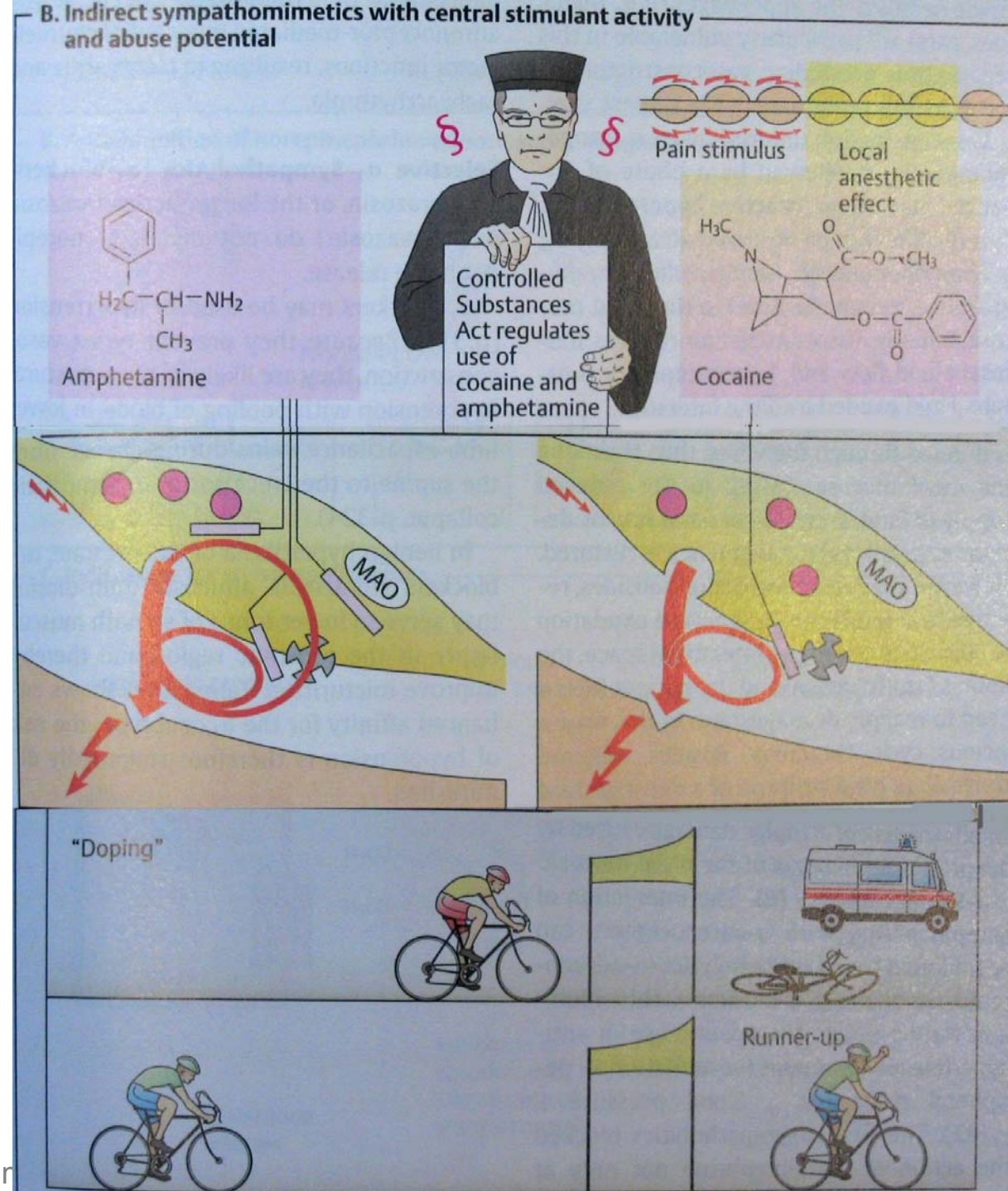


Delovanje indirektnih simpatikomimetikov



