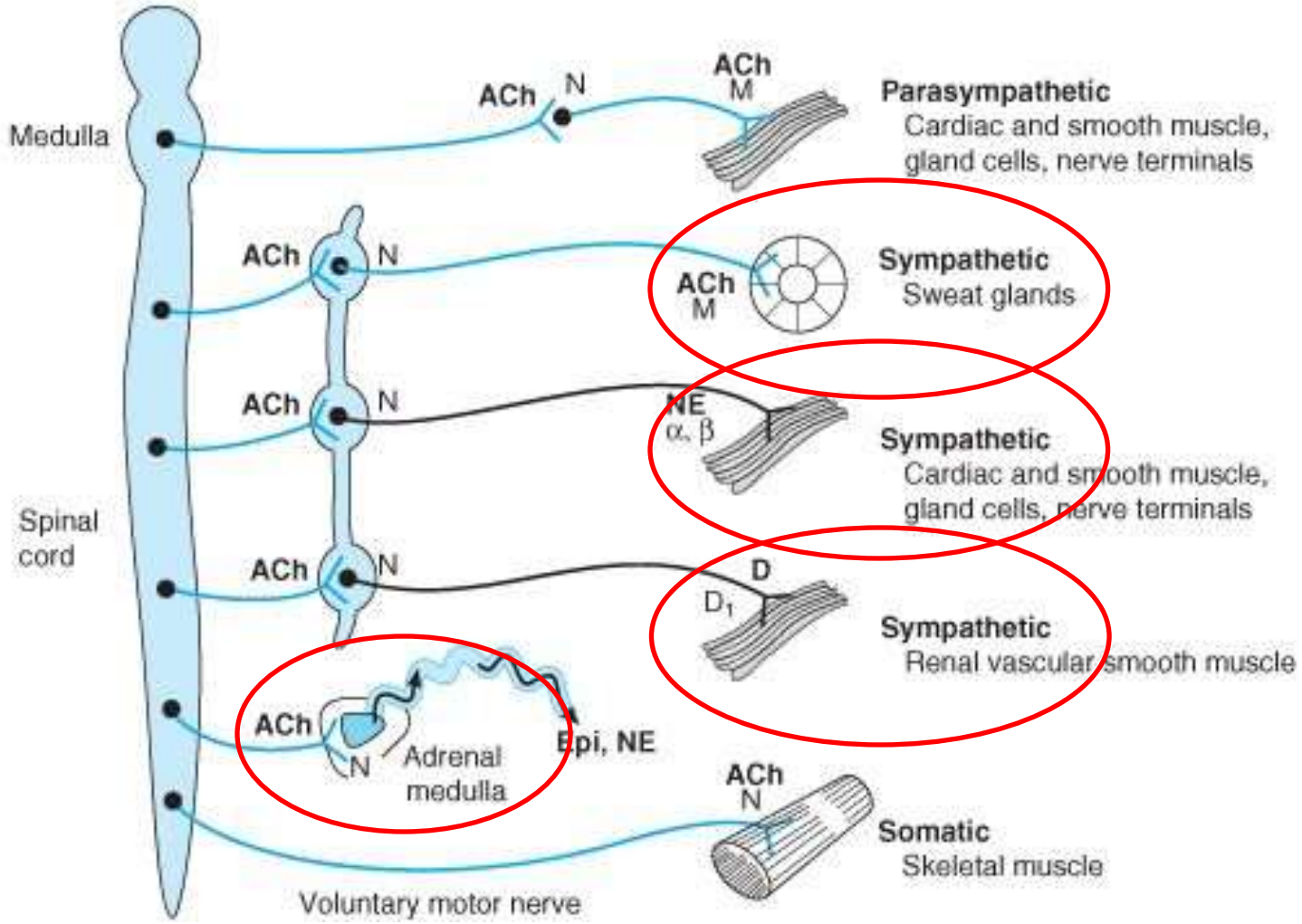
Sympathetic nervous system

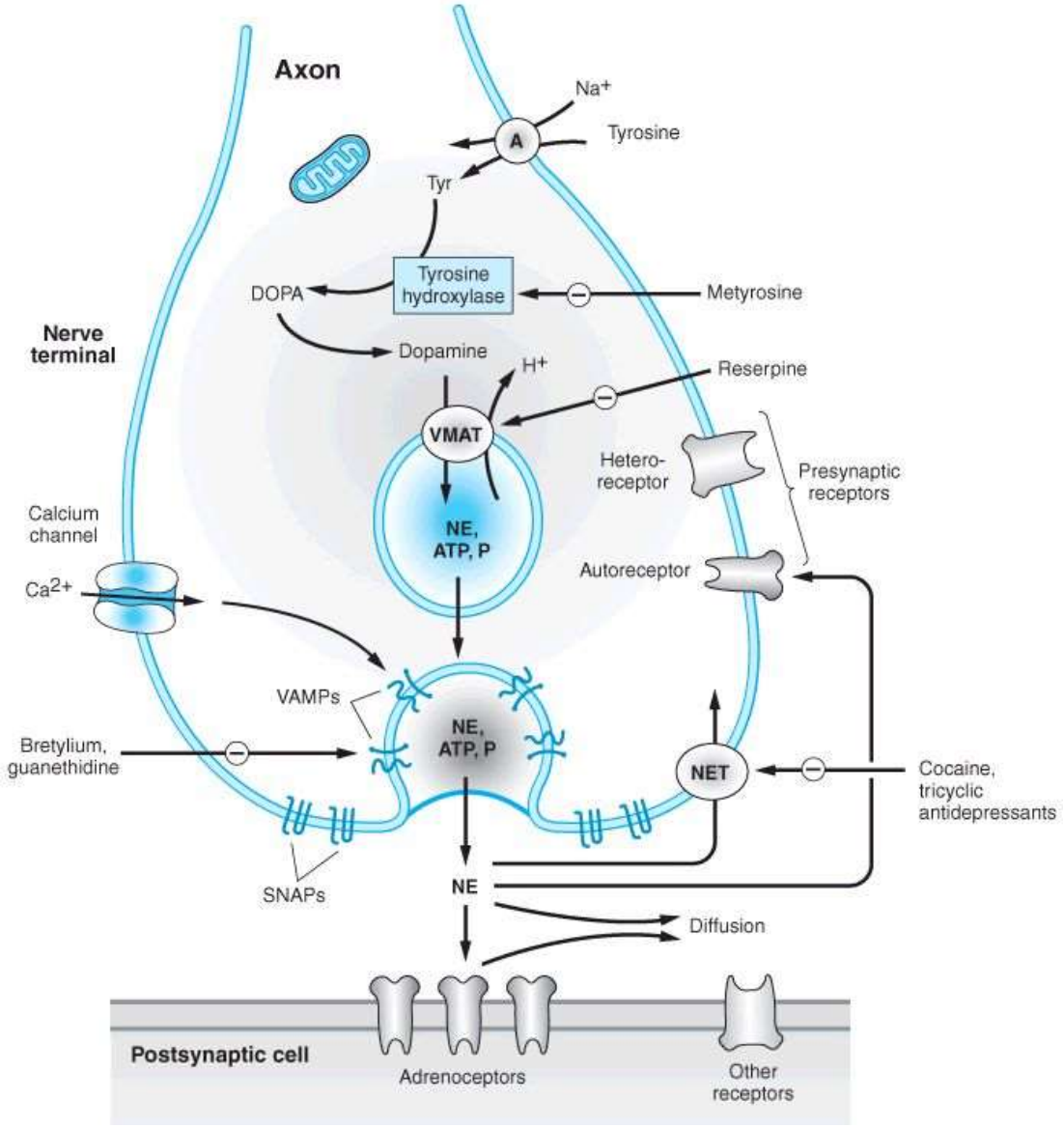
- function e.g.
  - blood pressure regulation
  - other
- anatomy
  - postganglionic fibers: NAdr – adrenoceptor
  - but in adrenal medulla
    - preganglionic fibers – ACh – Adr

