

NATURAL AND SYNTHETIC ILLICIT DRUGS INTERFERING WITH ADRENERGIC RECEPTORS: THEIR CARDIOVASCULAR TOXICITY



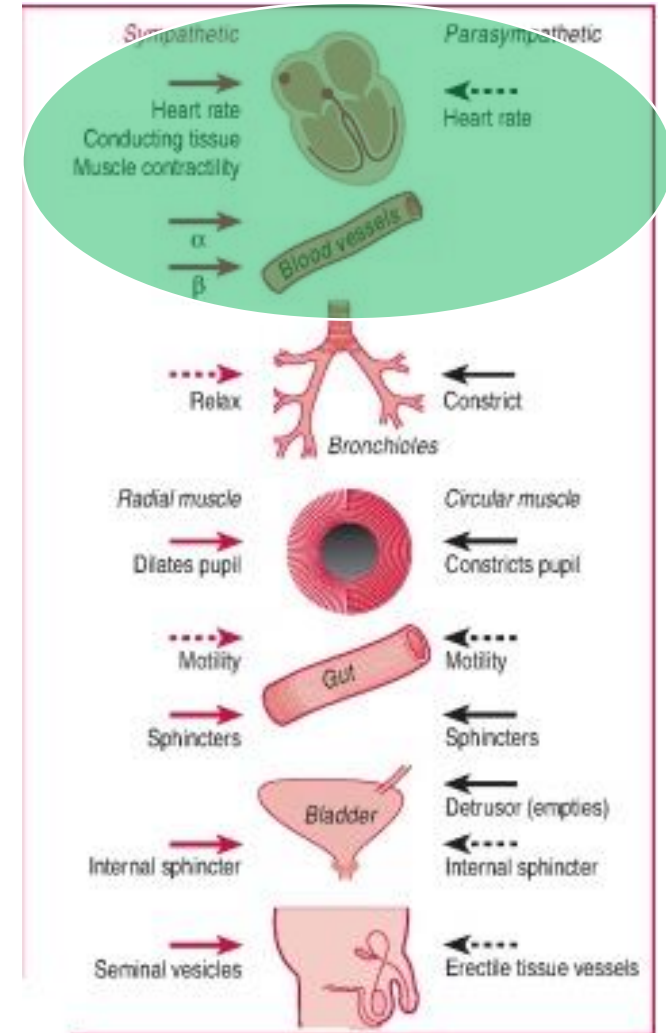
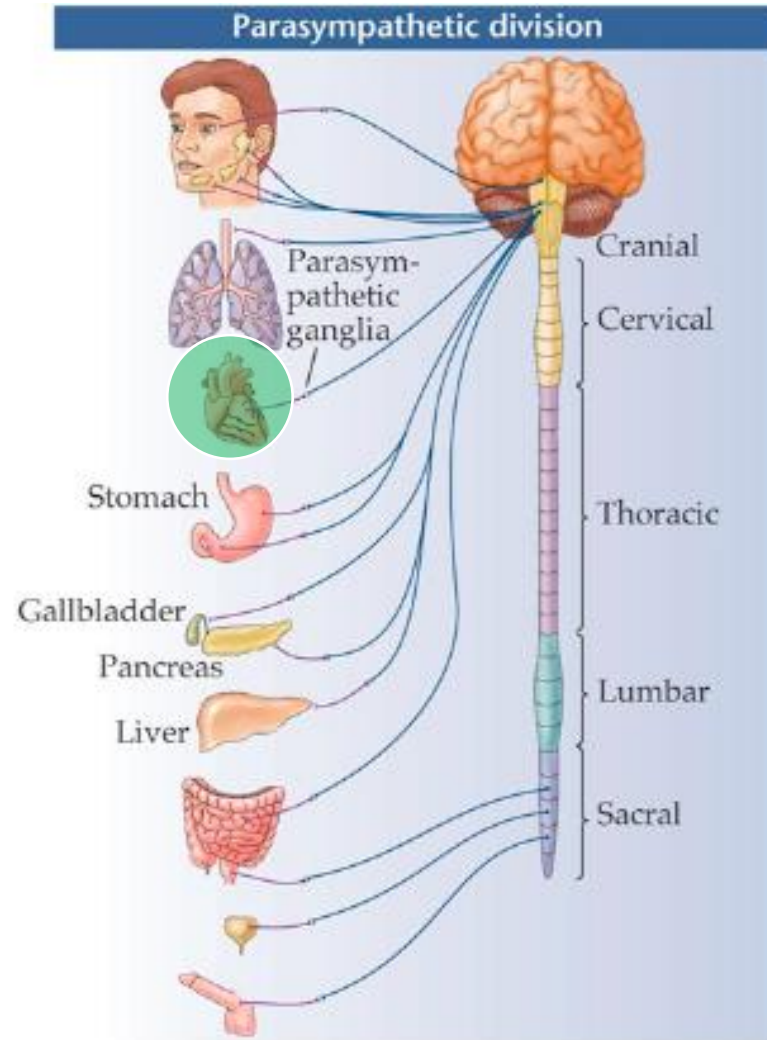
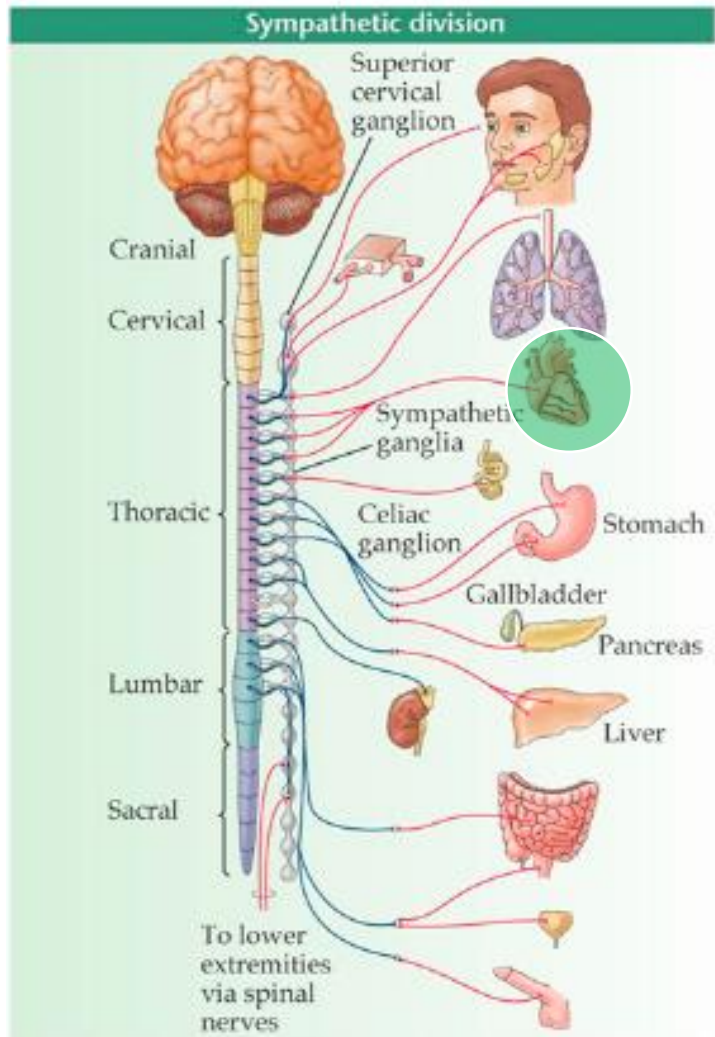
CHARLES UNIVERSITY
Faculty of Pharmacy
in Hradec Králové

Prof. Přemysl Mladěnka, Pharm.D., Ph.D.

Lecture layout

1. Sympathetic nervous system
2. Adrenergic receptors
3. Illicit drugs acting at those receptors
and their cardiovascular toxicity