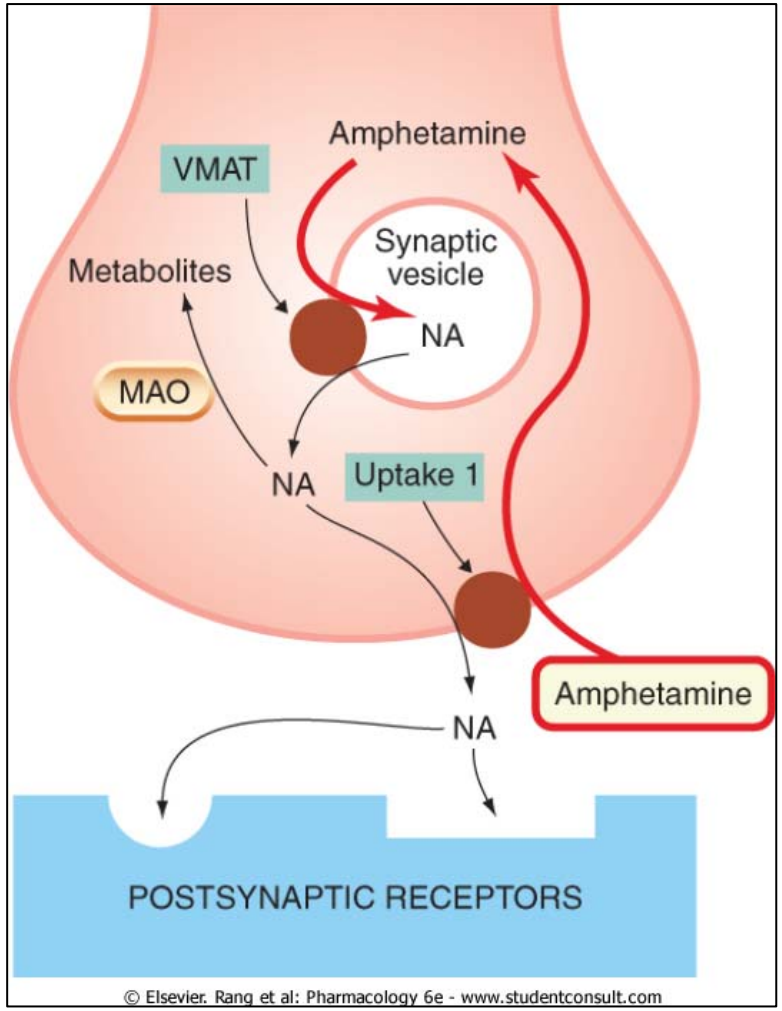
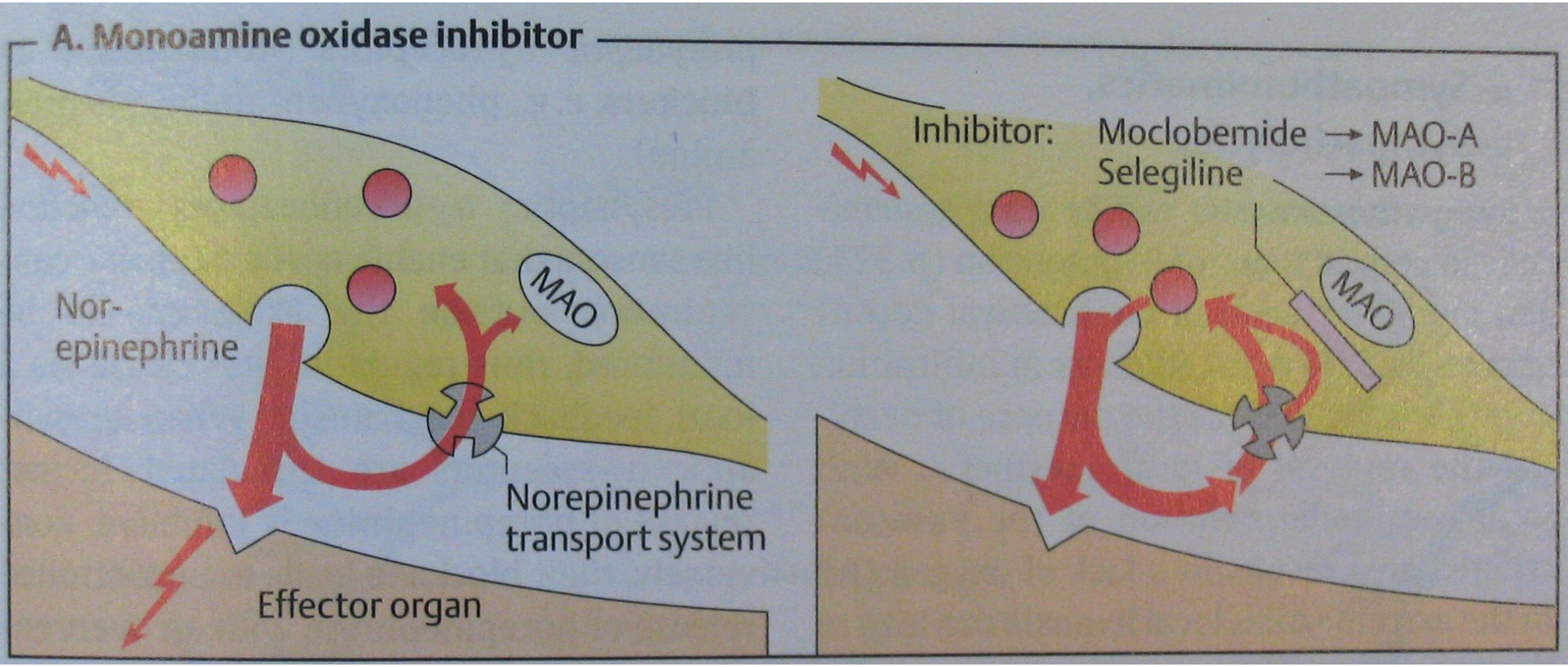