Anatomic aspects of the ANS

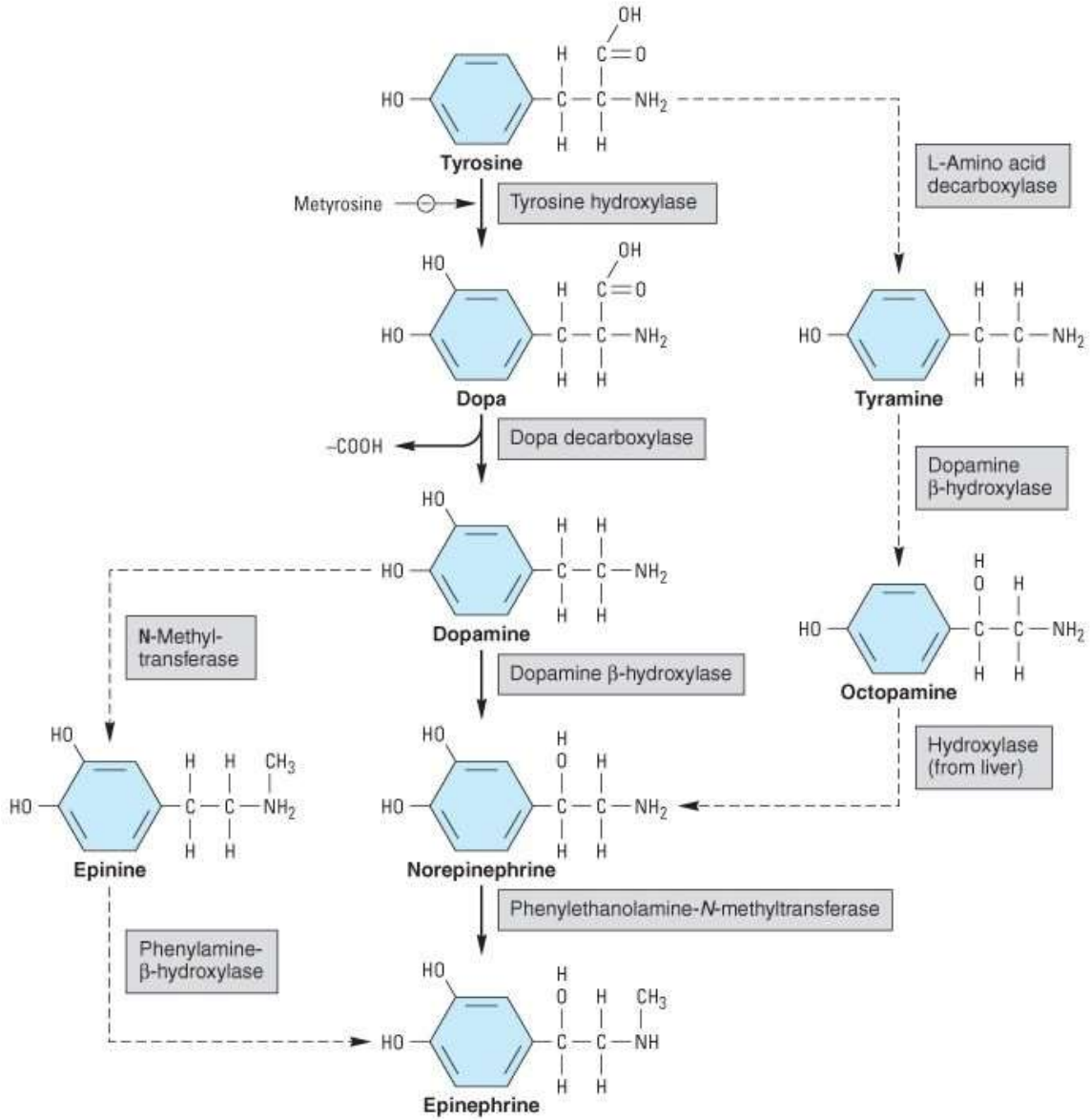


+ ENS = enteric nervous system

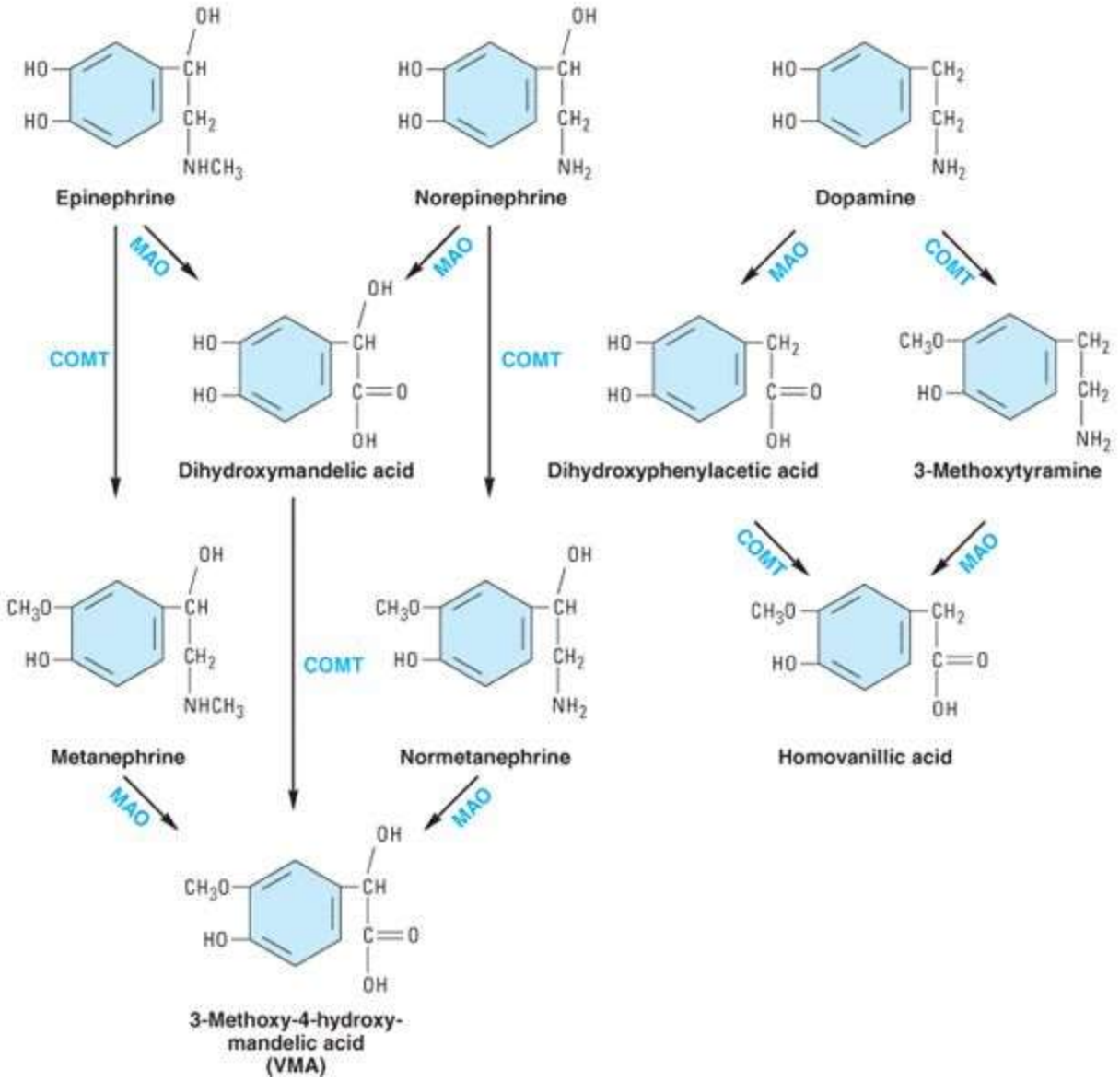
Adrenergic transmission



Biosynthesis of catecholamines



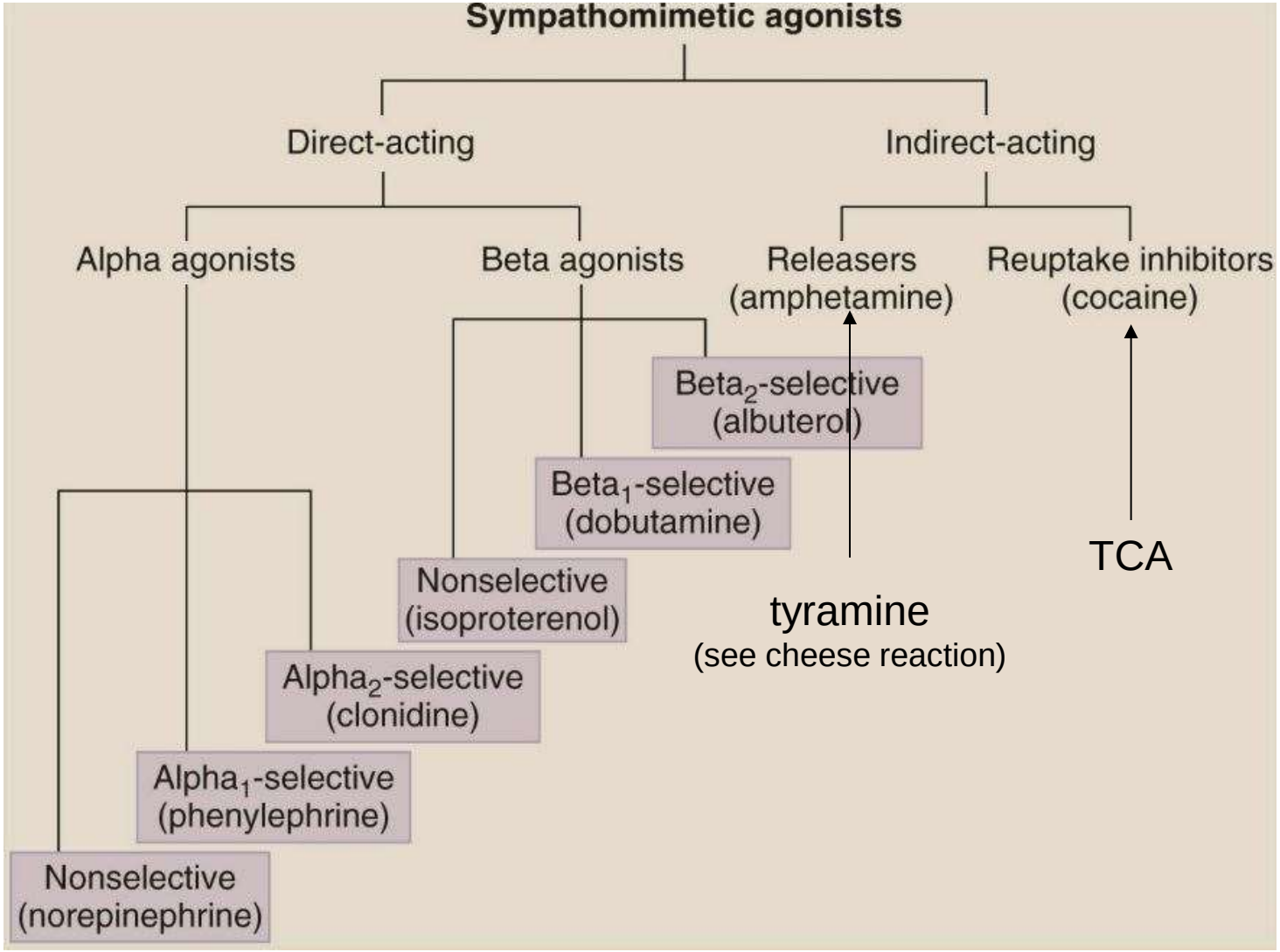
Metabolism of catecholamines



Major effects mediated by adrenoceptors

Type	Tissue	Actions
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erects hair
	Prostate	Contraction
	Heart	Increases force of contraction
α_2	Postsynaptic CNS neurons	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Some vascular smooth muscle	Contraction
	Fat cells	Inhibits lipolysis
β_1	Heart, juxtaglomerular cells	Increases force and rate of contraction; increases renin release
β_2	Respiratory, uterine, and vascular smooth muscle	Promotes smooth muscle relaxation
	Skeletal muscle	Promotes potassium uptake
	Human liver	Activates glycogenolysis
β_3	Fat cells	Activates lipolysis
D_1	Smooth muscle	Dilates renal blood vessels
D_2	Nerve endings	Modulates transmitter release