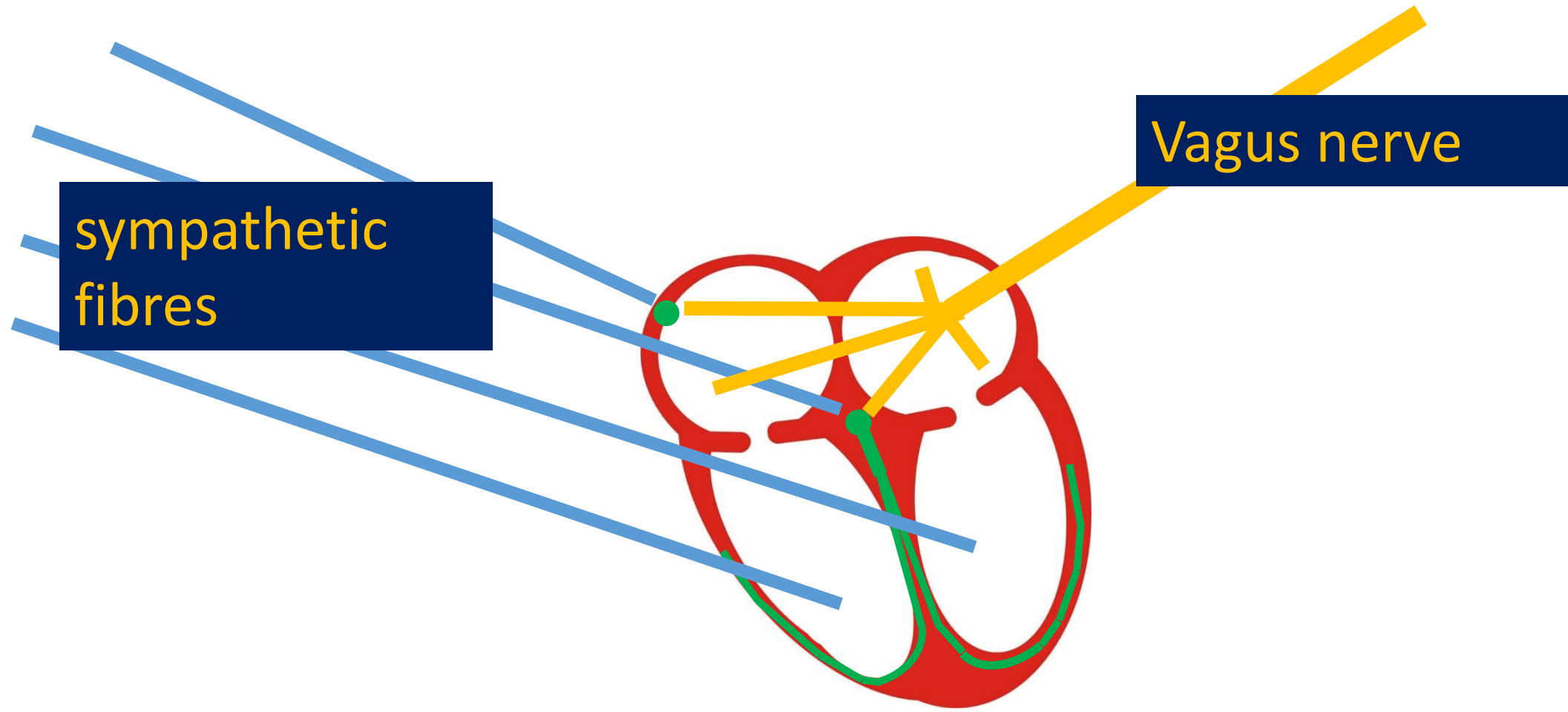
Autonomic nervous system



heart

sympathetic NS
innervation

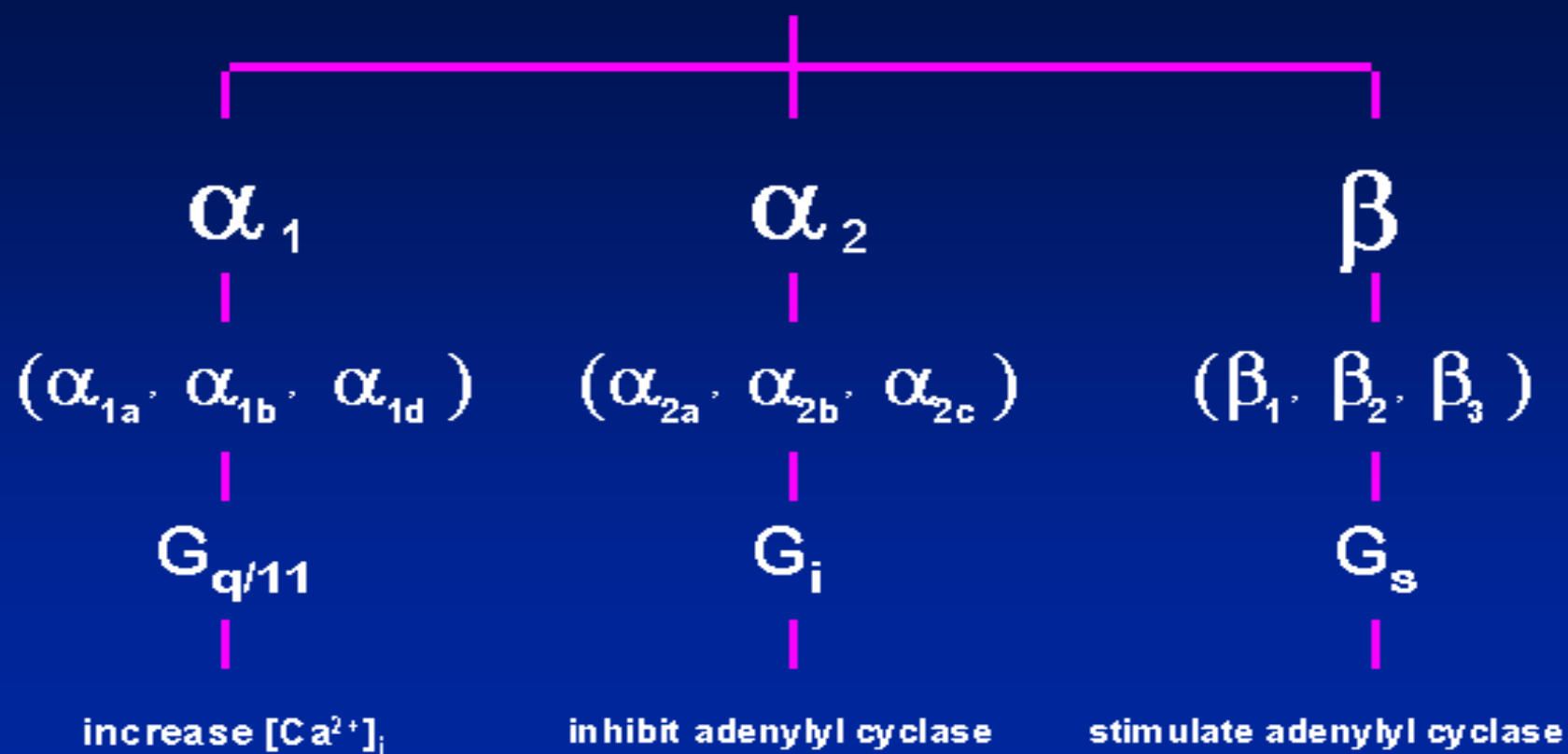
parasympathetic
NS innervation

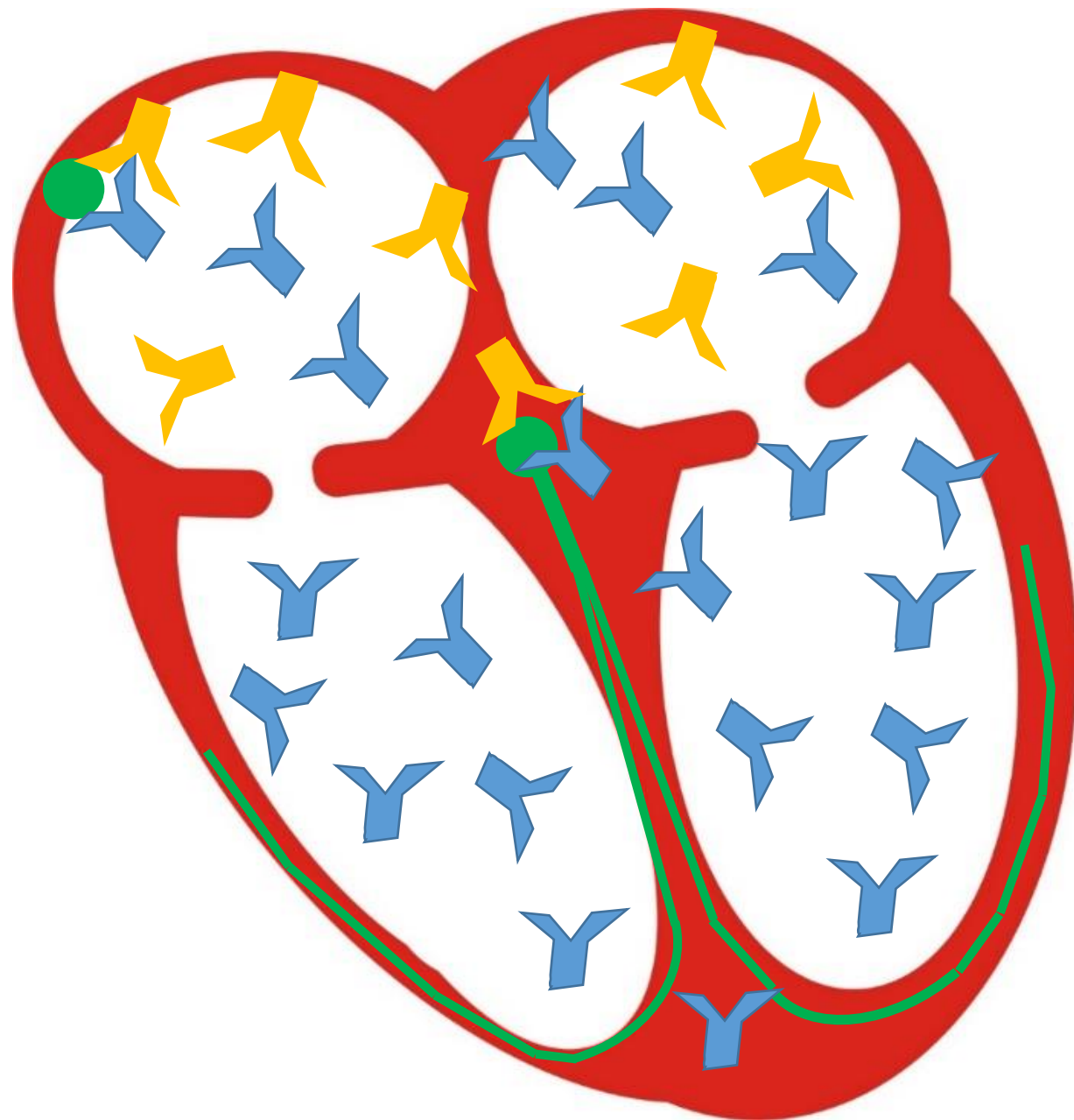


sympathetic
fibres

Vagus nerve

Adrenergic Receptors





<https://toxoyer.com/>



Learning Toxicology
through Open
Educational Resources
Welcome to TOX-OER

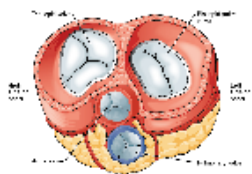


5.1 Target Organ Toxicity and Biomarkers - Cardiovascular (2 ECTS)

Home / Courses / TOX-OER MOOC platform / Module 5. Target Organ Toxicity and Biomarkers / 5.1 / Enrolment options

