NEUROTRANSMISSION in the ANS

Drugs affecting adrenergic – sympathetic - nervous system

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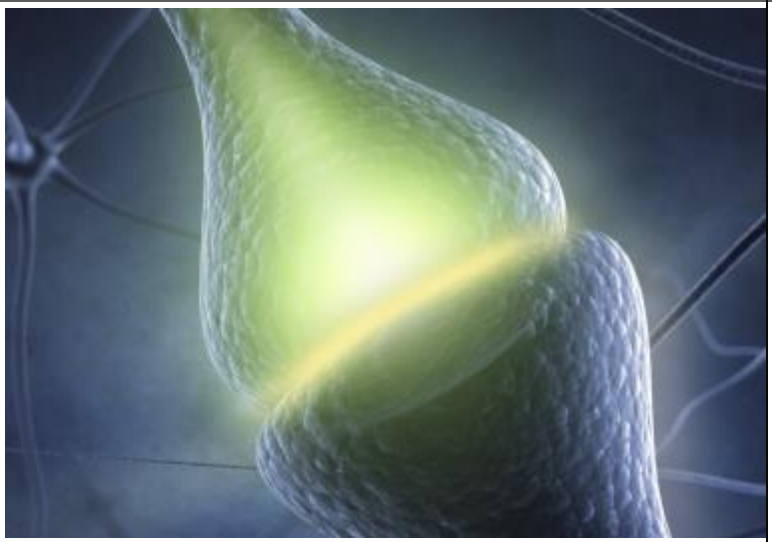
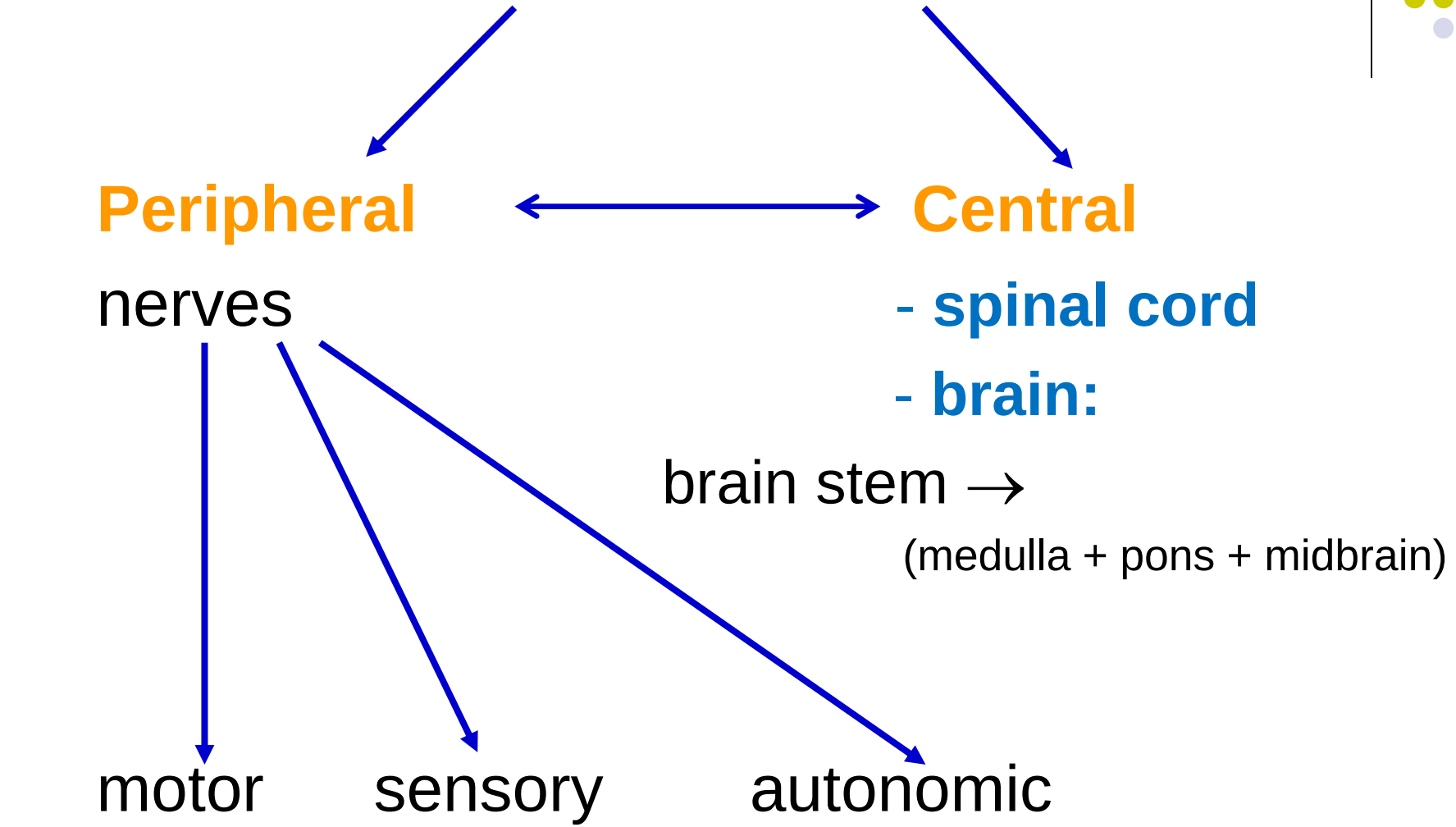
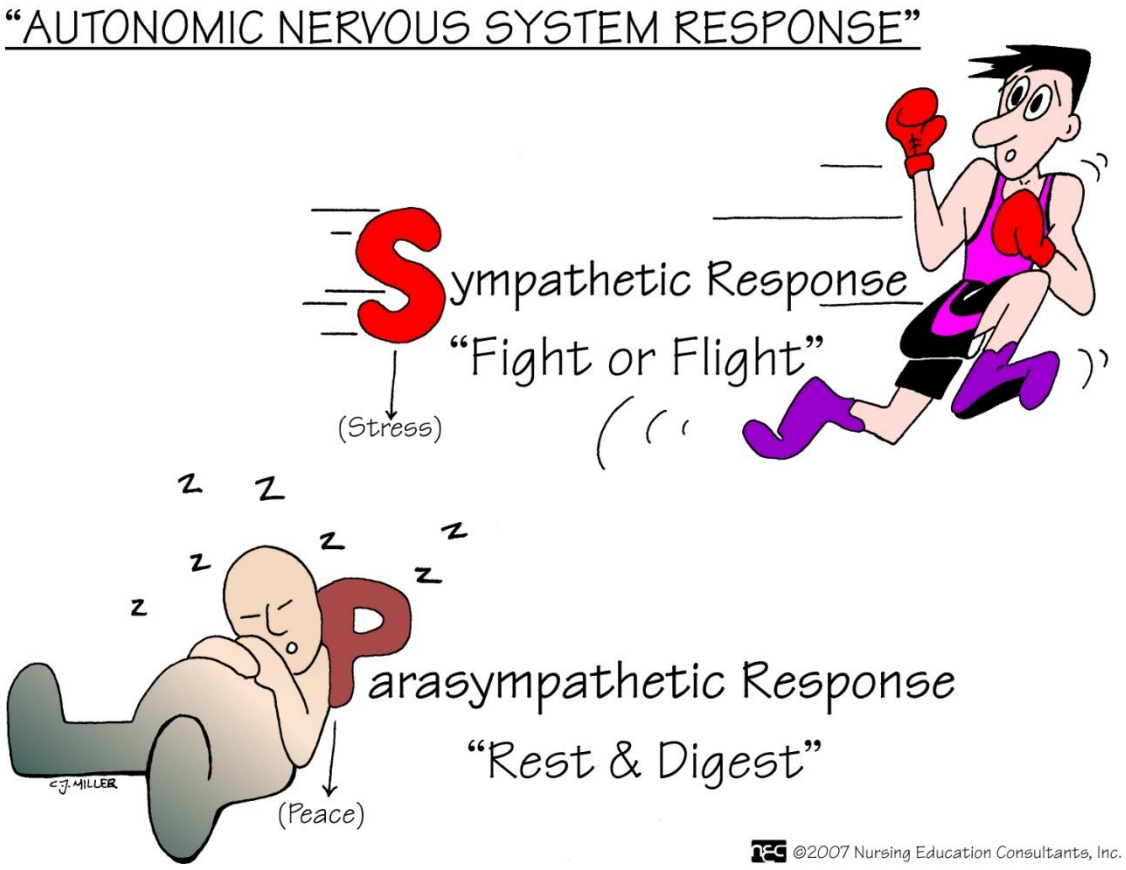


Nervous system

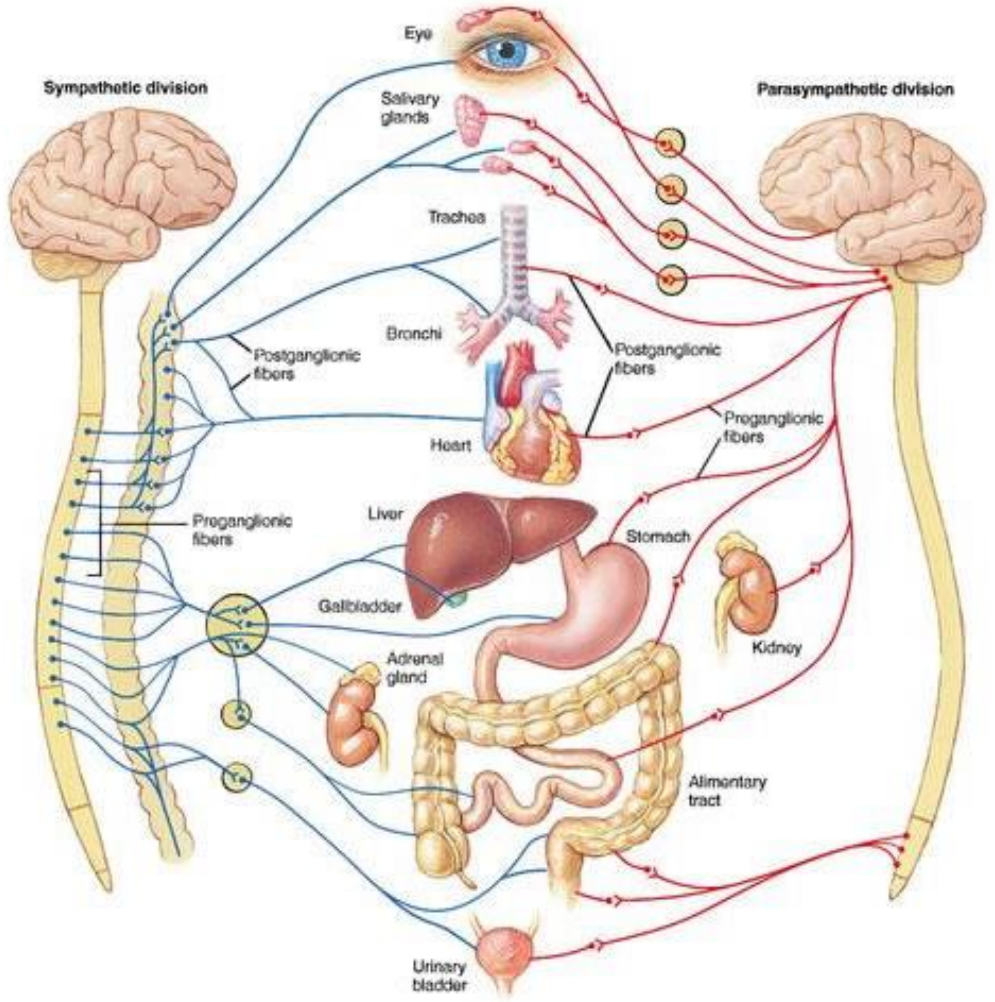


Autonomic nervous system ANS

- **Sympathetic** – activated at body charge (stress, physical activity, disease)
- **Parasympathetic** – activated at rest (sleep, digestion)