Classification of sympathomimetics

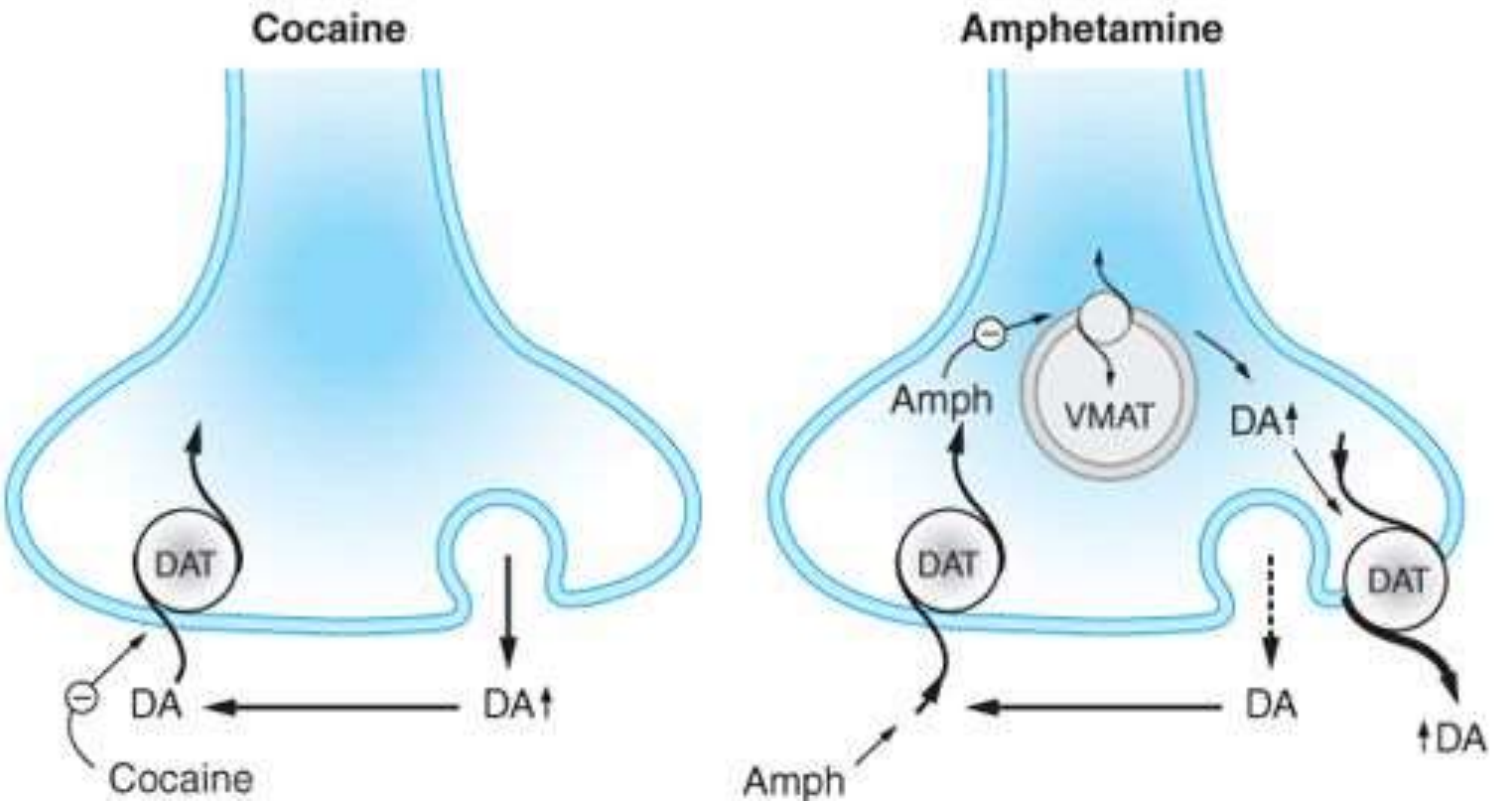


direct AND indirect: ephedrine

Indirect sympathomimetic effect

- displace stored catecholamines
  - e.g. tyramine, amphetamine
- ↓ clearance of released norepinephrine
  - inhibit reuptake
    - cocaine
    - tricyclic antidepressants
  - prevent enzymatic metabolism
    - monoamine oxidase inhibitors
    - catechol-O-methyltransferase inhibitors

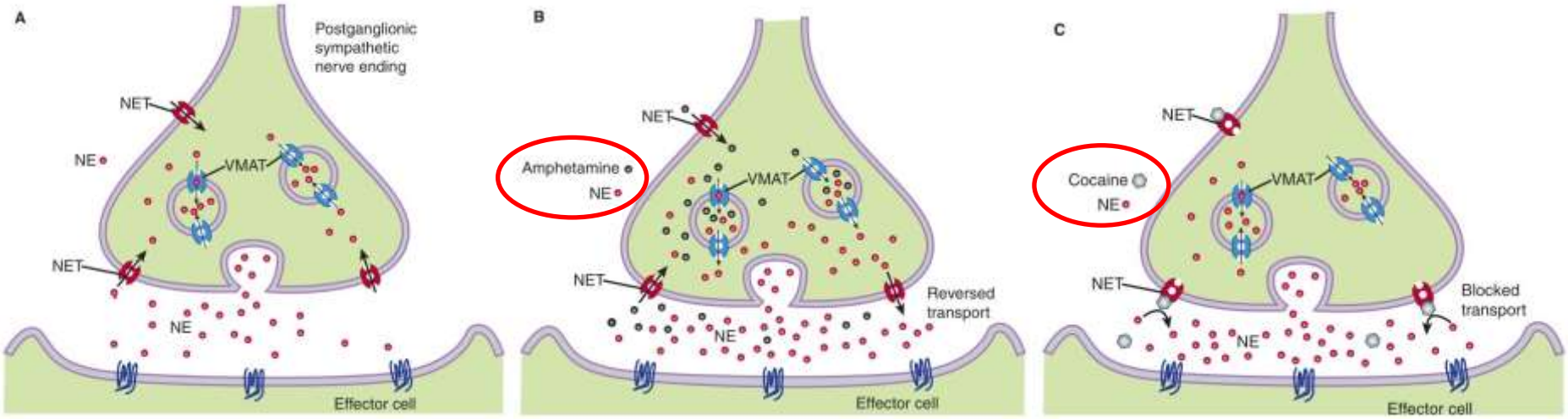
Mechanism of action of cocaine and amphetamine



calcium-independent, nonvesicular

DAT: dopamine transporter
VMAT: vesicular monoamine transporter

amphetamine: releaser / cocaine: uptake blocker



calcium-independent, nonvesicular

NET: norepinephrine transporter
VMAT: vesicular monoamine transporter

Effects are determined by

- direct
  - relative affinity for adrenoceptor subtypes
    - see next slide
  - relative expression of these receptor subtypes
    - e.g. β1 vs. β2
- indirect
  - sympathetic activity
  - status of norepinephrine stores and release
    - e.g. MAO block – antidepressants, amphetamine
- both
  - route of administration
    - e.g. see oral epinephrine or nasal ephedrine

Relative selectivity of adrenoceptor agonists

	Relative Receptor Affinities
Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine[1]	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