Enrolment options

5.1 Target Organ Toxicity and Biomarkers - Cardiovascular (2 ECTS)



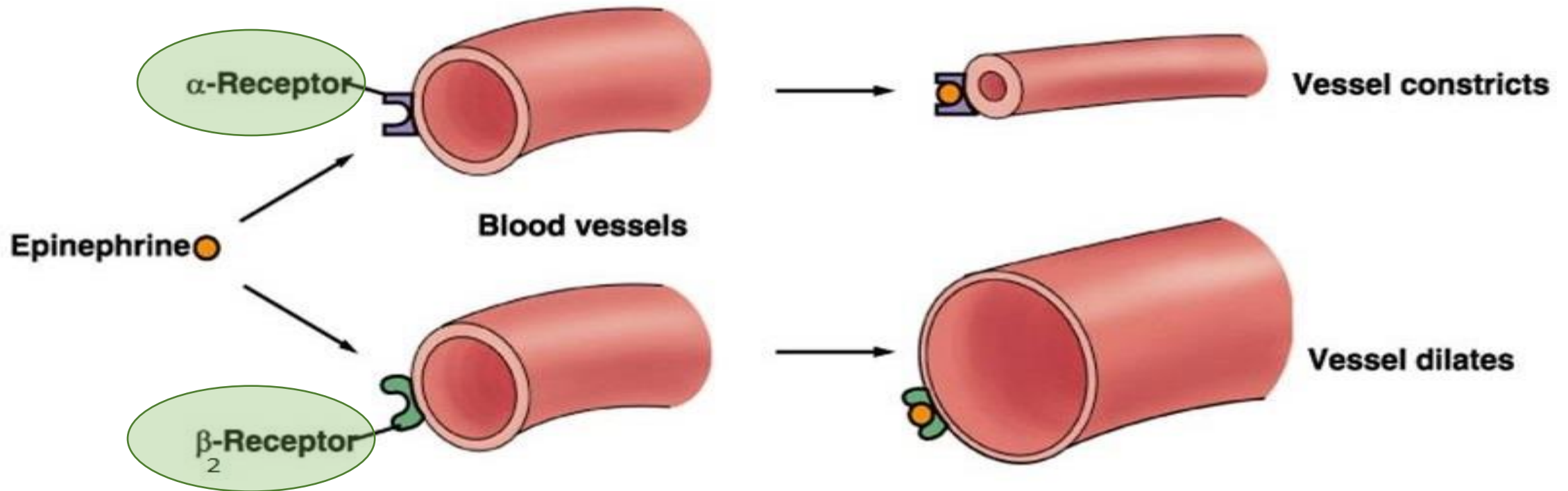
Teacher: Lenka Applova

Teacher: Premysl Mladenka

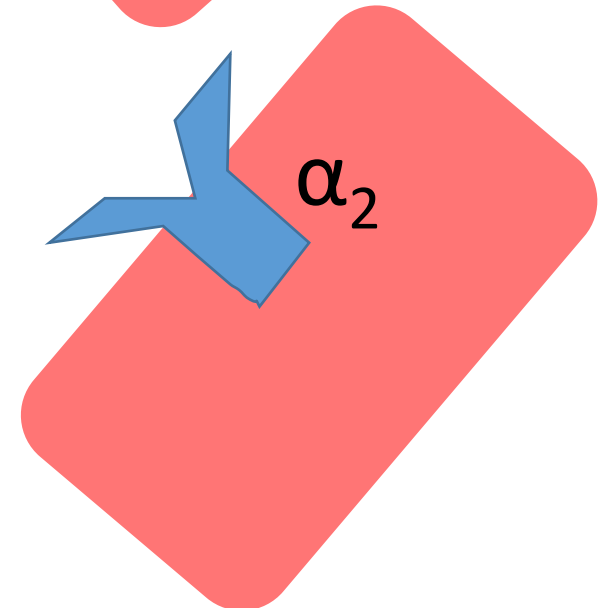
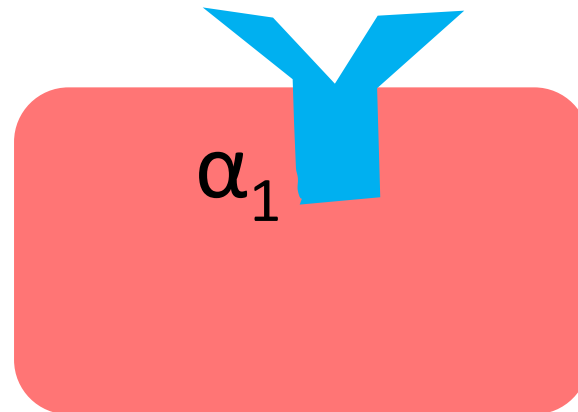
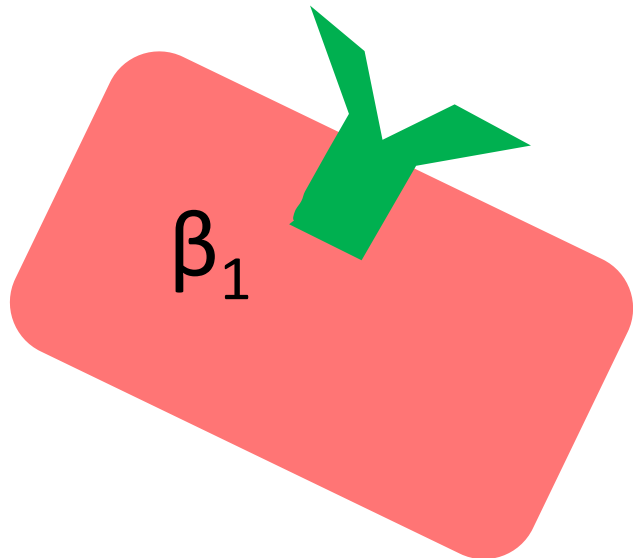
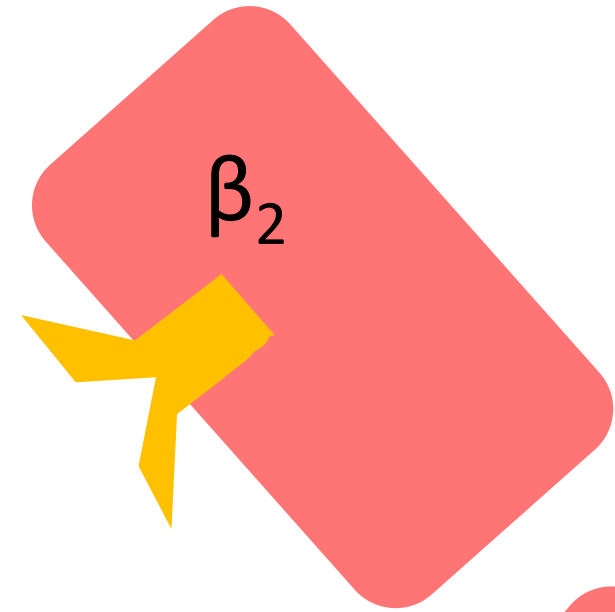
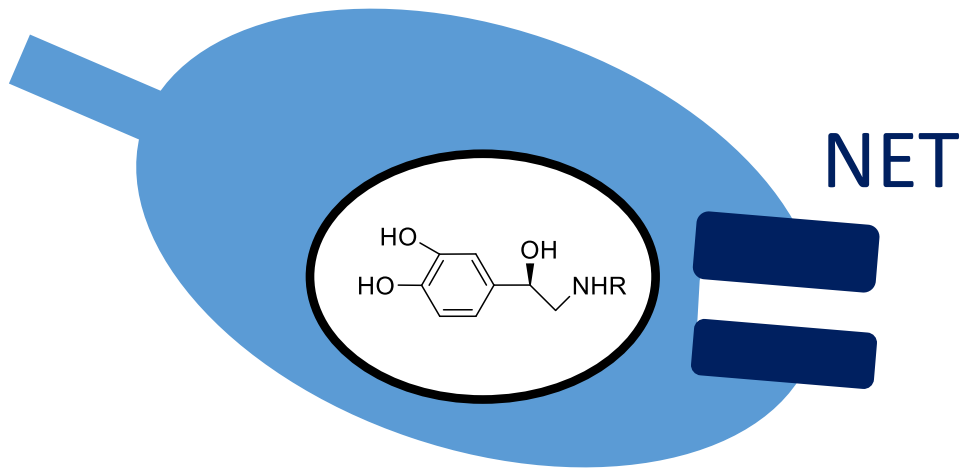
Teacher: Jana Pourova