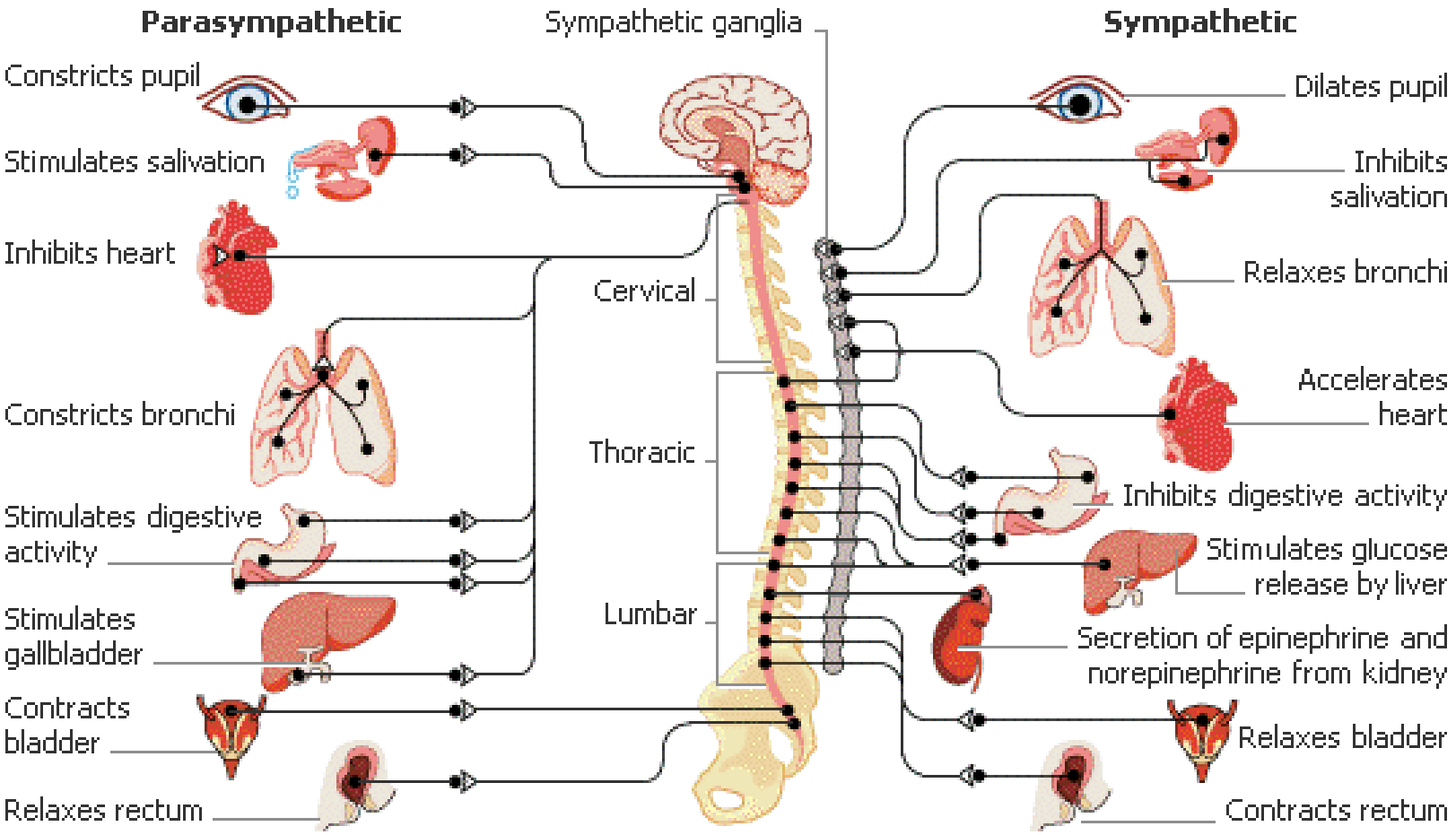


ANS - scheme



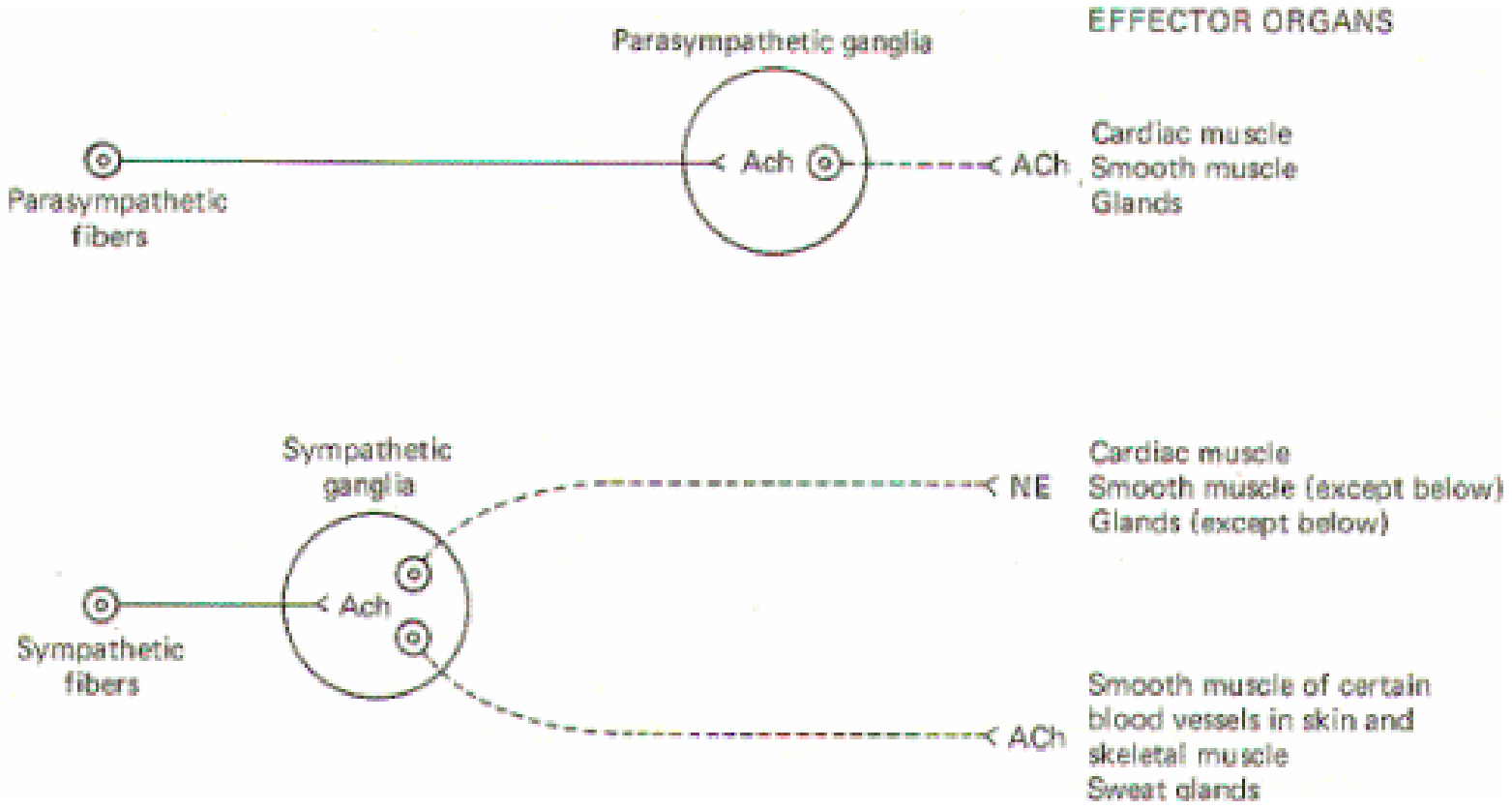
http://ardb.bjmu.edu.cn/main/ARDisease.htm

ANS - function



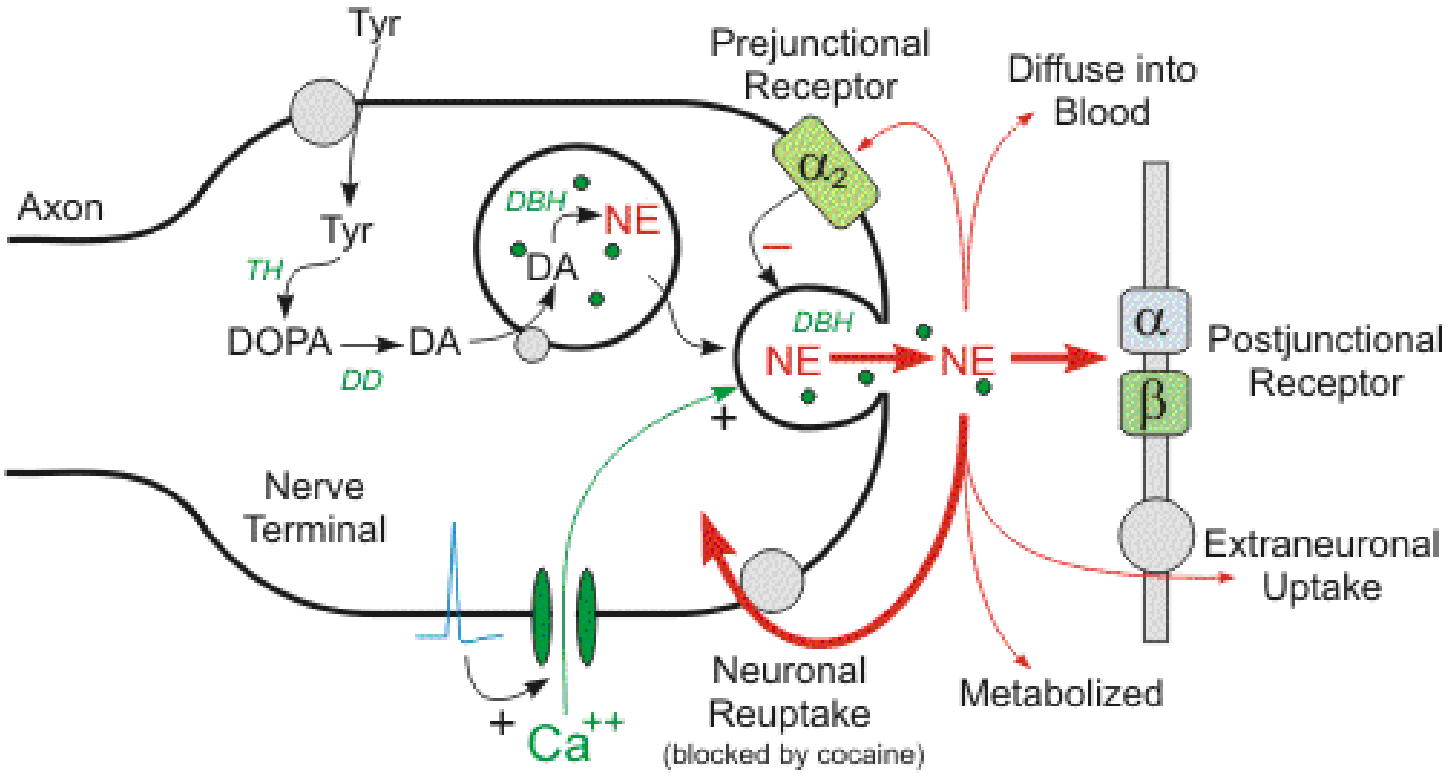
http://www.becomehealthynow.com/popups/sympth_parasympth.htm