Cardiovascular responses to sympathomimetic amines

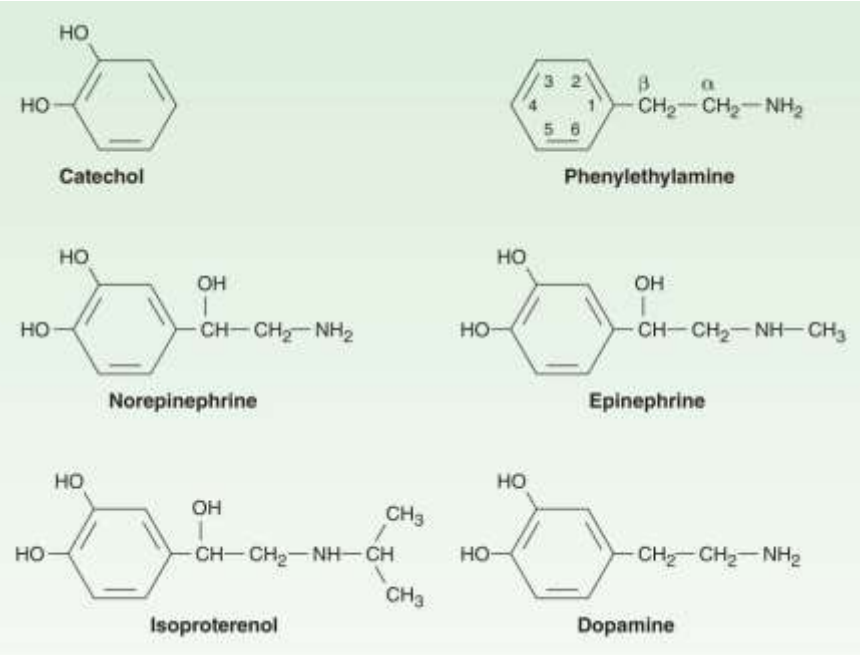
	Phenylephrine	Epinephrine	Isoproterenol
Vascular resistance (tone)			
Cutaneous, mucous membranes (α)	↑↑	↑↑	0
Skeletal muscle (β_2, α)	↑	↓ or ↑	↓↓
Renal (α, D_1)	↑	↑	↓
Splanchnic (α, β)	↑↑	↓ or ↑[1]	↓
Total peripheral resistance	↑↑↑	↓ or ↑[1]	↓↓
Venous tone (α, β)	↑	↑	↓
Cardiac			
Contractility (β_1)	0 or ↑	↑↑↑	↑↑↑
Heart rate (predominantly β_1)	↓↓ (vagal reflex)	↑ or ↓	↑↑↑
Stroke volume	0, ↓, ↑	↑	↑
Cardiac output	↓	↑	↑↑
Blood pressure			
Mean	↑↑	↑	↓
Diastolic	↑↑	↓ or ↑[1]	↓↓
Systolic	↑↑	↑↑	0 or ↓
Pulse pressure	0	↑↑	↑↑

[1]Small doses decrease, large doses increase.

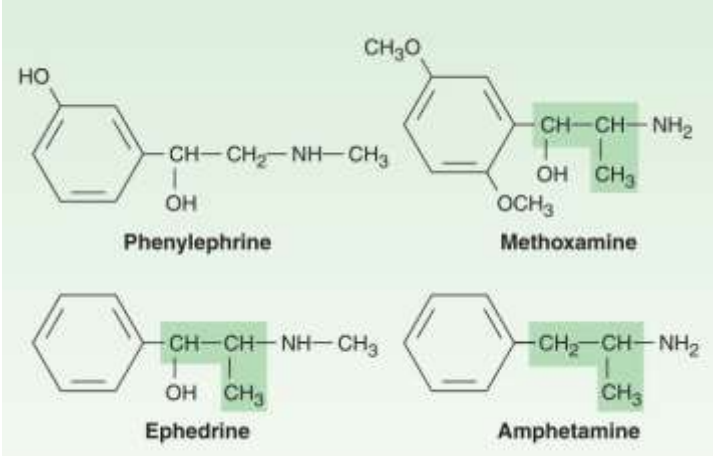
↑ = increase; ↓ = decrease; 0 = no change.

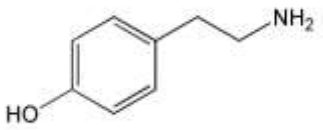
Chemical structures

Catecholamines



Non-catecholamines





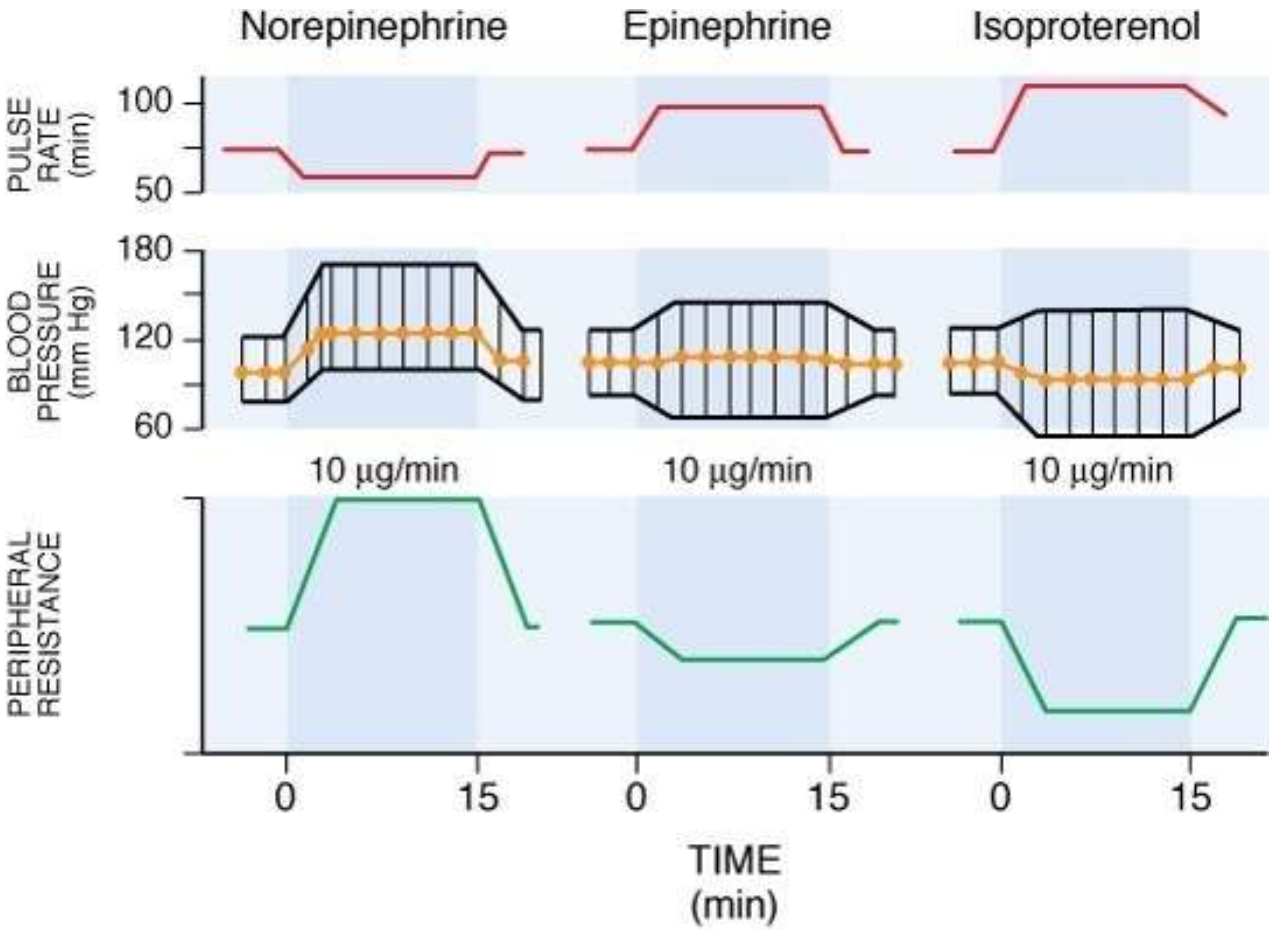
tyramine

affinity for α and β receptors
intrinsic ability to activate the receptors
pharmacokinetic properties (e.g. bioavailability)