Teacher: Marie Voprsalova

Adrenergic system and the vessels

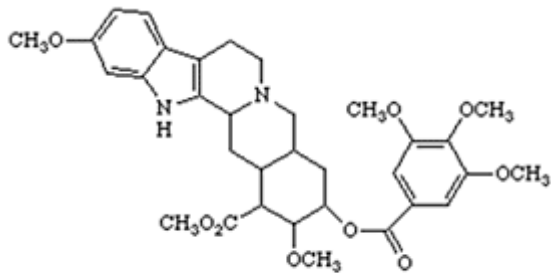


Agents acting at the level of adrenergic receptors



Agents acting at the level of adrenergic receptors

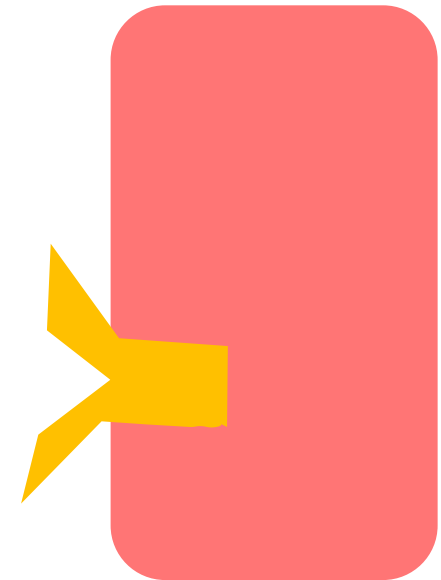
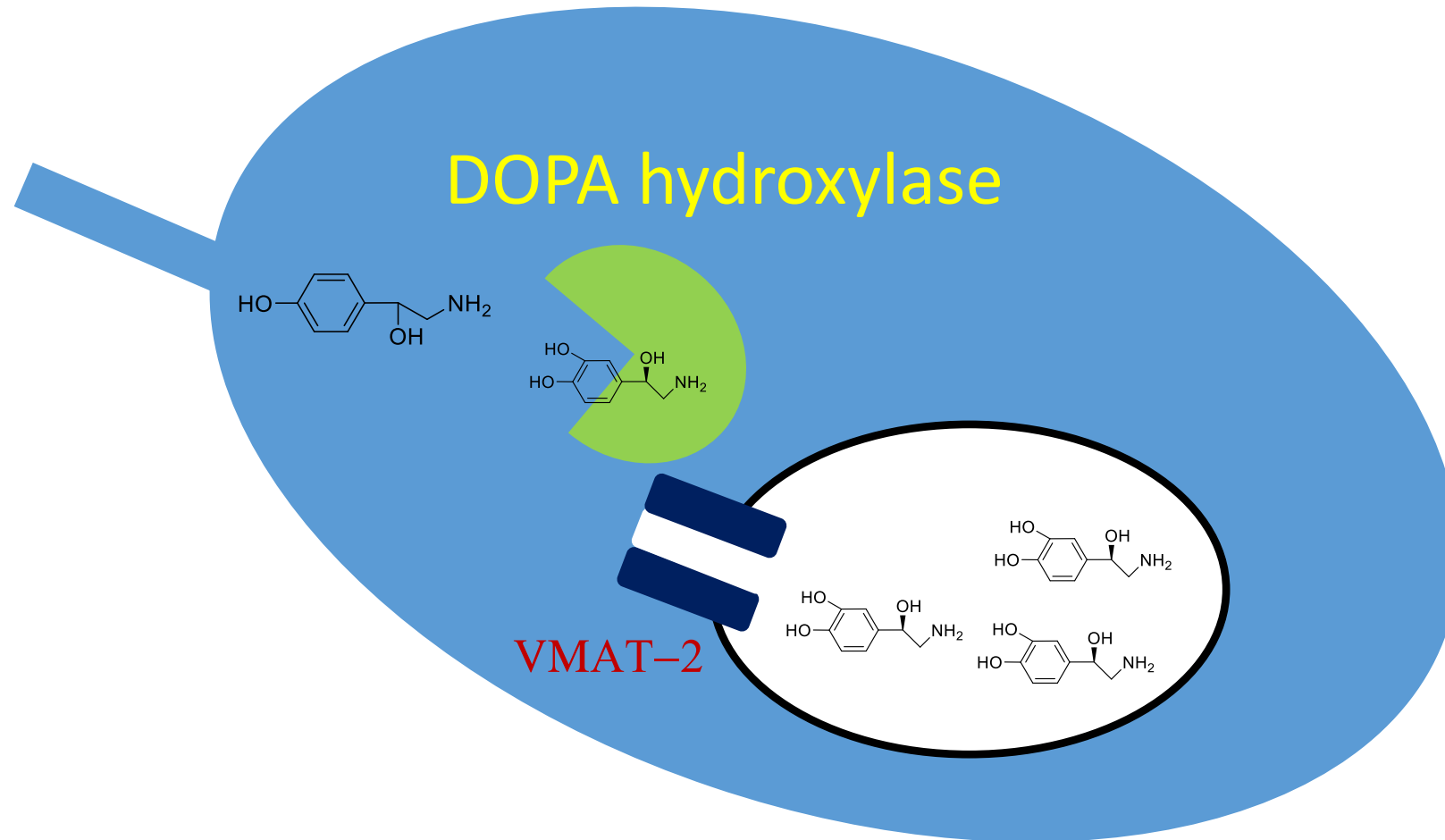
- **Sympathomimetics** – direct (can be specific) / indirect
- **Sympatholytics** - currently only direct (blockers) are used
 - historically reserpine (indirect)