Exception in adrenergic neurotransmission



http://www.neurophysiology.ws/autonomicns.htm

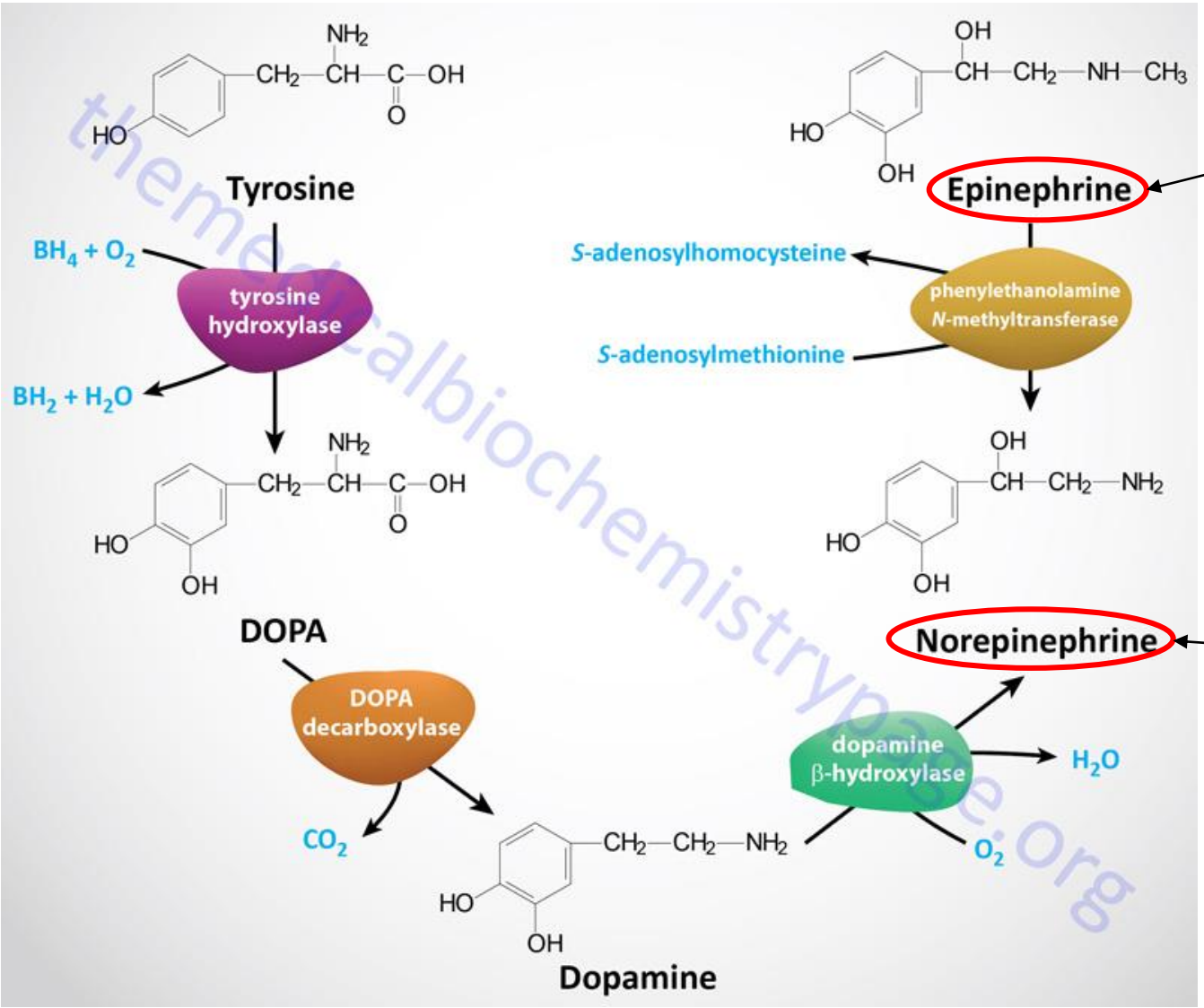
Norepinephrine synthesis, storage & release



Tyr = tyrosine; TH = tyrosine hydroxylase; DD = DOPA decarboxylase;
DA = dopamine; DBH = dopamine β-hydroxylase; NE = norepinephrine

http://www.cvpharmacology.com/norepinephrine.htm

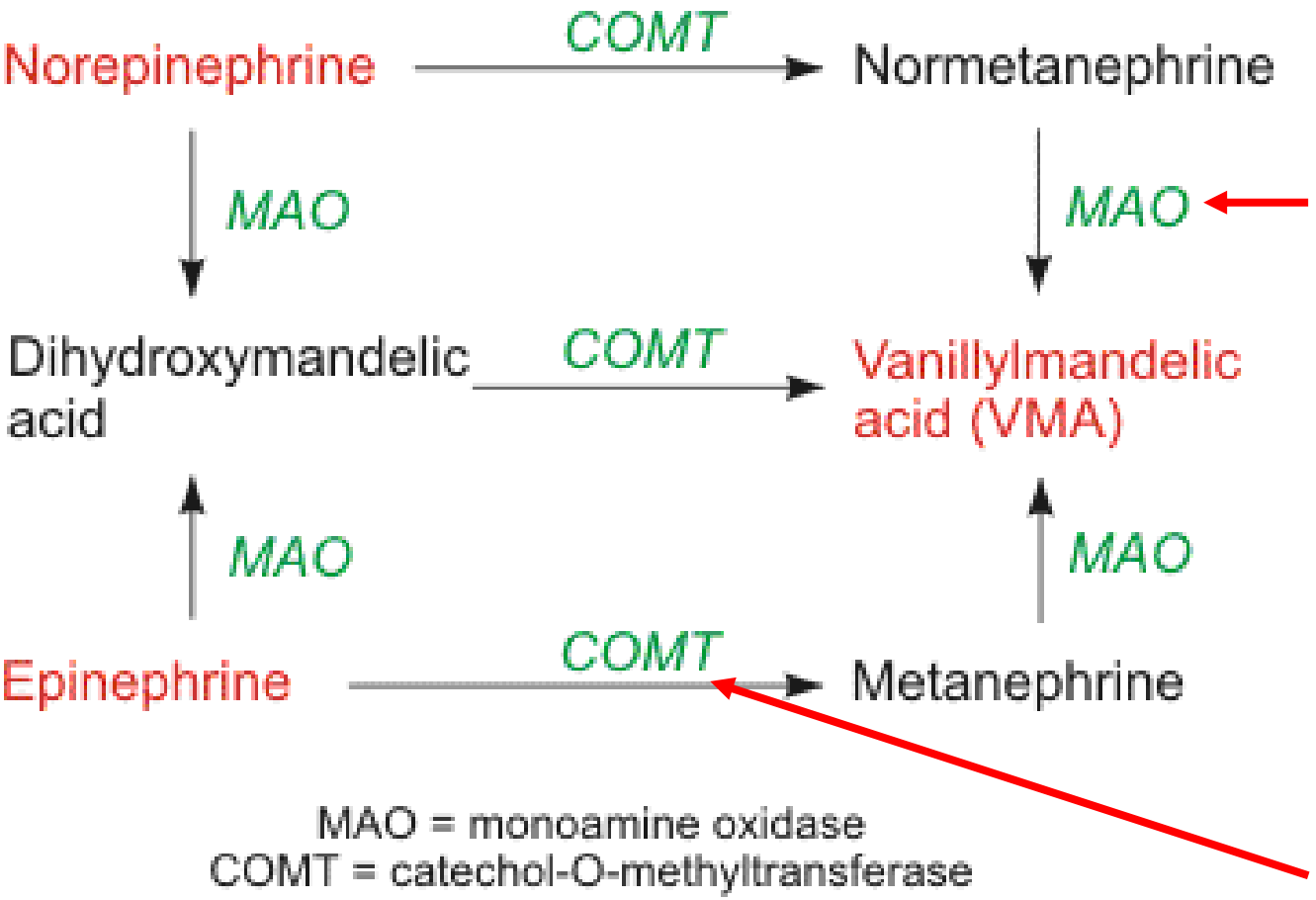
Synthesis of NE & E



Demethylation
(in adrenals)

Reuptake
(in nerve endings)

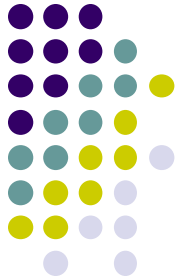
Metabolism of NE & E



- Monoamine oxidase (MAO)

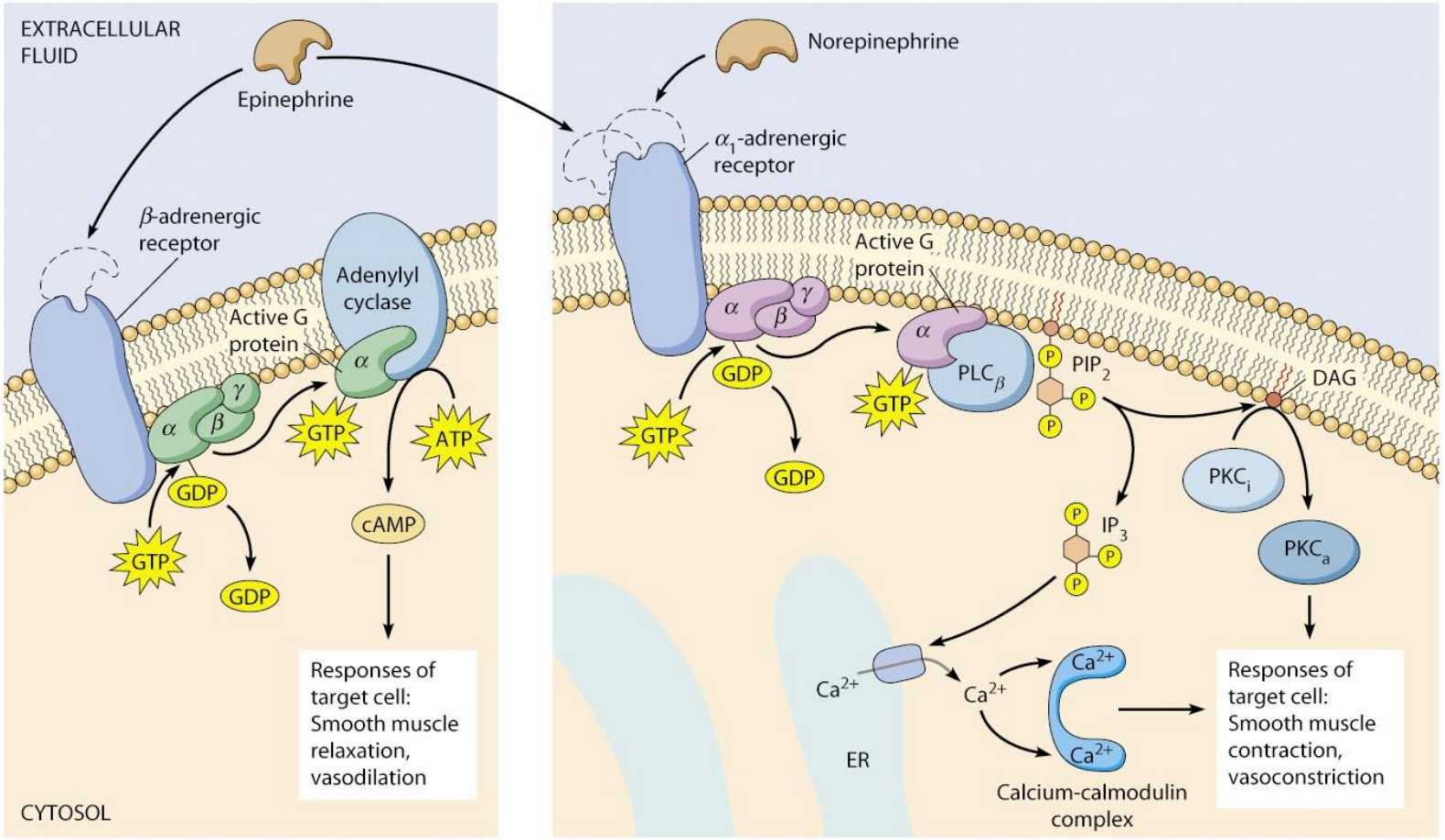
- Catechol-O-methyltransferase (COMT)

MAO substrates



Enzyme	Neurotransmitter metabolized
MAO - A	*Norepinephrine* *Epinephrine* *Serotonin* *Tyramine* *Dopamine*
MAO - B	*Dopamine*

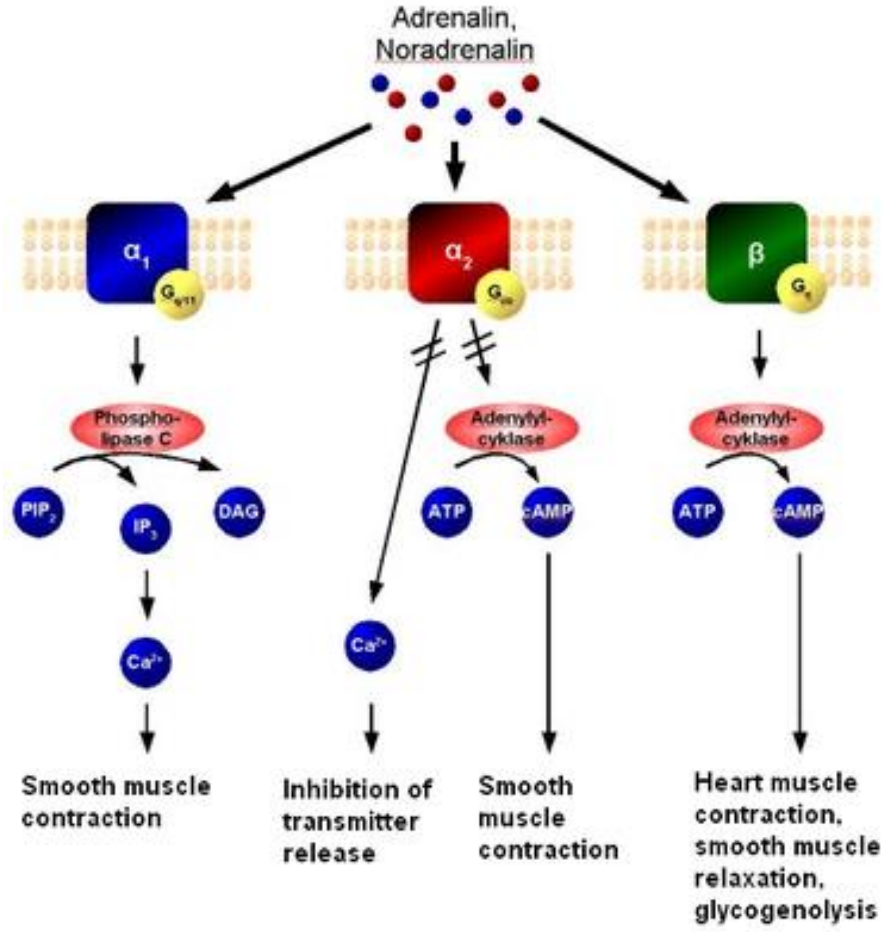
α_1- & β-receptor transduction pathways



(a) cAMP pathway initiated by activation of β-adrenergic receptor

(b) Inositol-phospholipid-calcium pathway initiated by activation of α_1-adrenergic receptor