Structure-activity relationships

- benzene ring → catecholamines
  - PD: higher potency
  - PK: COMT inactivation (↓ oral bioavailability) / CNS
- amino group
  - PD: bulky alkyl → β
- α carbon
  - PK: resistance to MAO – longer duration
  - PD: displace catecholamines
- β carbon
  - PD: -OH – direct agonist (except dopamine)
  - storage in vesicles

Effects of catecholamines on blood pressure



$\alpha_1=\alpha_2$; $\beta_1>>\beta_2$	$\alpha_1=\alpha_2$; $\beta_1=\beta_2$	$\beta_1=\beta_2$ >>>> α

Dopamine

- infusion
  - low rate: renal insuff. - D_1
  - middle rate: heart failure - β_1
  - high rate: shock - α

- **fenoldopam**
  - agonist for peripheral D_1 receptors
  - calibrated infusion pump
  - for short term control of severe hypertension

Dobutamine

- selective β_1 receptor agonist
  - but racemic mixture
- for short-term iv. treatment of cardiac decompensation
- tachycardia is less frequent
- tolerance development

α_2-selective agonists

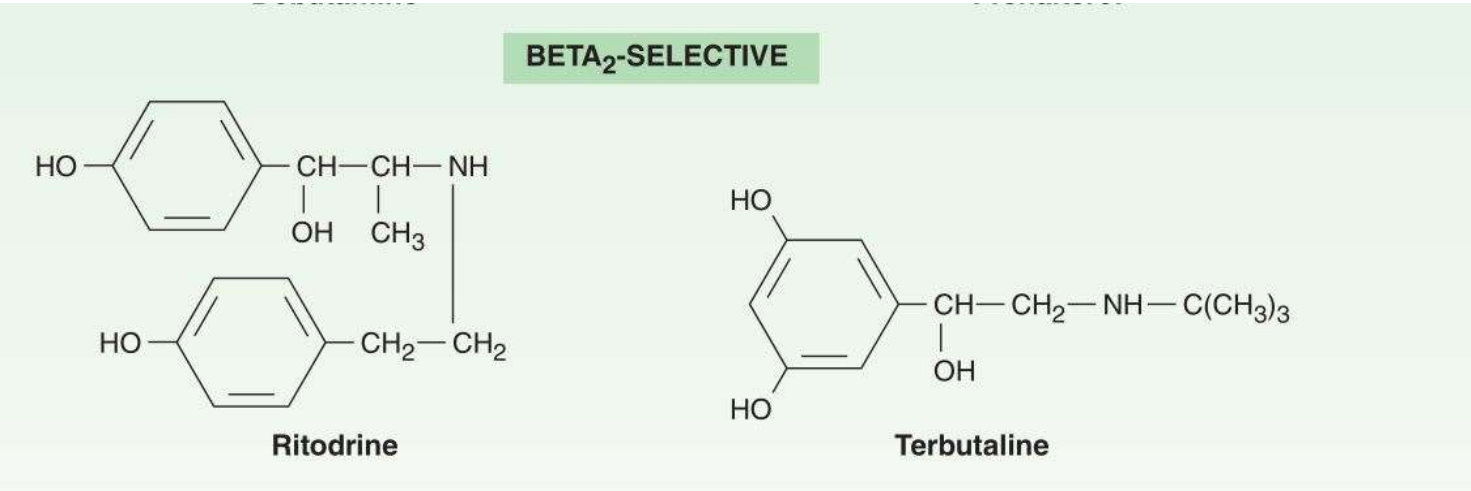
- clonidine, methyldopa, guanfacine
- decreased blood pressure – central
  - used in hypertension
- sedation
  - imidazoline receptor agonists – moxonidine
  - dexmedetomidine
- central spasmolytic
  - tizanidine

Nasal decongestans

- ephedrine, xylometazoline, oxymetazoline
- short term topical administration
  - rebound
- phenylephrine, pseudoephedrine
  - in oral preparations for nasal congestion
- adverse effects
  - CNS stimulation
  - hemorrhagic stroke?

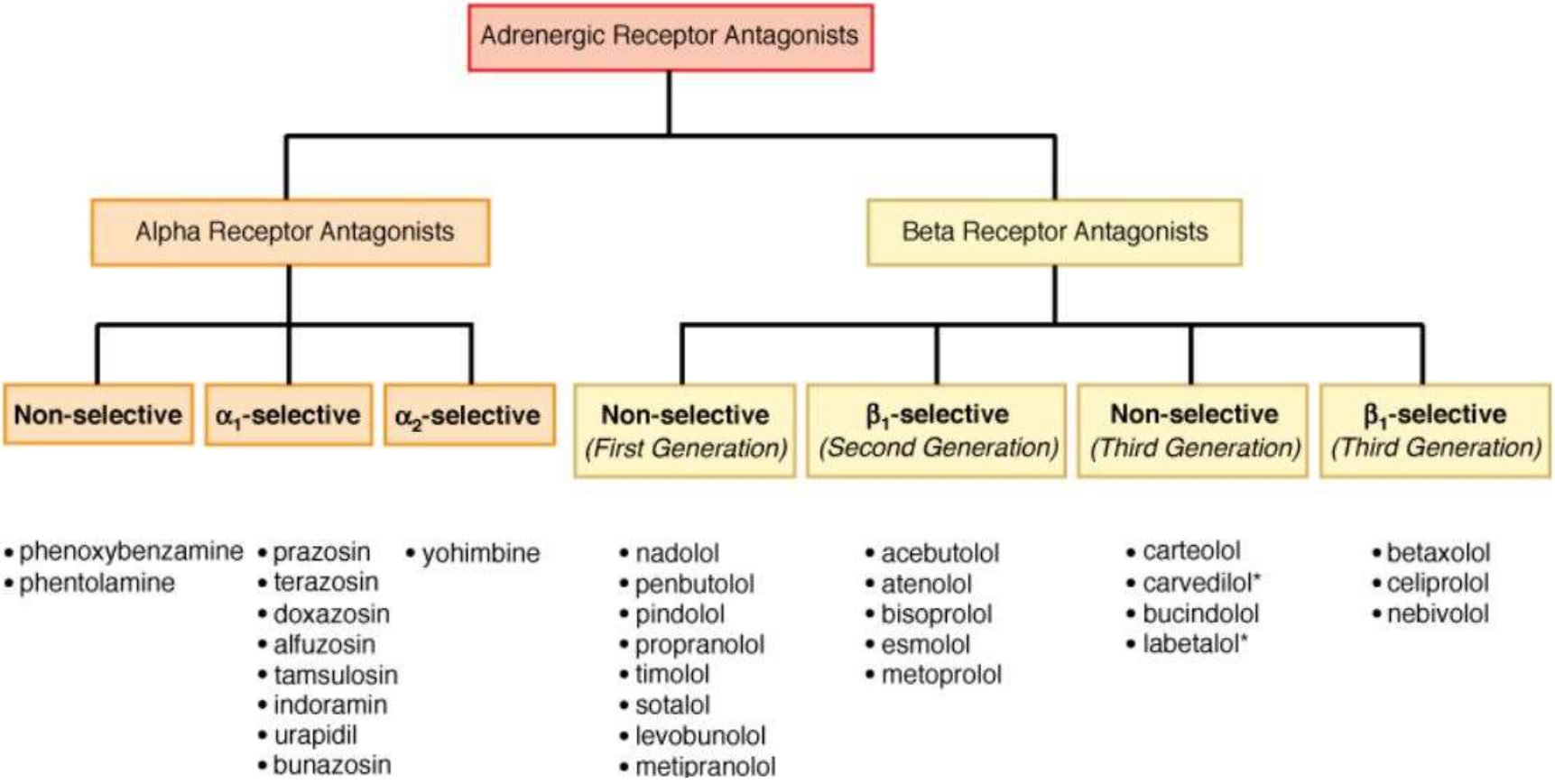
Selective β_2 agonists

- effects / use
  - bronchodilation / bronchial asthma
  - uterus relax / preterm labor



short term / long term (salmeterol / formoterol)