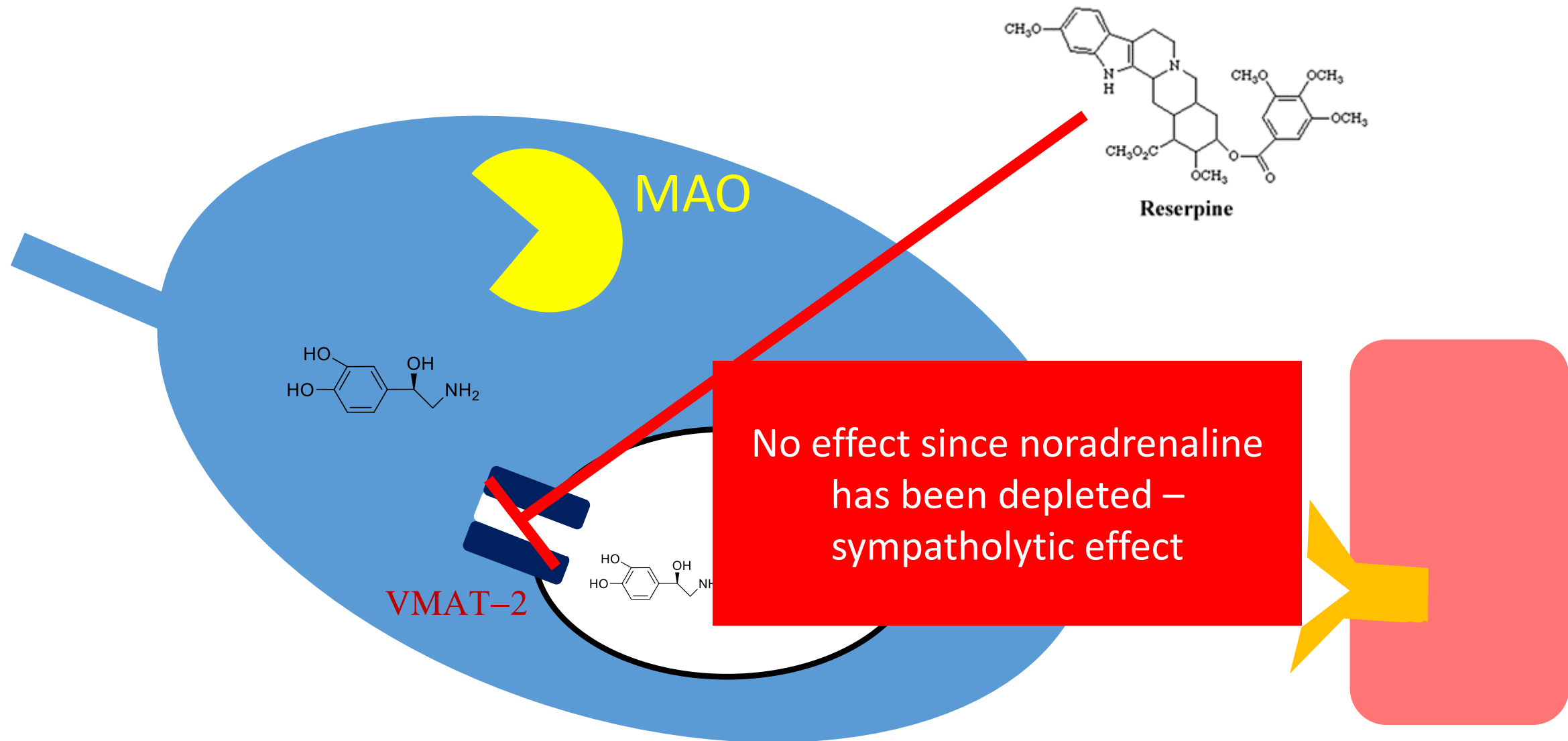
Reserpine



Sympathetic nerve terminal

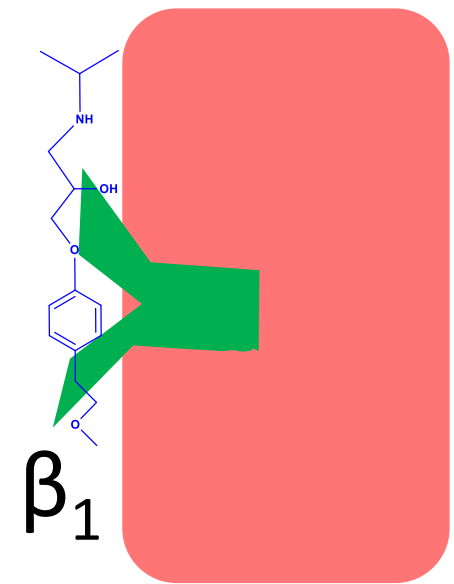
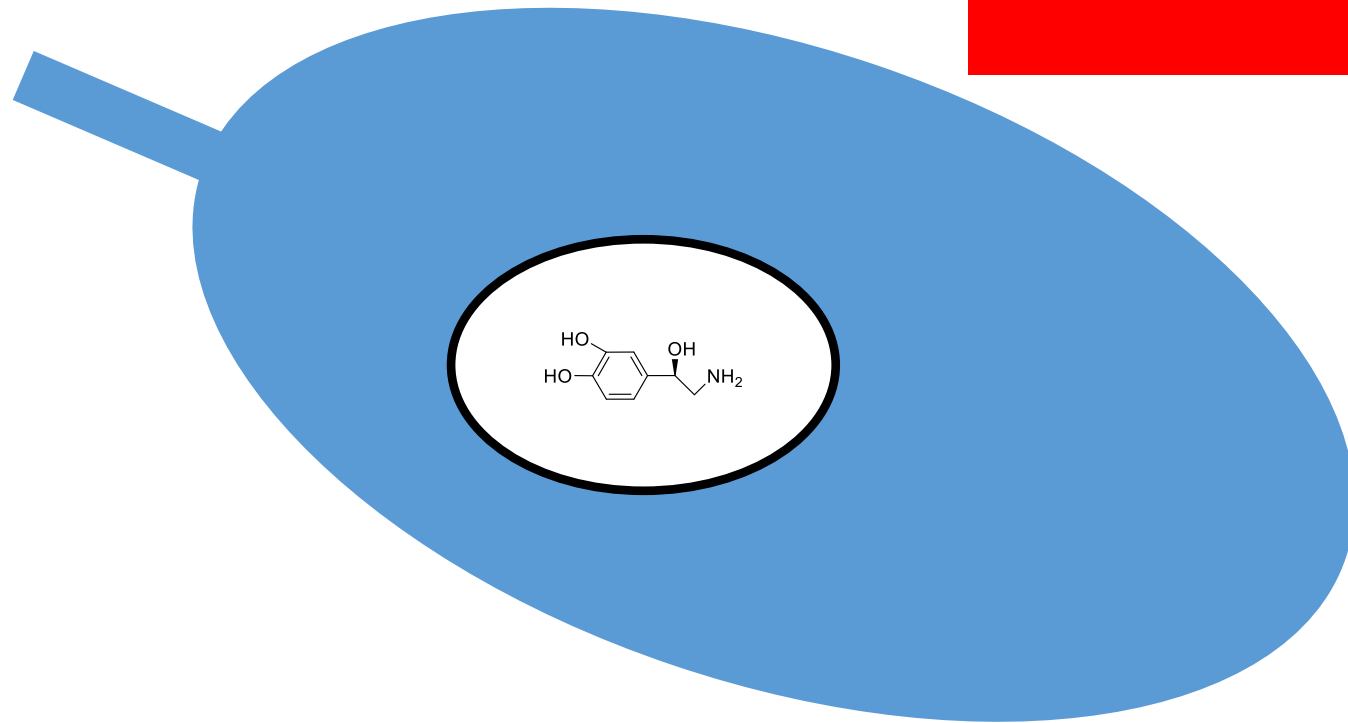


Sympathetic nerve terminal – indirect sympatholytic effect



Direct sympatholytic effect

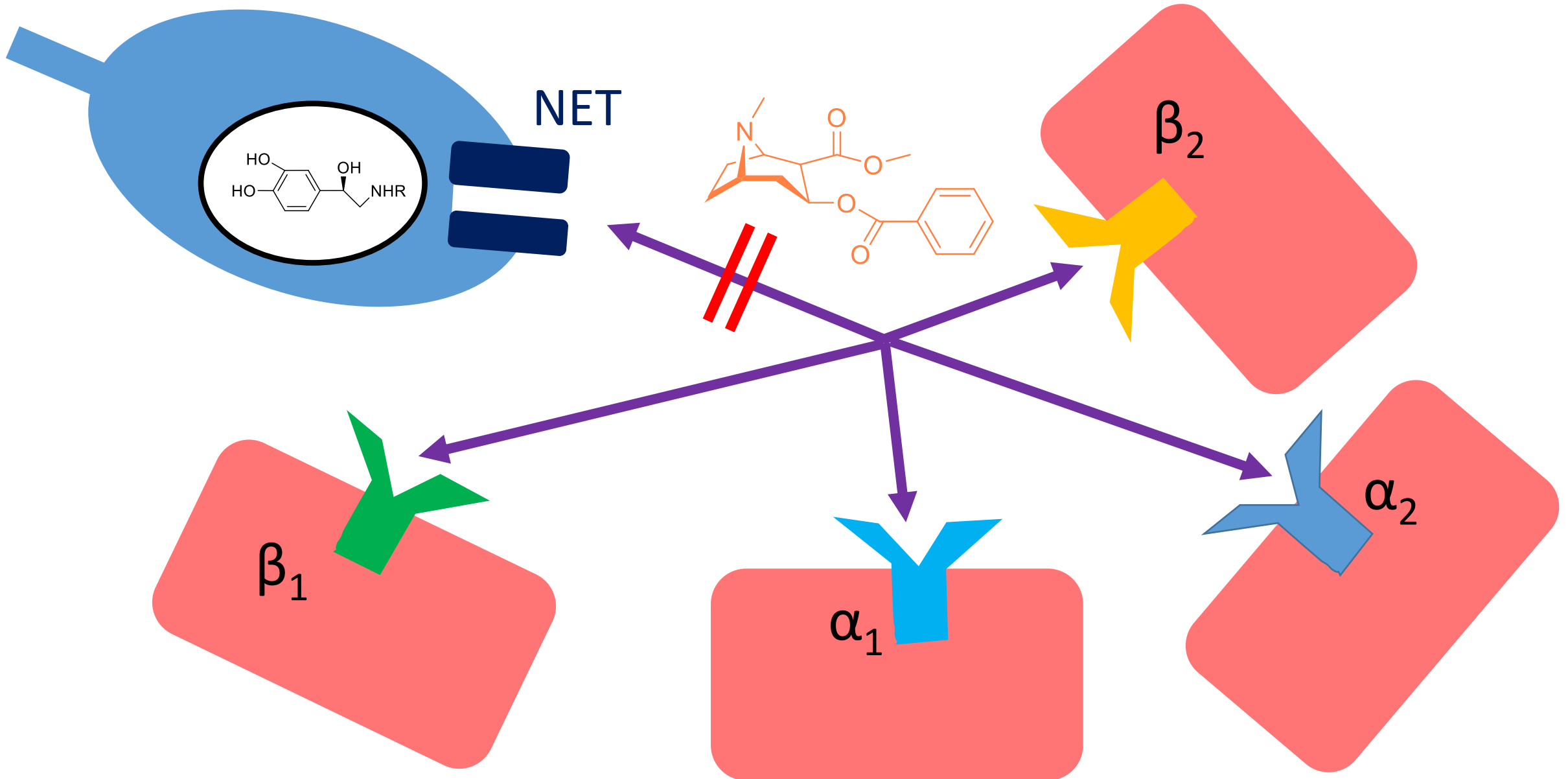
Noradrenaline is released but
has no effect