Categories of sympathetic receptors



http://en.wikipedia.org/wiki/Adrenergic_receptor

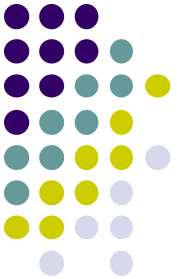
Sympathetic NS

α-receptors - localization

Receptor	Tissue
α_1	**vascular smooth muscle** papillary dilator muscle pilomotor smooth muscle **prostate** heart
α_2	**prejunctional CNS adrenoceptors** pancreatic β-cells platelets adrenergic & cholinergic nerve terminals vascular smooth muscle fat cells

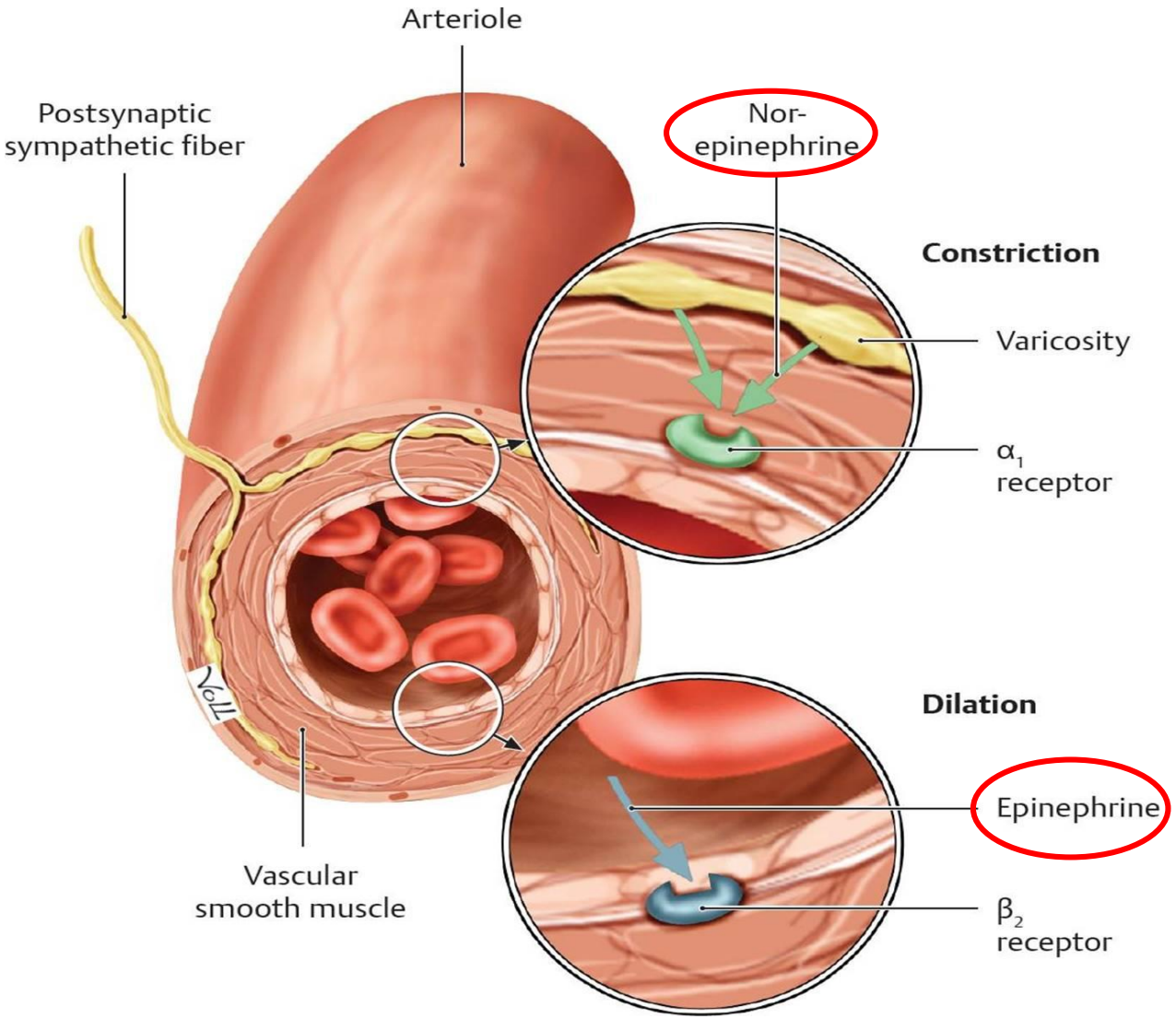
Sympathetic NS

ß- & D-receptors - localization



Receptor	Tissue
$ß_1$	**heart** **juxtaglomerular cells**
$ß_2$	**respiratory** **uterine & vascular smooth muscle** **skeletal muscle** **liver**
D_1	**smooth muscle**
D_2	nerve endings

α_1- & β_2-receptor
Blood vessel function

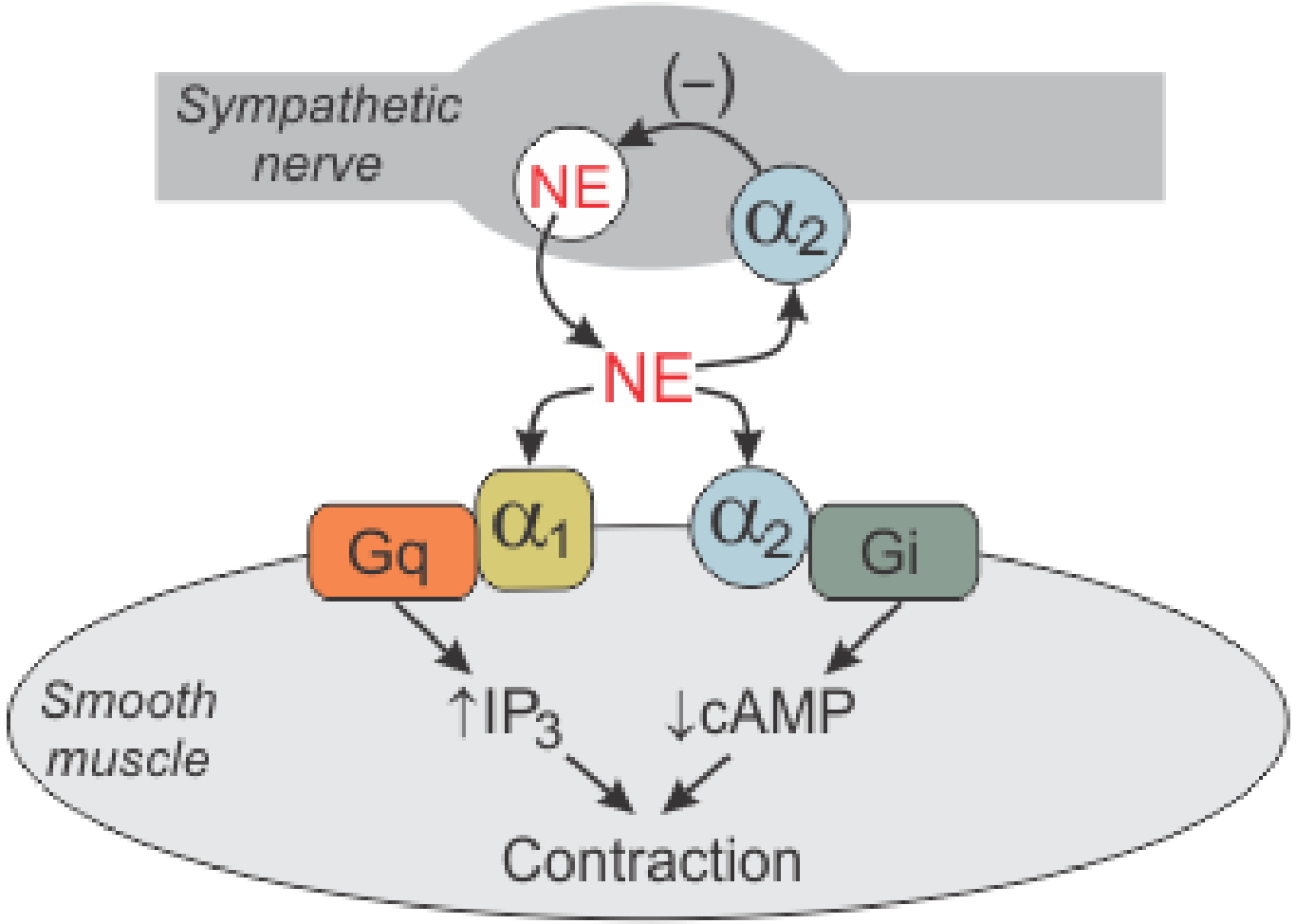


Role of α- & β- receptors

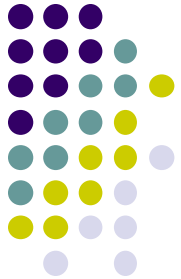
In the heart & smooth muscles

Receptor	Heart	Smooth muscle
α_1	?	Contraction
α_2	?	Contraction
β_1	Contraction	?
β_2	?	Relaxation

α-adrenergic control of smooth muscle contraction



β-receptor: modulation of cardiac contraction



- It is regulated by **cAMP- & calmodulin**-dependent (CaM) phosphorylation reactions
- Both work in parallel

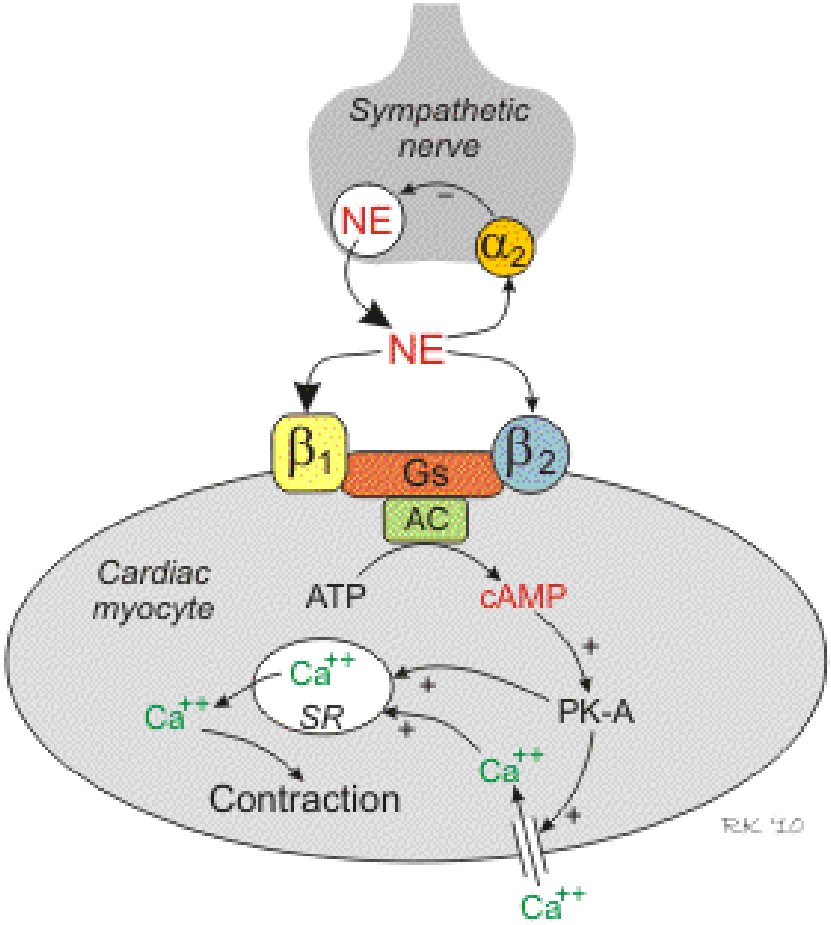
- Activation of cAMP – PKA cascade results in:

➢ phosphorylation of L-type Ca^{2+} channels (⇑ Ca^{2+})

➢ phosphorylation of ryanodine-sensitive receptors of sarcoplasmatic reticulum (⇑ Ca^{2+})

➢ phosphorylation of light chain of myosine (⇑ contraction)

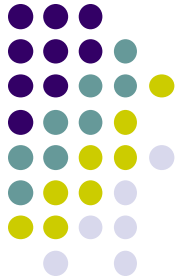
Adrenergic control of cardiac muscle contraction



Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; AC, adenylyl cyclase; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum

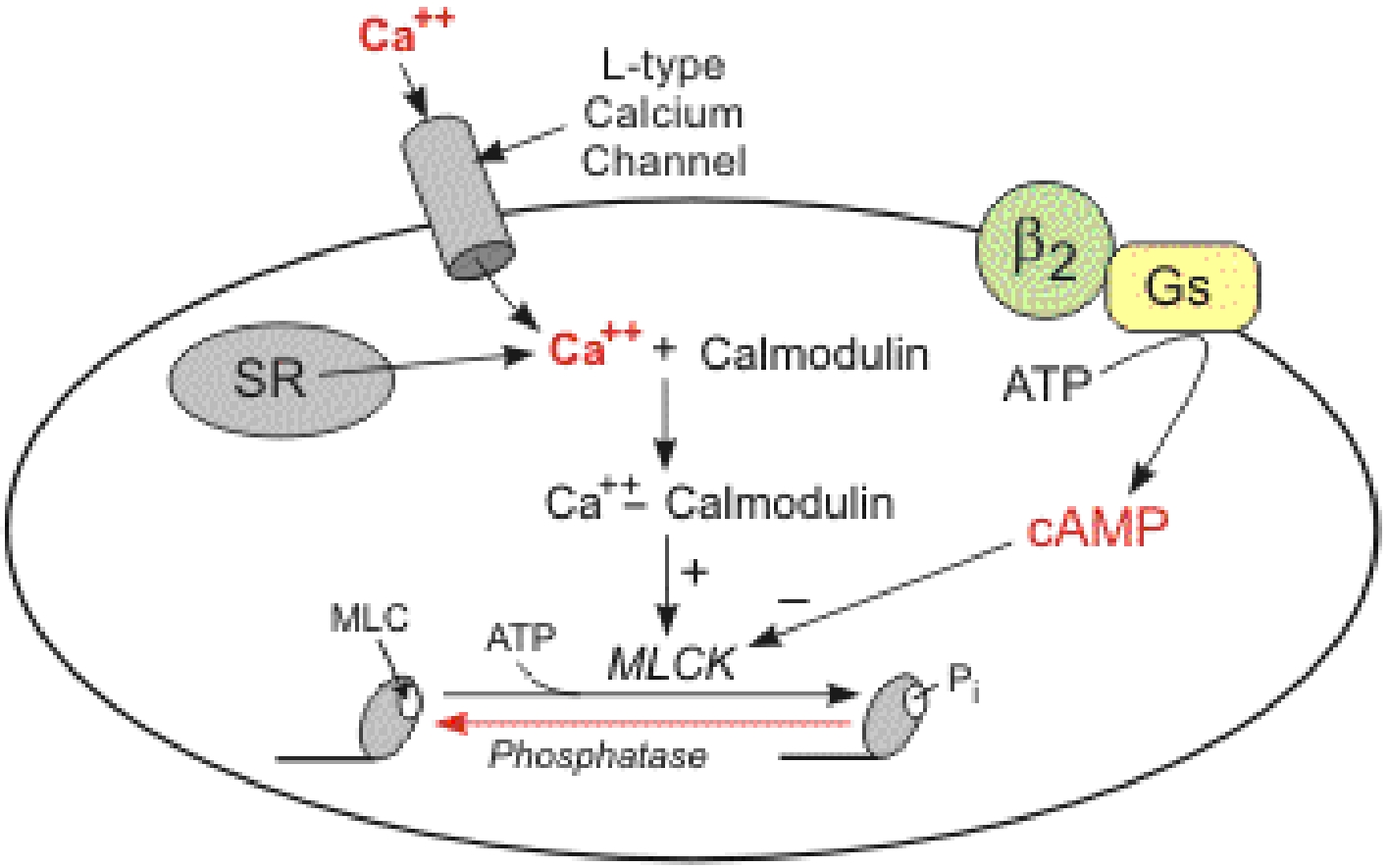
β-receptor

Modulation of smooth muscle relaxation



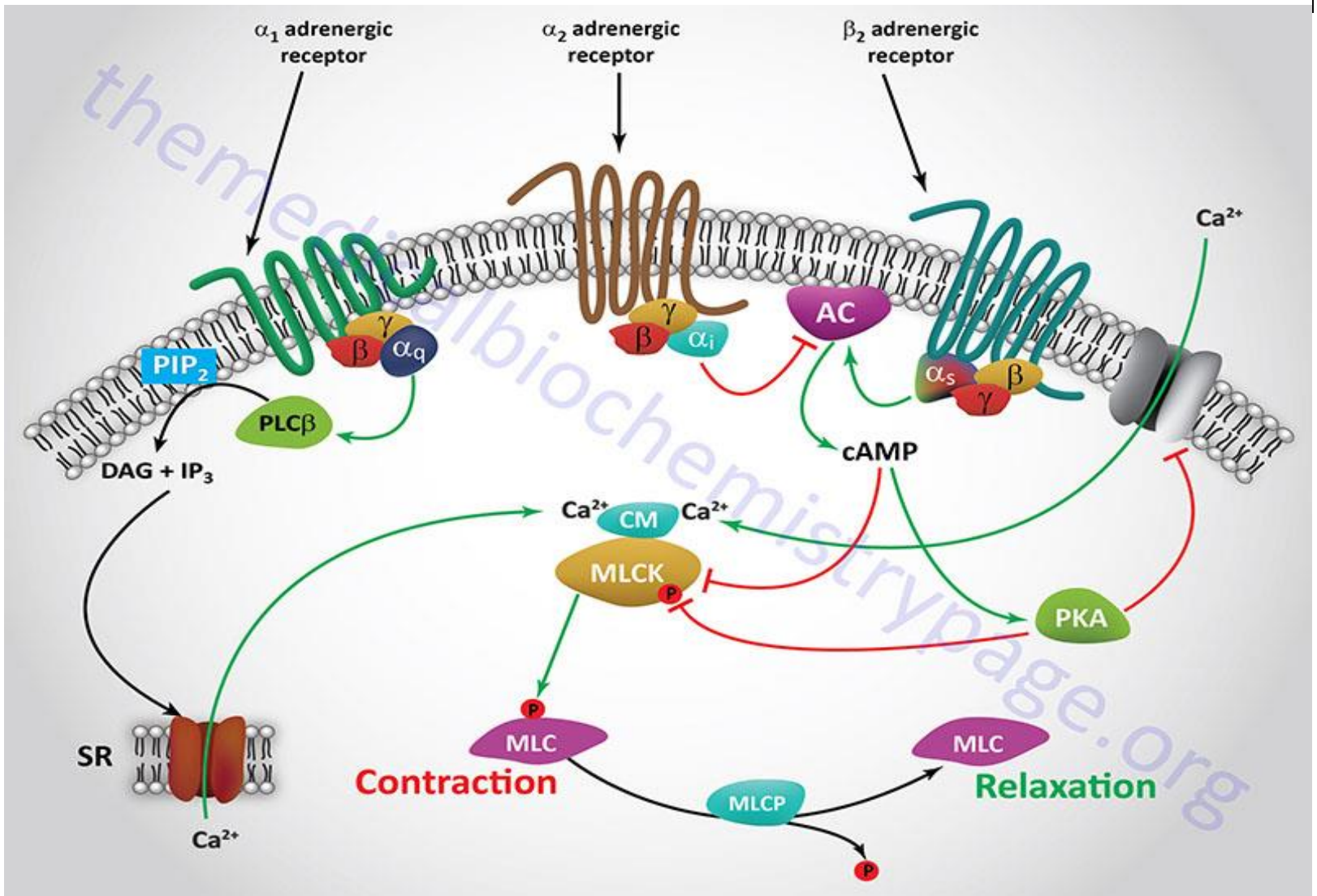
- It is regulated by **cAMP- & caldesmone**-dependent phosphorylation reactions (CaM-binding protein – inhibitor of Ca^{2+}-dependent smooth muscle contraction)
- Both are dependent on Ca^{2+} & CaM
- Activation of cAMP – PKA cascade results in:
  - phosphorylation of **myosine light-chain kinase**
  - ⇓ its affinity for Ca^{2+}- CaM complex
  - ⇓ its ability to phosphorylate **myosine light chain**
  - alternative, cAMP-independent pathways activate membrane K^+ channels (⇓ contraction)

β-adrenergic control of smooth muscle relaxation



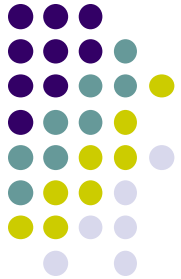
Abbreviations: SR, sarcoplasmic reticulum; Gq, Gs-protein; MLC, myosin light chain; MLCK, myosin light chain kinase; Pi, myosin phosphorylation

Adrenergic smooth muscle contraction/relaxation control



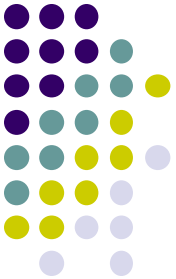
Sympathetic NS

α-receptors - function



Receptor	Major effects
α_1	mydriasis **vasoconstriction = ⇑ BP** ⇓ urination ⇑ glycogenolysis ejaculation
α_2	**inhibition of NE release (central effect)** inhibition of insulin release platelet aggregation

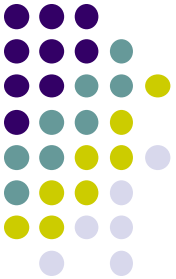
Sympathetic NS
ß-receptors - function



Receptor	Major effects
$ß_1$	⇑ heart rate ⇑ conduction velocity ⇑ force of heart contraction ⇑ renin release
$ß_2$	Relaxation of smooth muscle: uterine respiratory (bronchodilation) vascular (vasodilation) ⇑ insulin secretion ⇑ potassium uptake ⇑ glycogenolysis

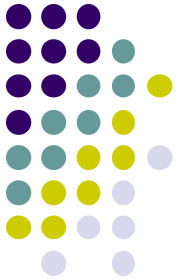
Sympathetic NS

D-receptors - function



Receptor	Major effects
D_1 (peripheral)	**Vasodilation of vasculature:** **coronary** **renal** **mesenteric** ⇑ **renal blood flow** ⇑ glomerular filtration rate ⇑ sodium excretion

Direct sympathomimetic agents



Stimulate sympathetic system via particular receptors:

α_1: *NE, E, naphazoline, phenylephrine*

Vasoconstriction: systemic or local (nasal mucosa)

α_2: *clonidine, α-methyldopa*

Hypertension

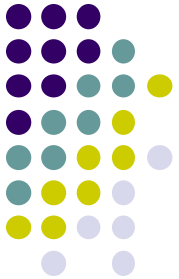
ß$_1$: *D, dobutamine*

Shock, cardiac failure

ß$_2$: isoproterenol, salbutamol, fenoterol, formoterol

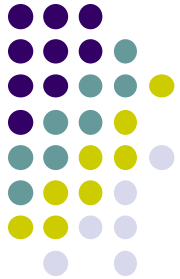
Bronchial asthma

Selectivity of sympathomimetic agents



Agent	Receptor
Norepinephrine	$\alpha > \beta_1$
Epinephrine	$\beta > \alpha$
Isoproterenol	$\beta_1 = \beta_2$
Dopamine	$D > \beta > \alpha$
Dobutamine	$\beta_1 > \beta_2$
Phenylephrine	$\alpha_1 > \alpha_2$
Fenoterol	β_2

Effects of some direct sympathomimetic agents



Agent	Effect
Norepinephrine	Systemic vasoconstriction
Epinephrine	Local vasoconstriction (local anaesthesia), cardiac support, anaphylaxis
Naphazoline	Local vasoconstriction (decongestion)
Dopamine	Vasodilation (renal, mesenteric), shock
Dobutamine	⇑ cardiac output (without affecting renal blood flow - CHF)
Fenoterol	Bronchial asthma, tocolysis

Norepinephrine
Emergent indications

Hypotension refractory to IVF
(i.v. fluid)

MOA: α_1- & β_1-agonist

- **Doses:**
  - 1 - 30 µg/min i.v.