Classification



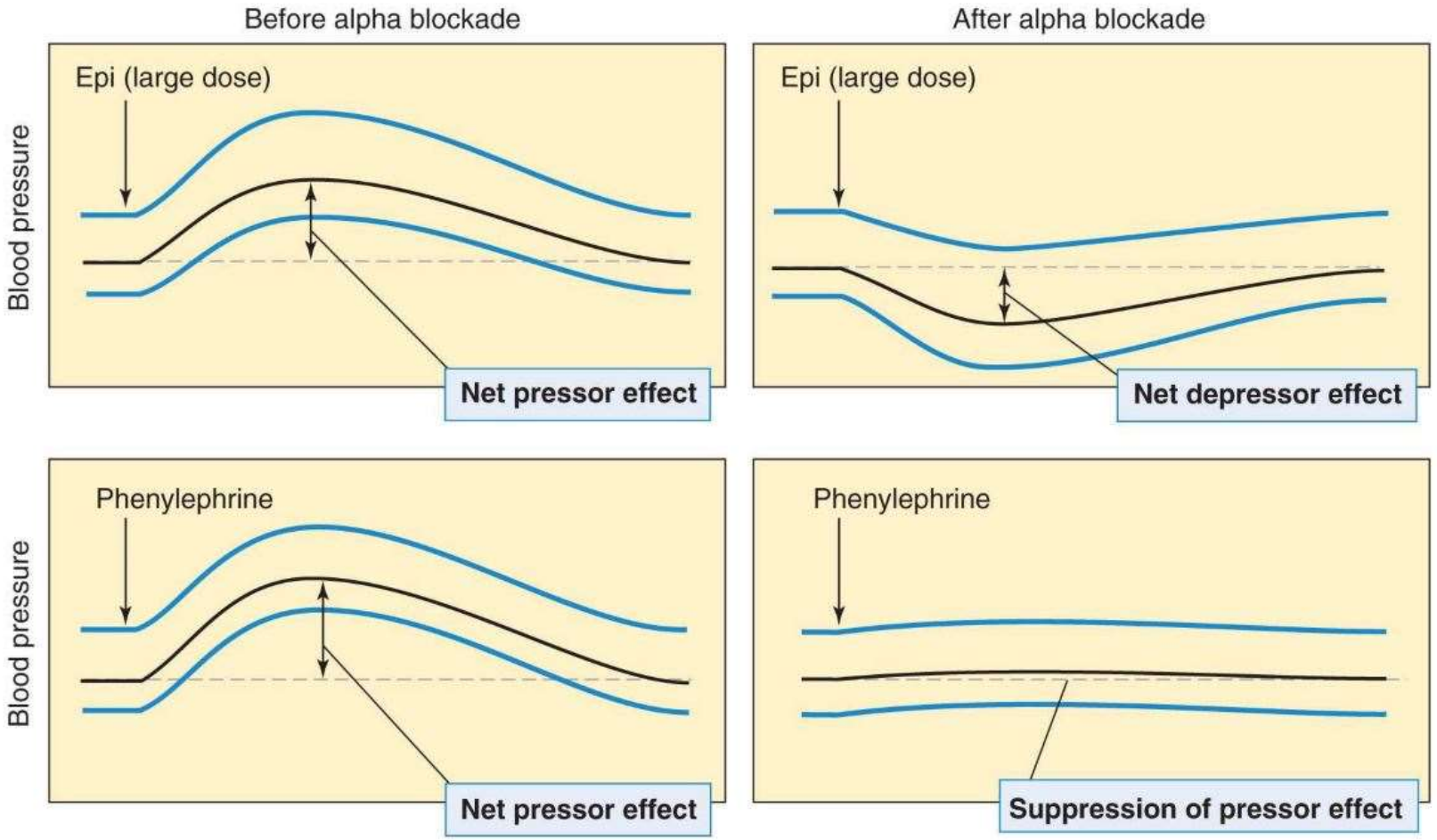
Relative selectivity of adrenoceptor antagonists

	Receptor Affinity
Alpha antagonists	
Prazosin, terazosin, doxazosin	$\alpha_1 >>>> \alpha_2$
Phenoxybenzamine	$\alpha_1 > \alpha_2$
Phentolamine	$\alpha_1 = \alpha_2$
Yohimbine, tolazoline	$\alpha_2 >> \alpha_1$
Mixed antagonists	
Labetalol, carvedilol	$\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$
Beta antagonists	
Metoprolol, acebutolol, alprenolol, atenolol, betaxolol, celiprolol, esmolol, nebivolol	$\beta_1 >>> \beta_2$
Propranolol, carteolol, penbutolol, pindolol, timolol	$\beta_1 = \beta_2$
Butoxamine	$\beta_2 >>> \beta_1$

α receptor blockers

- non-selective
  - phenoxybenzamine – irreversible
  - pentolamine – reversible
- effects
  - vasodilation
- adverse effects
  - orthostatic hypotension
  - baroreceptor reflex mediated tachycardia (block α_2)
- clinical use
  - pheochromocytoma

Epinephrine reversal



α receptor blockers

- selective
  - prazosin, doxazosin, terazosine, tamsulosin
- clinical use
  - hypertension
  - BPH
- adverse effects
  - similar to non-selective
  - less tachycardia