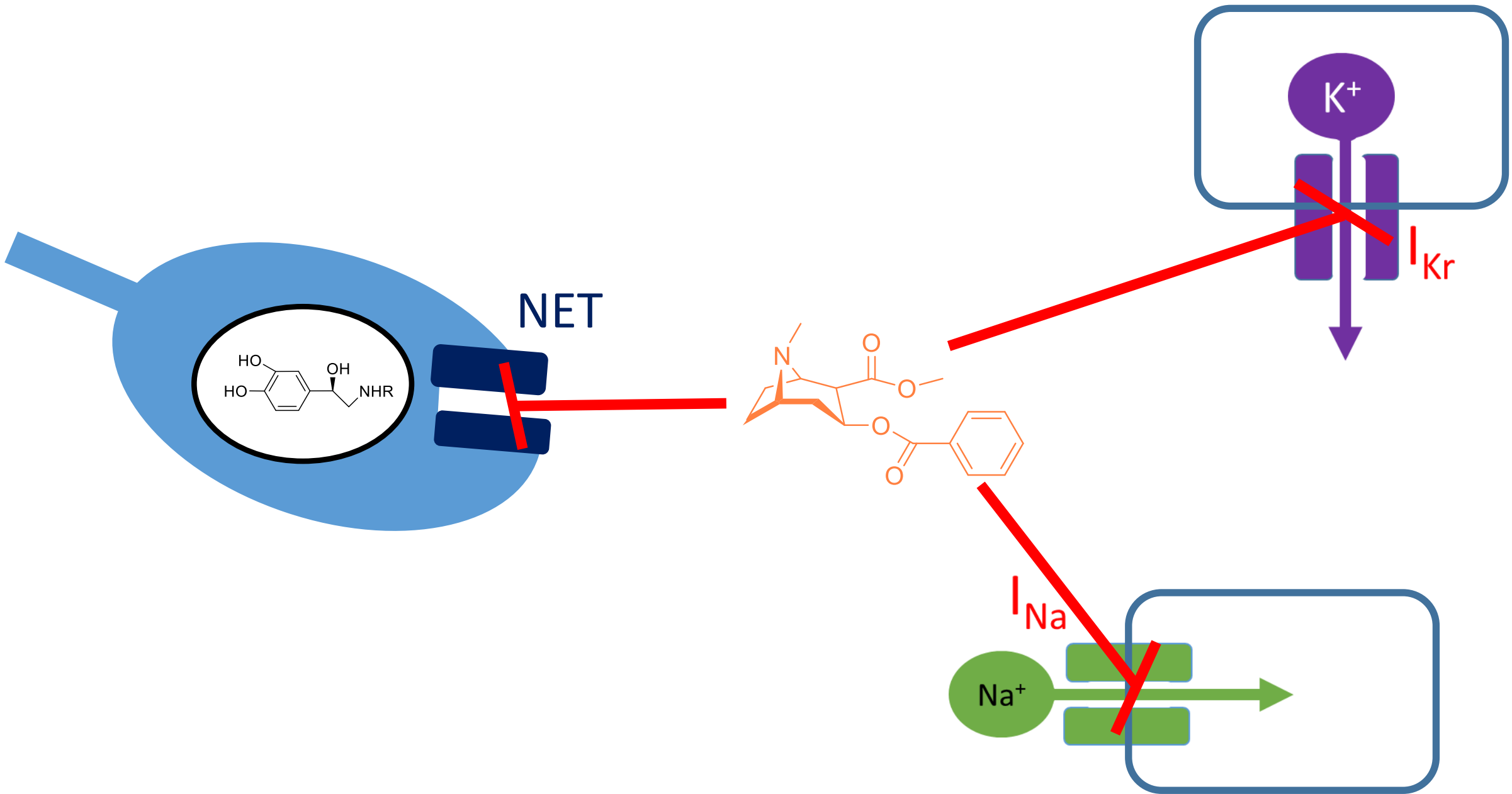


Classification of drugs acting at adrenergic receptors




















- Indirect sympathomimetics
- Drugs acting at α_1 -receptors – agonists and antagonists
- Drugs acting at α_2 -receptors – agonists and antagonists
- Drugs acting at β -receptors – agonists and antagonists

Indirect sympathomimetics I - cocaine





Cocaine: An Updated Overview on Chemistry, Detection, Biokinetics, and Pharmacotoxicological Aspects including Abuse Pattern

by  Rita Roque Bravo ^{1,2,†} ,  Ana Carolina Faria ^{1,2,†} ,  Andreia Machado Brito-da-Costa ^{1,2,3}  ,
 Helena Carmo ^{1,2}  ,  Přemysl Mladěnka ⁴  ,  Diana Dias da Silva ^{1,2,3,*}  ,
 Fernando Remião ^{1,2,*}   and on behalf of The OEMONOM Researchers ‡

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⁴ Department of Pharmacology and Toxicology, Faculty of Pharmacy, Charles University, 500 05 Hradec Králové, Czech Republic

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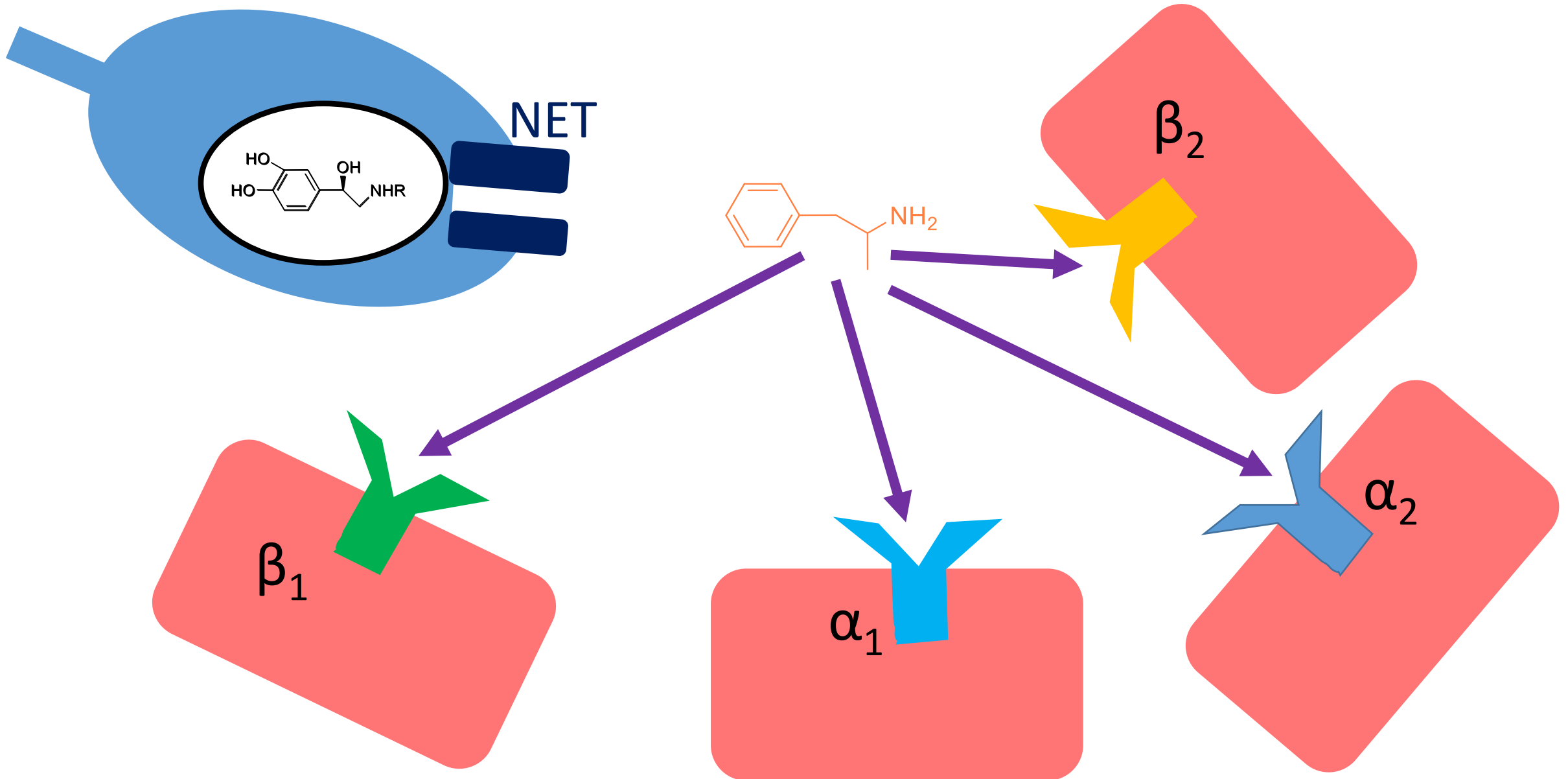
† These authors contributed equally to this work.

‡ Listed at the end of the acknowledgments.