- **Troubles:** tachydysrhythmias, tissue necrosis if catheter infiltrates or administered through an arterial line (therefore needs to be given via a central venous line)

Epinephrine
Emergent indications

Anaphylaxis; adult, pediatric, neonatal cardiac arrest; severe asthma

- **MOA:** β- & α-agonist
- **Doses:**
  - Adult cardiac resuscitation: 1 mg 1:10,000 i.v.
  - Peds cardiac resuscitation: 0.01 mg/kg 1:10,000 i.v.
  - Anaphylaxis: 0.1 - 0.5 mg 1:1,000 i.m./s.c. (i.m. preferred)
  - Peds anaphylaxis/asthma: 0.01 mg/kg 1:1,000 i.m./s.c. (max single dose 0.3 mg)
  - Hypotension refractory to IVF (i.v. fluid): 1 - 10 µg/min i.v.
- **Troubles:** dosing errors, tissue necrosis (needs to administered via central venous line), dysrhythmias

Dopamine
Emergent indications

Decompensated heart failure, hypotension

- **MOA:** α_1-, β_1-, & dopaminergic agonist
- **Doses:**
  - < 5 µg/kg/min i.v. dopaminergic effects (not recommended)
  - 5-10 µg/kg/min i.v. primarily β-effects
  - 10-20 µg/kg/min i.v. primarily α-effects

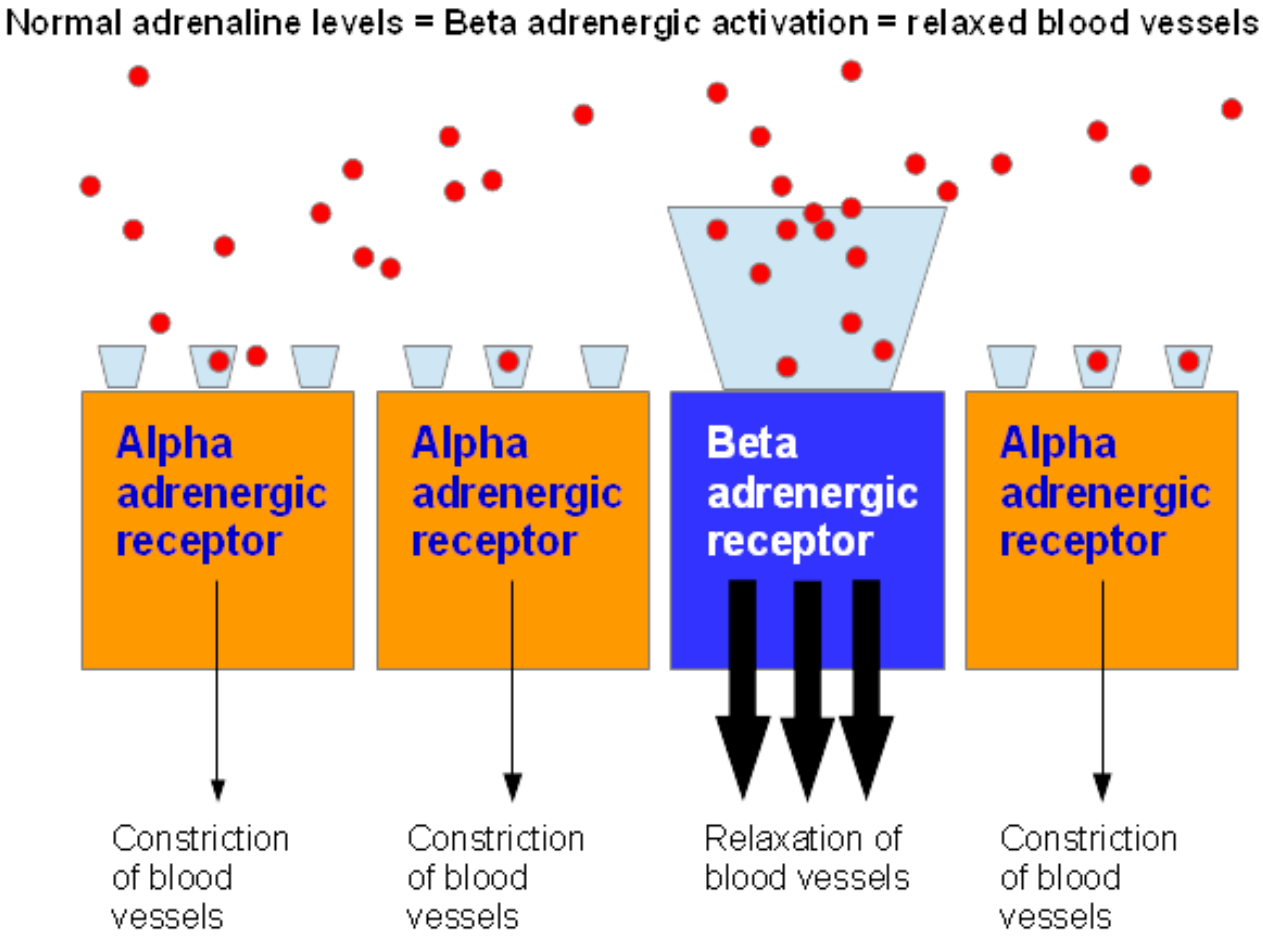
- **Troubles:** tachydysrhythmias, tissue necrosis if extravasation or arterial administration (therefore needs to be given through central venous line)

Dobutamine
Emergent indications

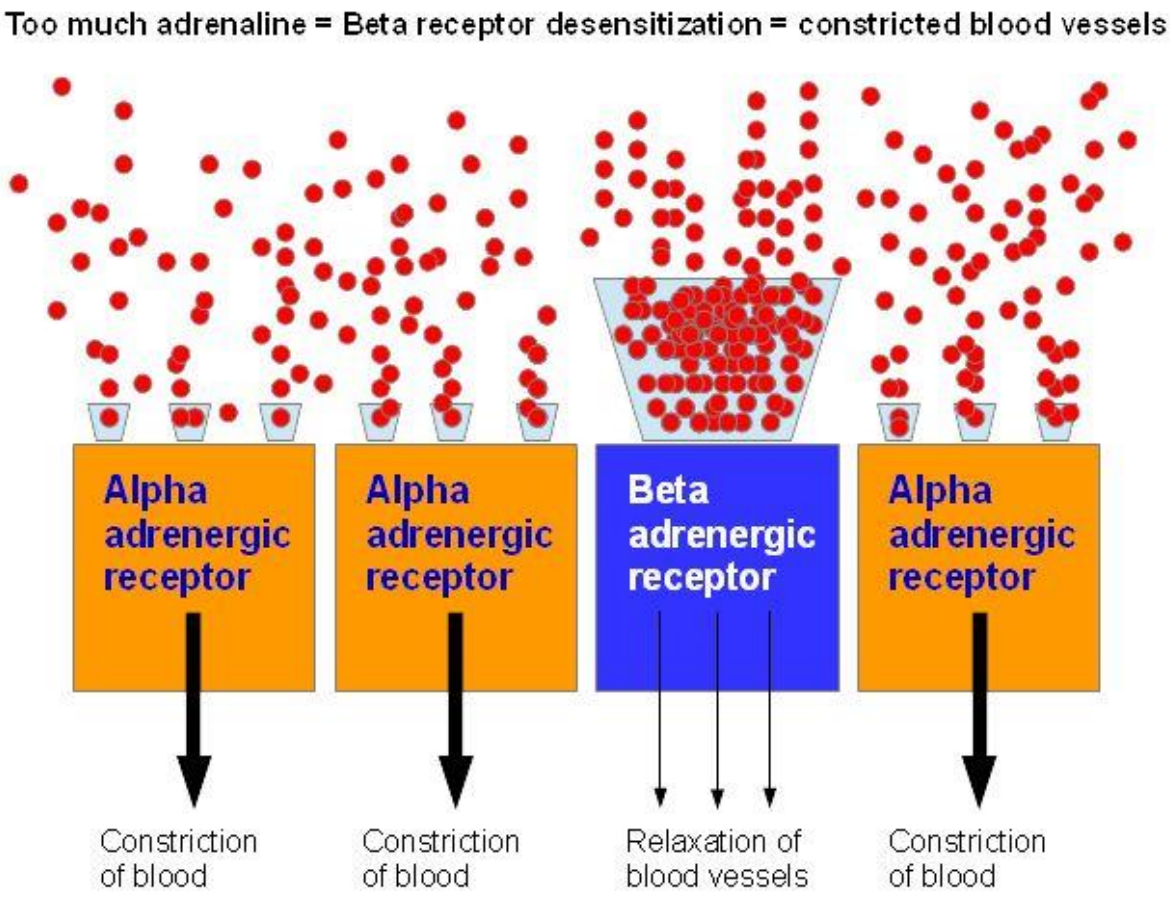
Decompensated heart failure, refractory hypotension

- **MOA:** β_1-agonist > β_2-agonist
- **Doses:**
  - 2 - 20 µg/kg/min i.v.
- **Troubles:** tachycardia, hypotension (if not euvolemic), premature ventricular contraction (also known as a premature ventricular complex - *PVC*),

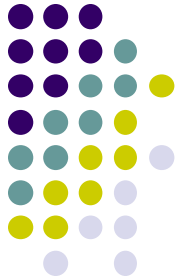
Dual effect of adrenaline - vasodilation



Dual effect of adrenaline - vasoconstriction

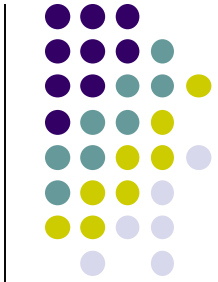


Concentrations of *E* in principal applications



Diagnosis	Concentration of *epinephrine*
Anaphylaxis	1 : 1000
Cardiac life support protocol	1 : 10.000
Combination with local anaesthetic	1 : 100.000

SE of sympathomimetics



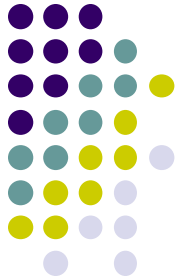
α- receptor stimulation

- ⇑ BP
- ⇓ oxygen delivery

β_1- receptor stimulation

- Tachycardia
- Palpitation
- Dysrhythmia (⇑ myocardial oxygen consumption)
- Dizziness
- Headache

Indirect sympathomimetic agents



Stimulate sympathetic system like NE by:

1. Releasing stored NE into the synaptic cleft:
amphetamine, ephedrine, tyramine

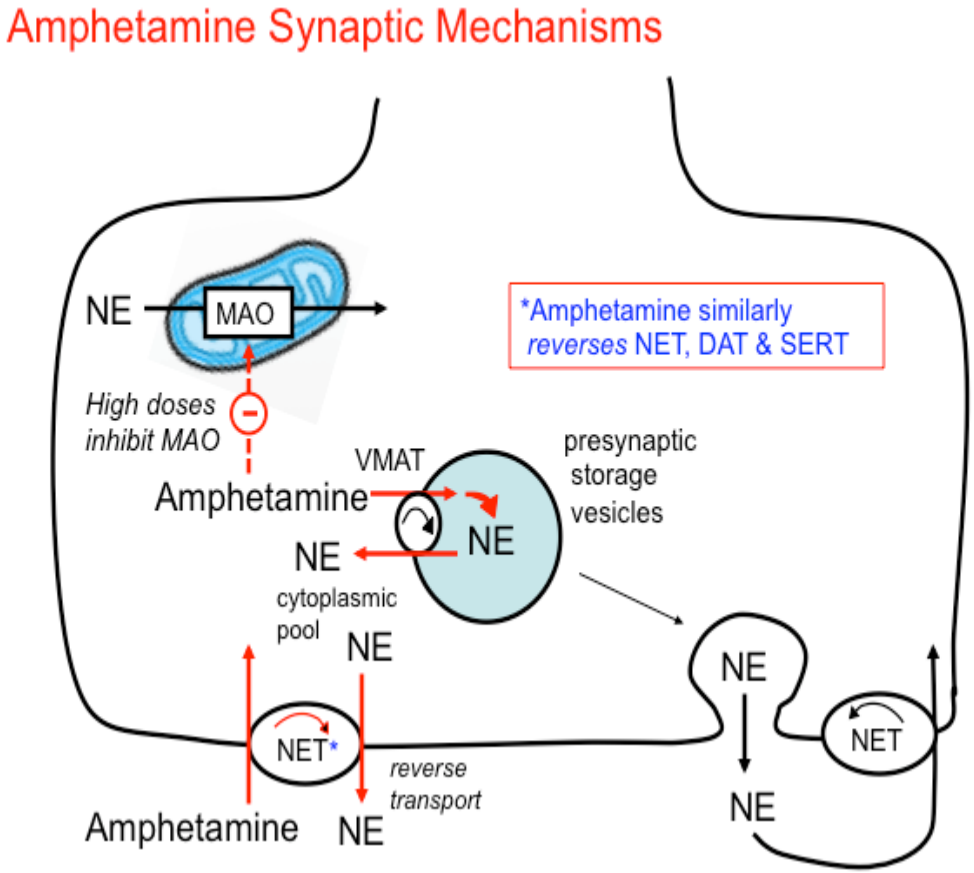
2. Blocking reuptake of NE back into the presynaptic neuron:

some *antidepressants, cocaine*

3. ⇓ NE metabolism by:

- ⇓ of MAO – A: some *antidepressants*
- ⇓ of MAO – B: *selegiline*
- ⇓ of COMT: *entacapone*

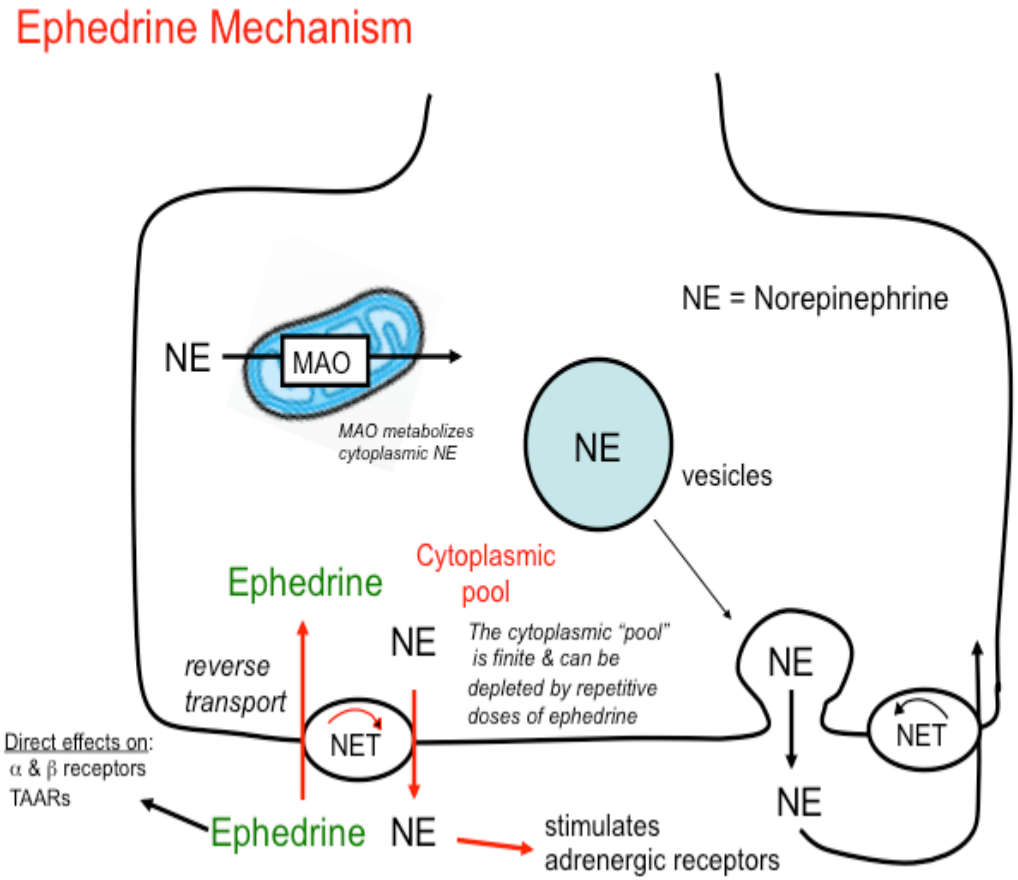
Amphetamine
MOA



- stimulate the release of NE from **central** adrenergic neurons
- release of D – high dose (mesocorticolimbic & the nigrostriatal D systems)
- acts as a direct agonist on central 5-HT receptors & may inhibit MAO
- in the **periphery** - the release of NE by acting on the adrenergic nerve terminals

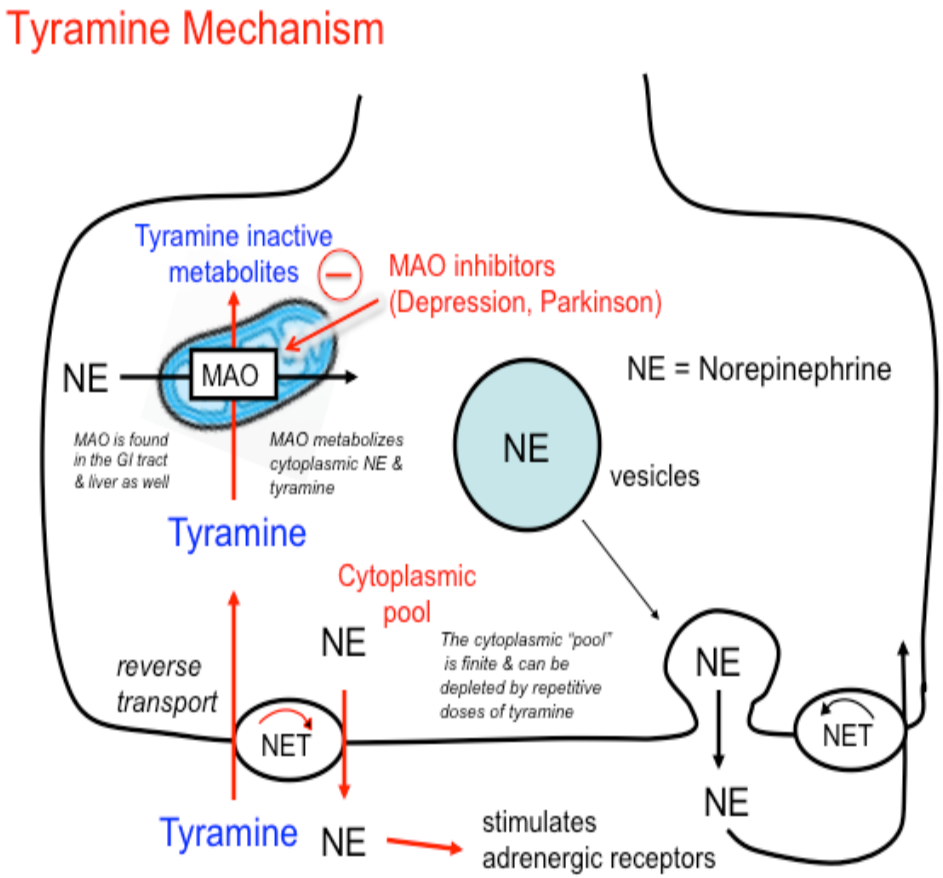
NET - norepinephrine transporter
VMAT - vesicular monoamine transporter
SERT - serotonin transporter

Ephedrine
MOA



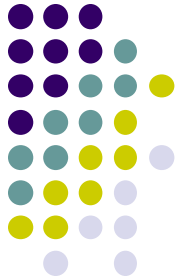
- Indirectly stimulates the adrenergic receptor system
- Possible direct interactions with α-receptors
- It stimulates NE & D release

Tyramine
MOA



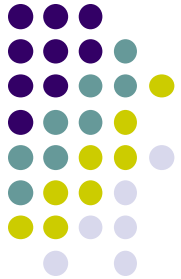
- It ⇑ availability of neurotransmitters
- It competes with axoplasmic NE for uptake into the synaptic vesicles
- Releases vesicularly stored ne from sympathetic nerve terminals

Effects of some indirect sympathomimetic agents



Agent	Effect
Amphetamine	Anorexia, abuse
Cocaine	Local anaesthesia, abuse
Tyramine	Hypertensive crisis (cheese + MAOI)
Pseudoephedrine	Local vasoconstriction (decongestion)
Moclobemide	Depression (MAO-A inhibitor)
Bupropion	Depression (NE & D reuptake inhibitor)
Selegiline	Parkinsonism (MAO-B inhibitor)
Entacapon	Parkinsonism (COMT inhibitor)

Direct sympatholytic agents



Block sympathetic system via particular receptors:

α_1: *Prazosin, terazosin, alfuzosin, tamsulosin*

Antihypertensive, benign prostatic hyperplasia (BPH)

α_2: *Yohimbine*

Postural hypotension, erectile dysfunction

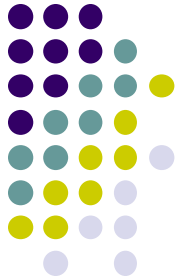
ß$_1$: *Atenolol, bisoprolol, metoprolol, acebutolol...*

Antihypertensive, antidysrhytmic, antianginal, anxiolytic, anti glaucoma

ß$_2$: ∅

No clinical value

Selectivity of α-receptor sympatholytic agents



Agent	Receptor
Phentolamine	$\alpha_1 = \alpha_2$ (competitive)
Phenoxybenzamine	$\alpha_1 = \alpha_2$ (irreversible)
Prazosin	α_1
Tamsulosin	α_{1A}
Yohimbine	α_2 (CNS prejunctional)
Mirtazapine	α_2 (CNS prejunctional)

Effects of some α-receptor sympatholytic agents

Agent	Effect/use
Phentolamine	Pheochromocytoma
Phenoxybenzamine	Pheochromocytoma
Tolazoline	Pulmonary hypertension
Yohimbine	Postural hypotension, impotence
Prazosin	Hypertension, BPH, m. Raynaud
Tamsulosin	BPH (more selective - α_{1A})
Mirtazapine	Depression (CNS prejunctional α_2)

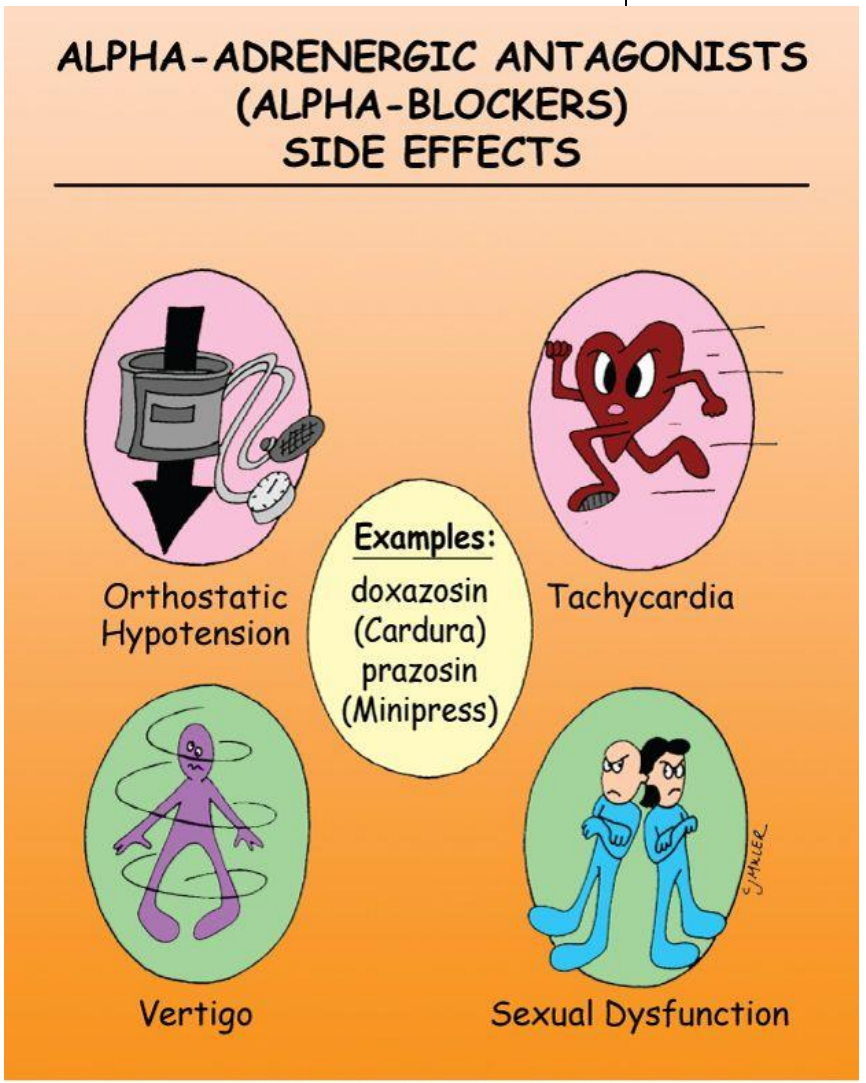
SE of α-blockers

1. Cardiovascular

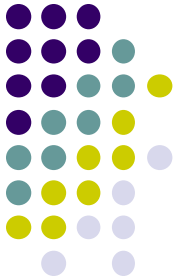
- Related to their principal α-blocking effect