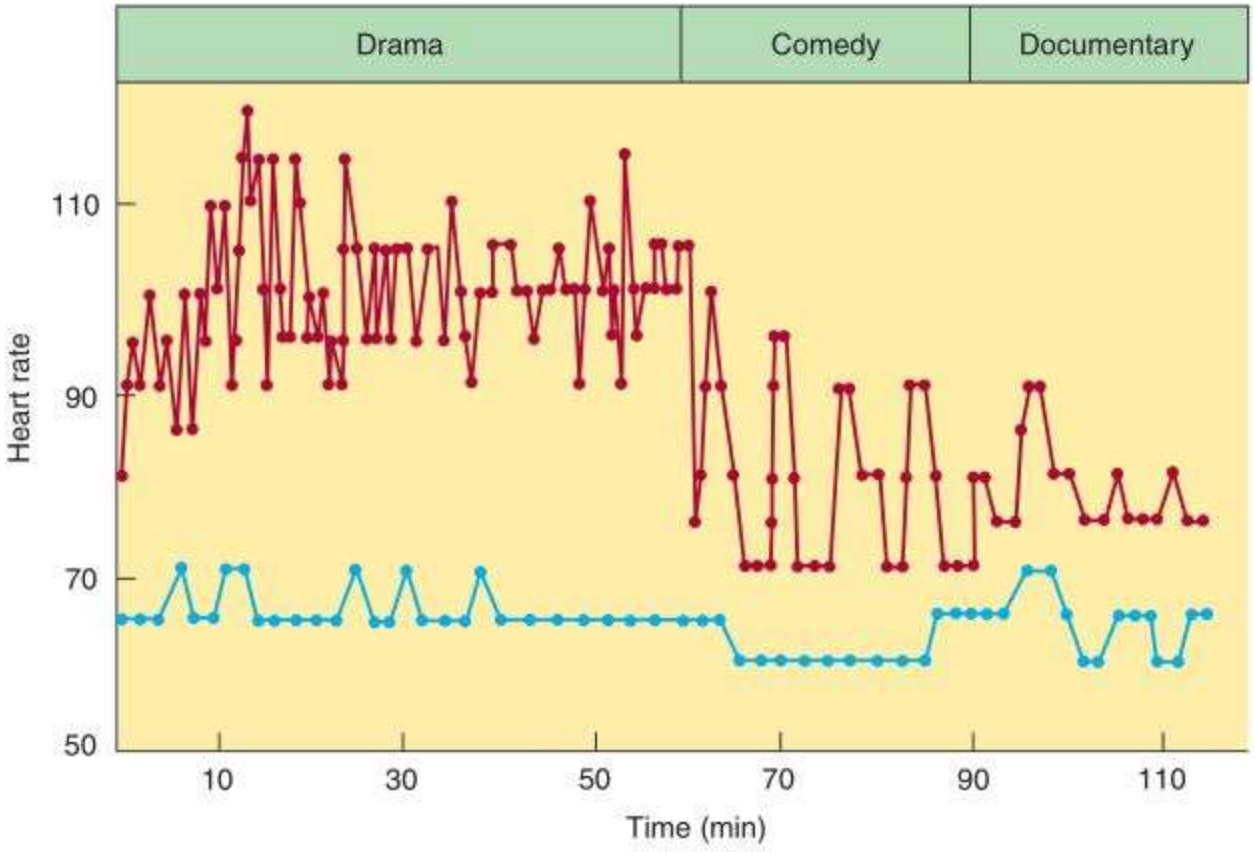
Properties of some β-receptor blocking drugs

property	example drugs
beta1 selectivity	metoprolol, nebivolol, atenolol
ISA	pindolol, acebutolol
local anesthetic action	metoprolol, pindolol, acebutolol
lipid solubility	propranolol
alpha blockade	labetalol, carvedilol
short half life	esmolol

Clinical applications of β-receptor blockers

- **hypertension**
- **angina pectoris**
- **arrhythmias**
  - post MI arrhythmia prophylaxis
  - supraventricular tachycardias
- ***heart failure***
- hypertrophic cardiomyopathy
- migraine
- tremor / “stage fright”
- hyperthyreosis
- glaucoma
- cirrhosis

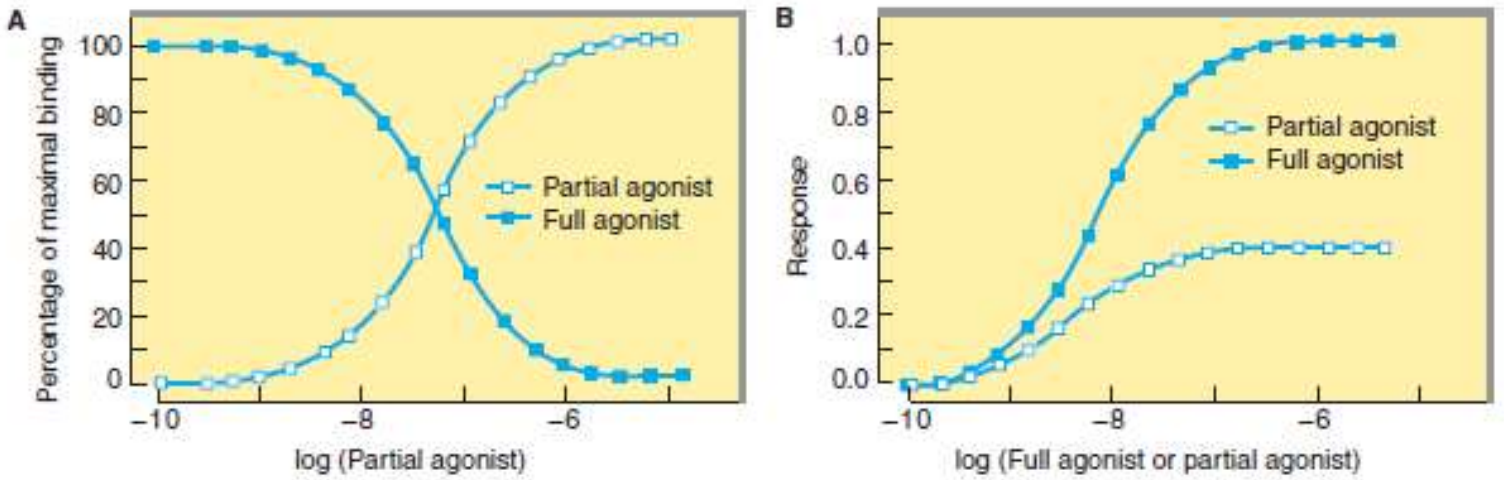
Effect of β-blockade on heart rate



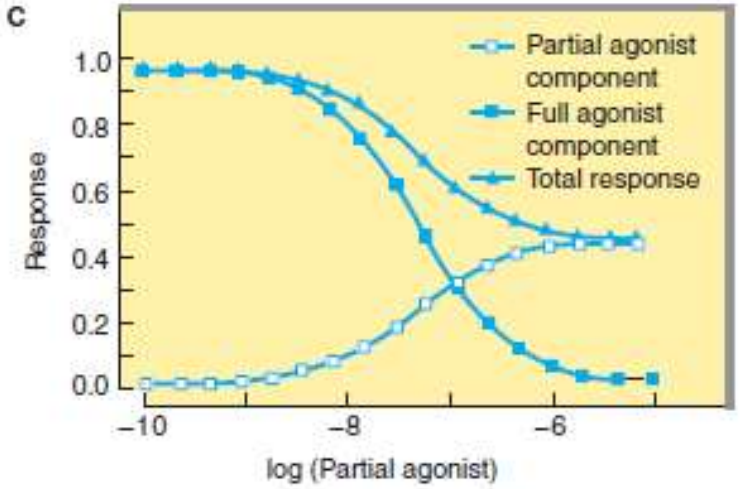
Effect of a partial agonist depends on full agonist concentration

occupancy, together

effect, alone



effect, together



Adverse effects of β-receptor blockers

- bradycardia
- bronchoconstriction (in asthma)
- cardiac decompensation
  - see interaction with verapamil
- cold hands and feet
- sedation, vivid dreams, depression
- VLDL ↑, HDL/LDL ratio ↓
- hypoglycemia ? – IDDM
- worsening of peripheral vascular disease
- β-receptor up-regulation
  - gradual dose tapering