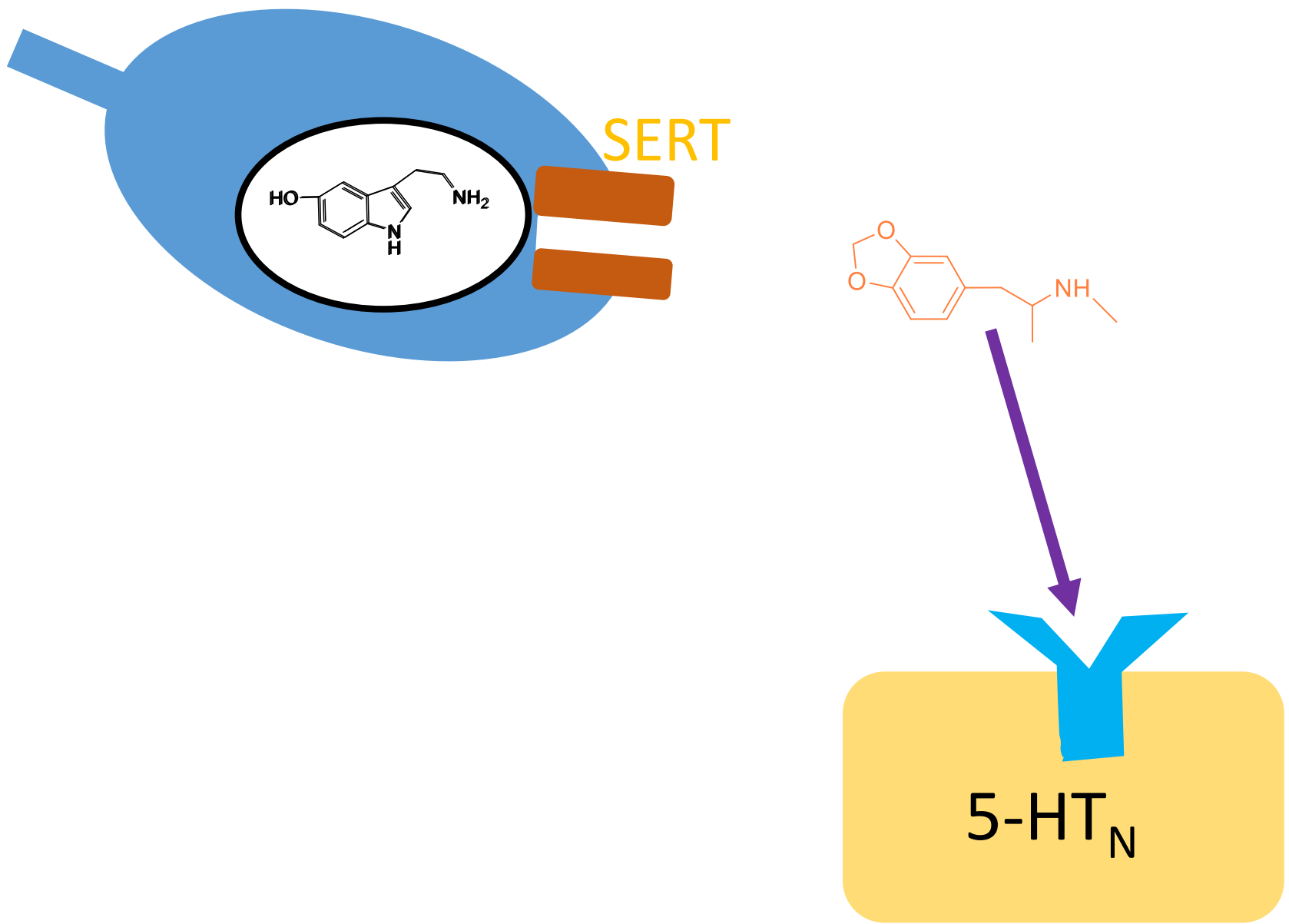
Toxins **2022**, *14*(4), 278; <https://doi.org/10.3390/toxins14040278>

Received: 7 March 2022 / Revised: 30 March 2022 / Accepted: 7 April 2022 / Published: 13 April 2022

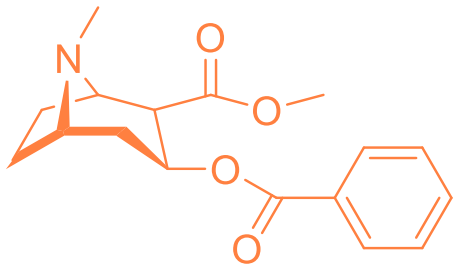
Indirect sympathomimetics II – amphetamine(s)



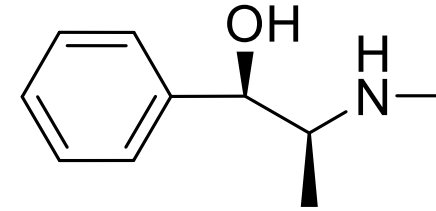
amphetamine(s) – effect on other neurotransmitters



cocaine



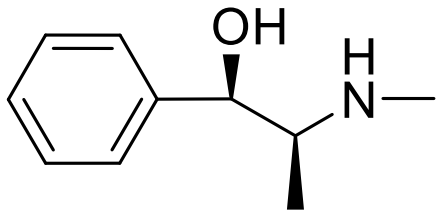
ephedrine



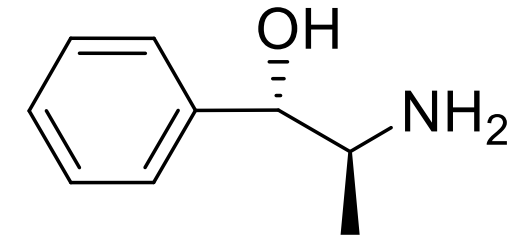
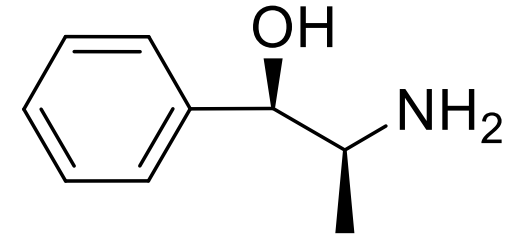
1R,2S-ephedrine /(-)-ephedrine/



Ephedra “ma huang”

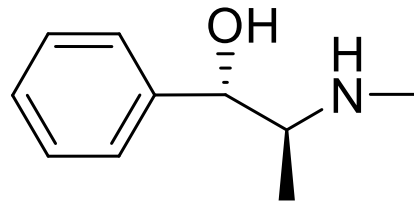


1R,2S-ephedrine /(-)-ephedrine/

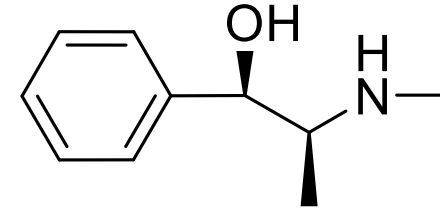


phenylpropanolamine

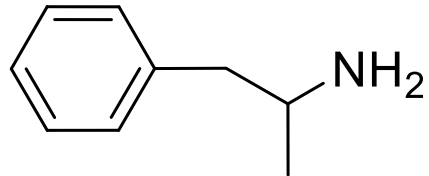
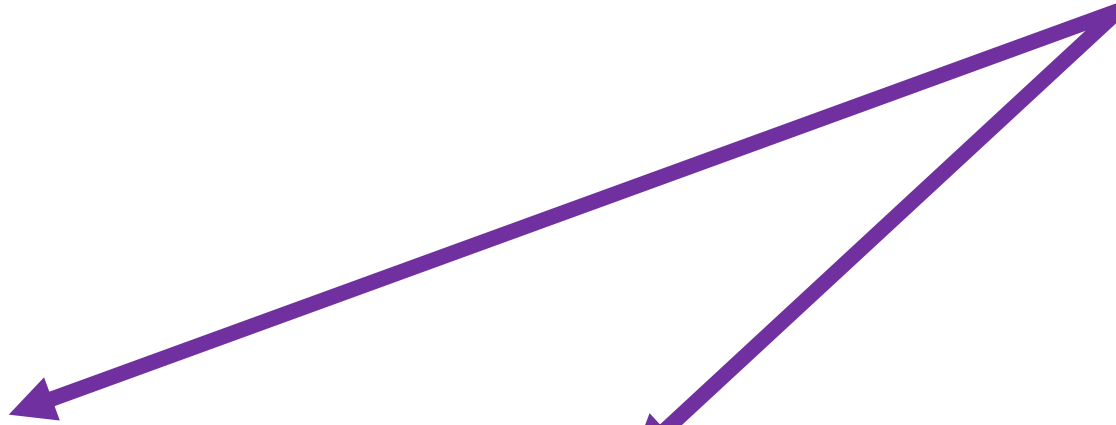
(norephedrine + norpseudoephedrine)



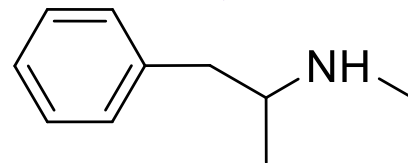
1S,2S-pseudoephedrine /(+)-pseudoephedrine/