2. Other

- Related to their principal MOA & as a result of ⇓ BP

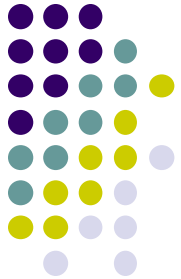


Selectivity of β-receptor sympatholytic agents



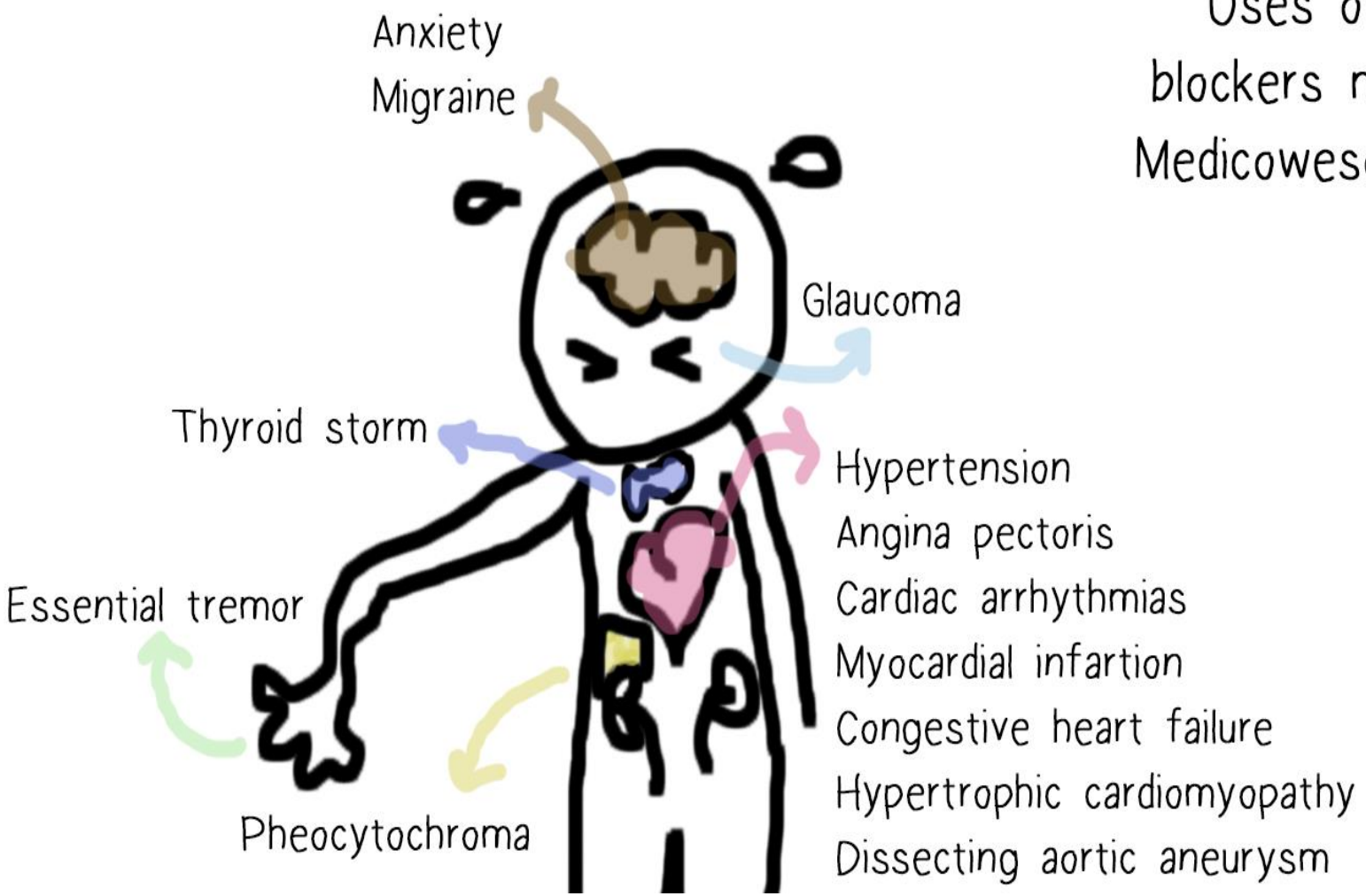
Agent	Receptor
Propranolol, timolol, pindolol, nadolol	β (nonselective)
Acebutolol, atenolol, bisoprolol, betaxolol, esmolol, metoprolol	β_1
Carvedilol, labetalol	α_1/β
Sotalol	β/K^+ channel blocker
Acebutolol, pindolol	With ISA

Effects of some β-receptor sympatholytic agents



Agent	Effect/use
Propranolol, timolol, pindolol, nadolol	Angina, dysrhythmias, hypertension, CHF, thyreotoxicosis, glaucoma
Acebutolol, atenolol, bisoprolol, betaxolol, esmolol, metoprolol	More specific = less SE
Carvedilol, labetalol	Valuable in CHF
Sotalol	Valuable in dysrhythmias
Acebutolol, pindolol	Valuable in CHF, hypertension

Clinical uses of β-blockers



Uses of beta blockers mnemonic
Medicowesome 2014

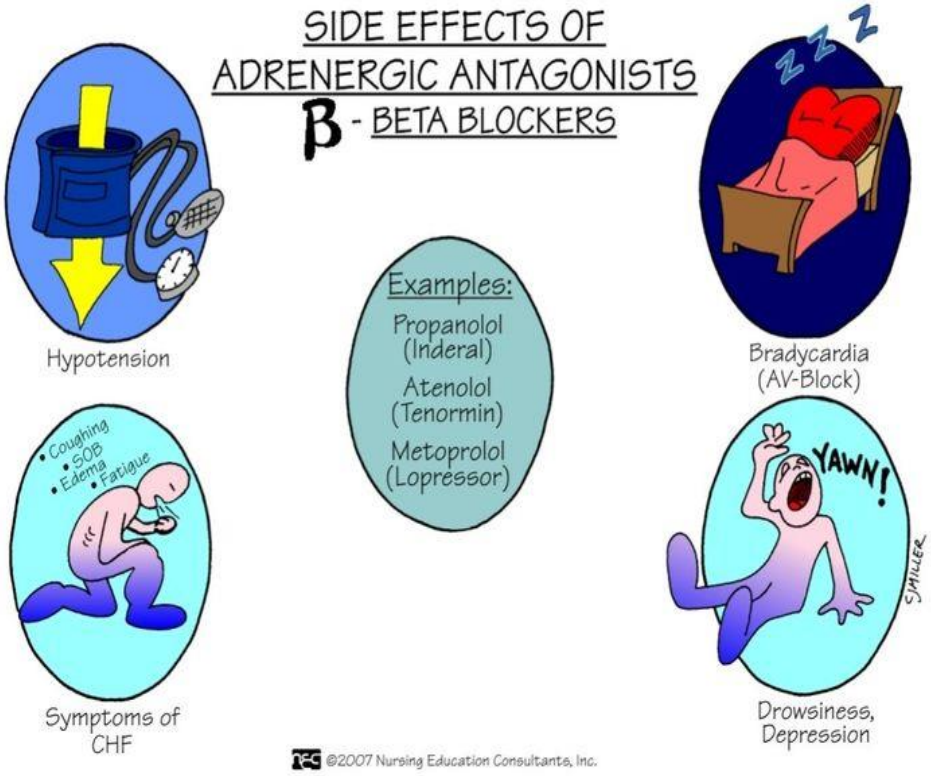
SE of β-blockers

1. Cardiovascular

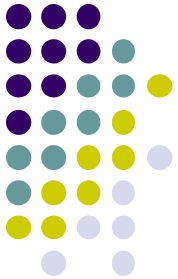
- Related to their principal β-blocking effect

2. CNS

- Related to their MOA in different organ levels
- Dependent on their ability to cross the BBB



Indirect sympatholytic agents



Block the effect of NE by:

1. ⇓ the transport of NE from the neuronal cytoplasm to the synaptic vesicles:

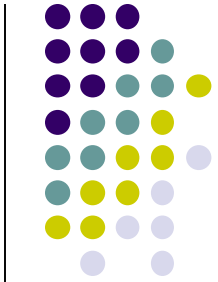
e.g. *reserpine* (no more in use)

2. Acting as „false mediators“:

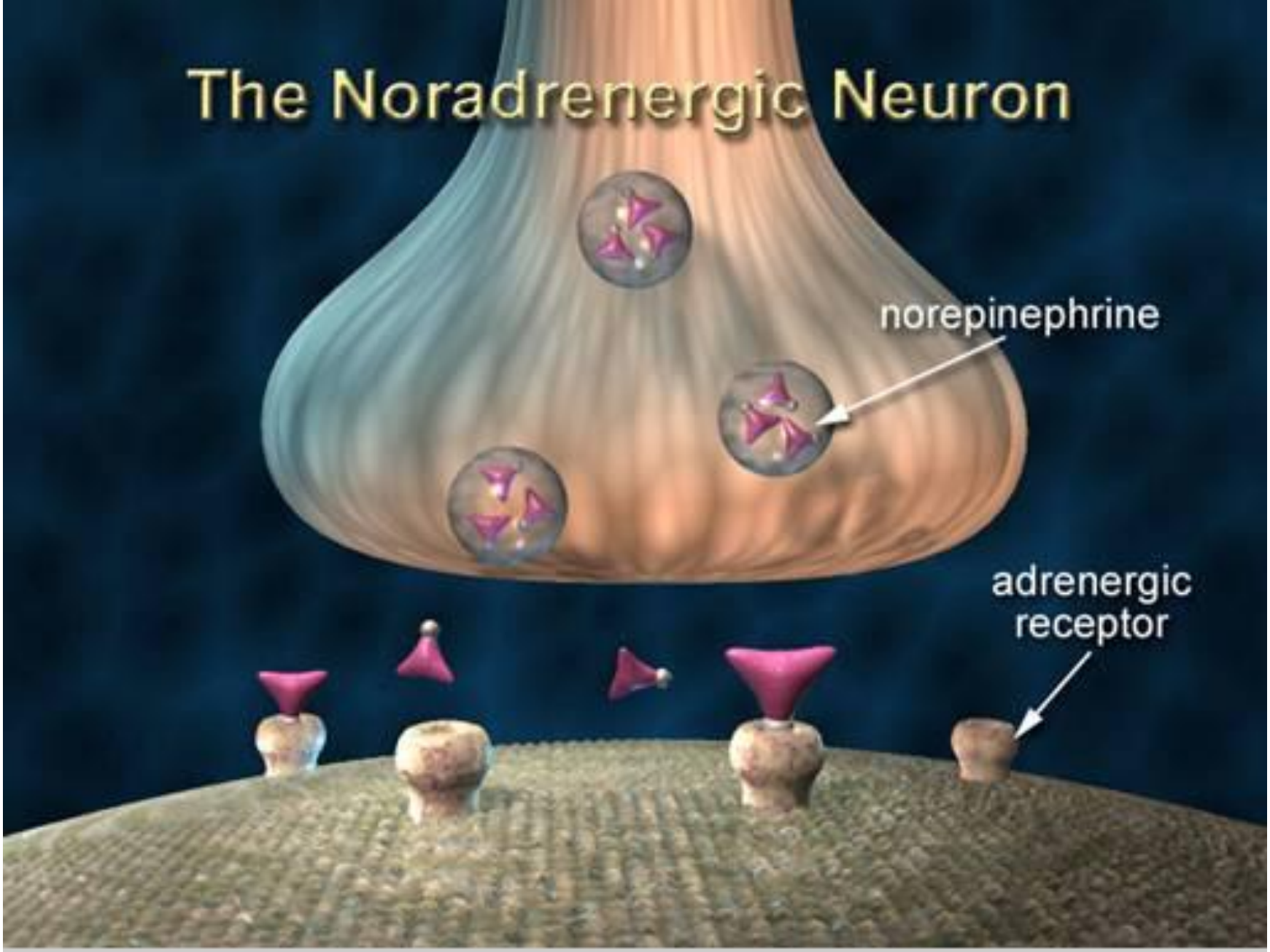
e.g. *methyldopa*

Both antihypertensive

Effects of some indirect sympatholytic agents



Agent	Effect/use
Reserpine	Hypertension (no more in clinical use because of non-selectivity & resulting in depression & sedation)
Methyldopa	Hypertension (mainly in **preeclampsia** – 1st choice drug, clinically approved safety even in 1st trimester)



Source: Adapted from < http://www.drugabuse.gov/pubs/teaching/Teaching4/Teaching.html >