Figure 11-8 The mode of action of amphetamine, an indirectly acting sympathomimetic amine. Amphetamine enters the nerve terminal via the noradrenaline (NA) transporter (uptake 1) and enters synaptic vesicles via the vesicular monoamine transporter (VMAT), in exchange for NA, which accumulates in the cytosol. Some of the NA is degraded by monoamine oxidase (MAO) within the nerve terminal and some escapes, in exchange for amphetamine via the noradrenaline transporter, to act on postsynaptic receptors. Amphetamine also reduces NA reuptake via the transporter, so enhancing the action of the released NA.

Delovanje inhibitorjev MAO



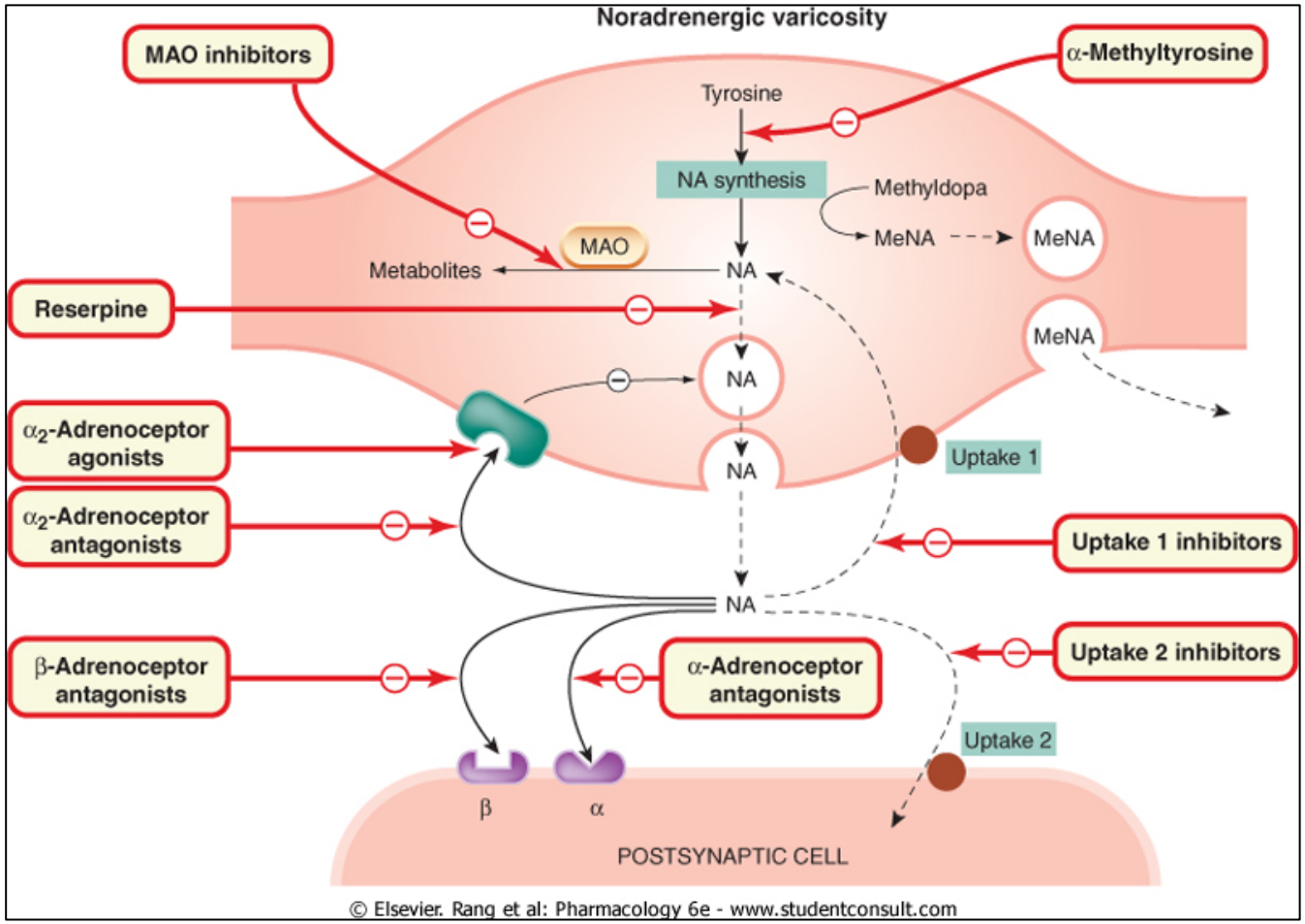


Figure 11-9 Generalised diagram of a noradrenergic nerve terminal, showing sites of drug action. MAO, monoamine oxidase; MeNA, methylnoradrenaline; NA, noradrenaline.