1R,2S-ephedrine /(-)-ephedrine/

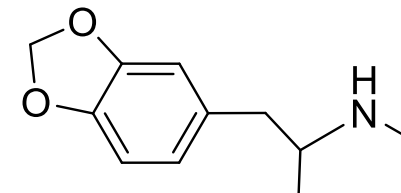


amphetamine



methamphetamine

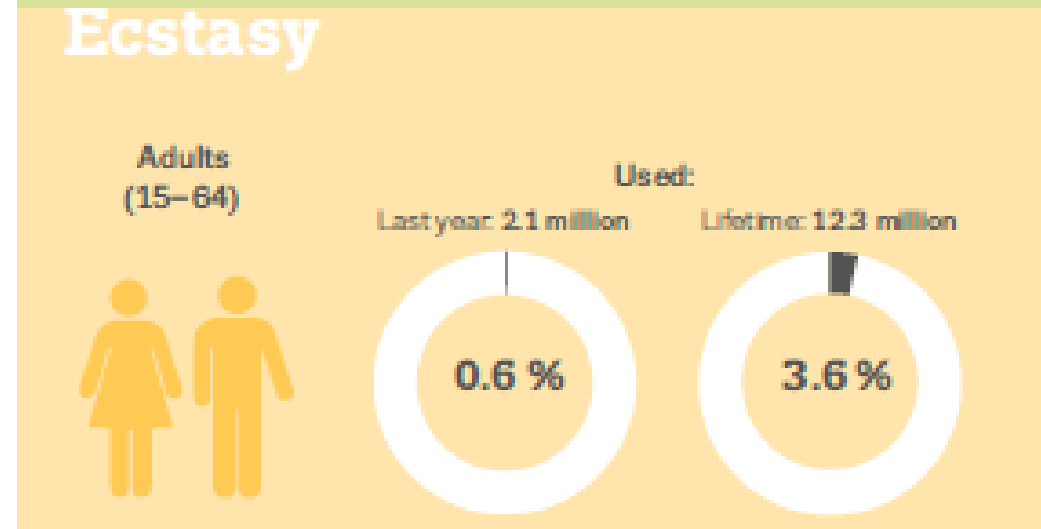
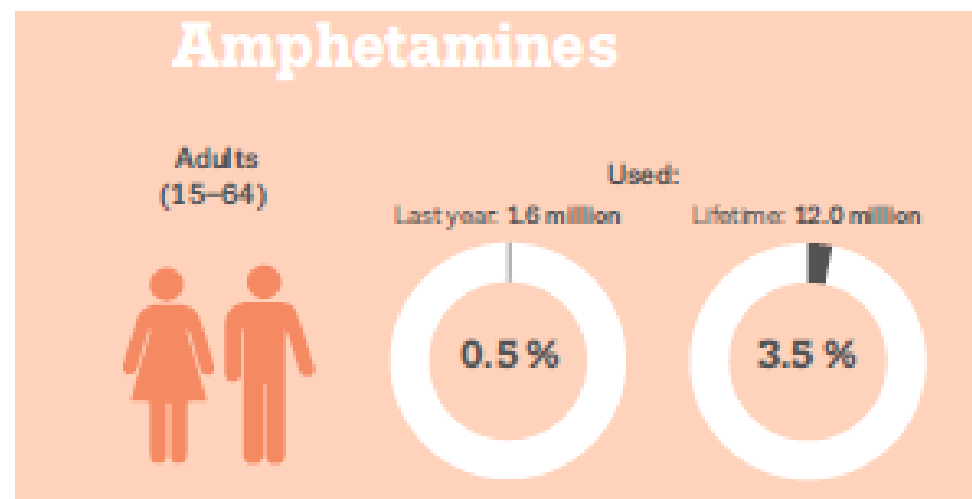
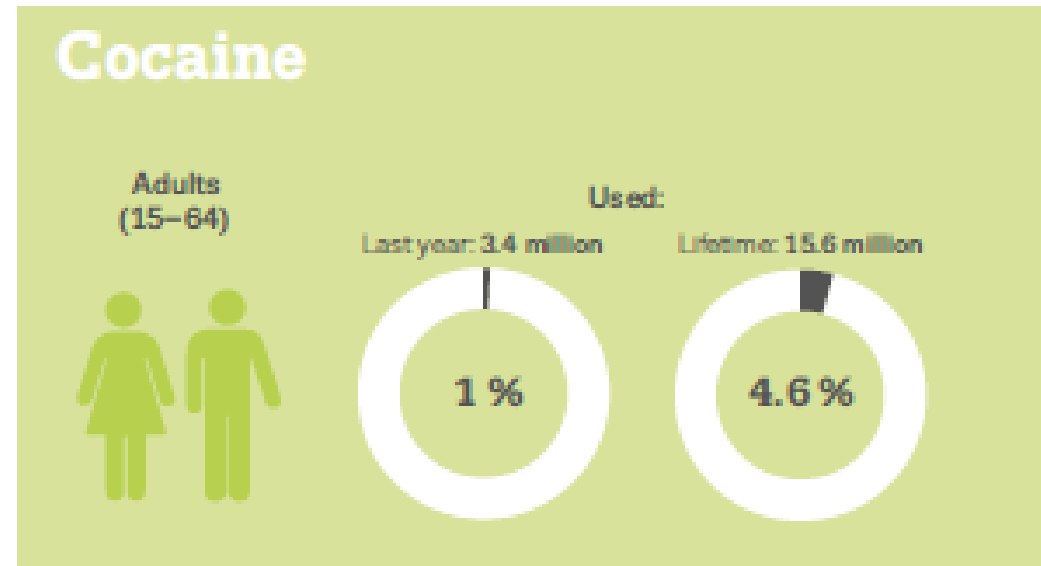
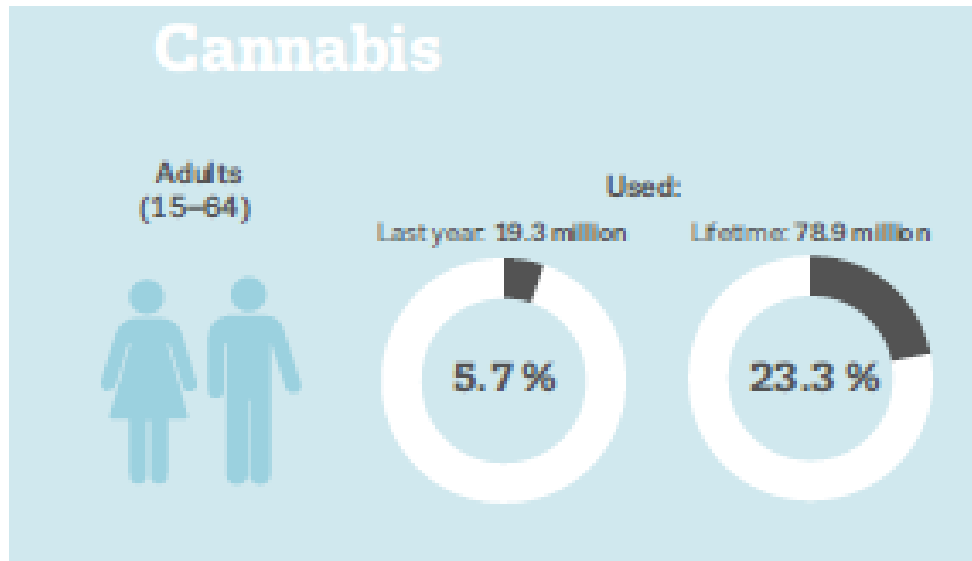
known also as **Pervitin**



methylenedioxymethamphetamine (MDMA)

known also as **Ecstasy**

Illicit drugs long-life experience (European drug report 2015)

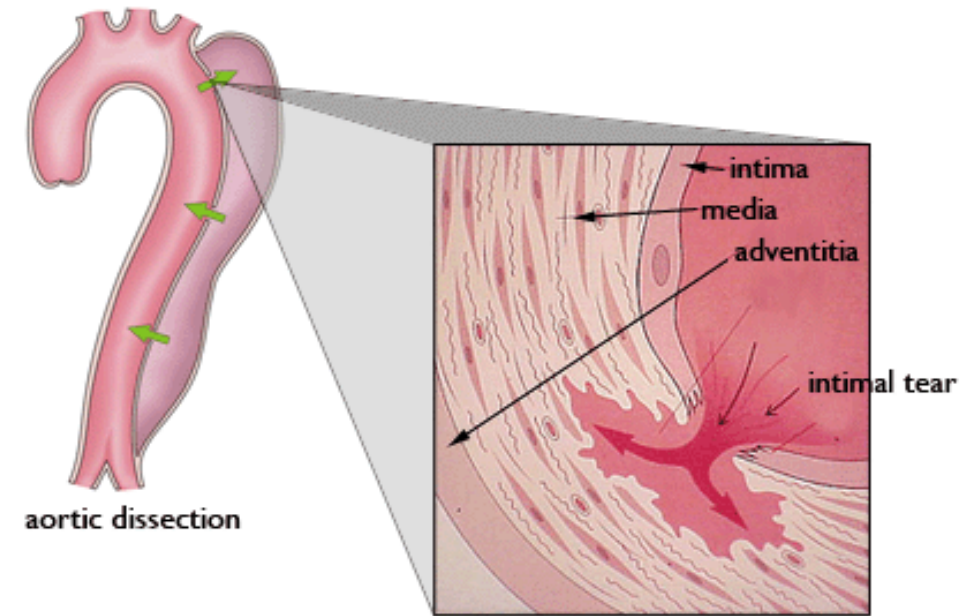


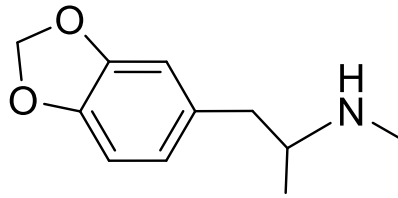
Therapeutic or claimed use of ephedra and purified alkaloids

- nasal decongestants, bronchodilators, CNS-stimulants, anti-obesity and anti-narcolepsy drugs, for ADHD and for improved athletic performance.
- Ephedra products were banned in the U.S. in 2003 with implementation in 2004
- Their stimulant properties were also enjoyed by soldiers in World War II, who were supplied amphetamines to counteract fatigue and to increase vigilance.

Cardiovascular adverse effects of sympathomimetics

- chest pain, hypertension and tachycardia
- acute myocardial infarction even in the absence of coronary artery disease
- dysrhythmias (probably more common in the case of cocaine)
- hemorrhagic and ischemic strokes and acute aortic dissection
- fatalities are mostly AMI, sudden cardiac death and aortic dissection (at least in the case of metamphetamine)
- long-term abuse cardiomyopathy
- amphetamines, in particularly MDMA, hyperthermia



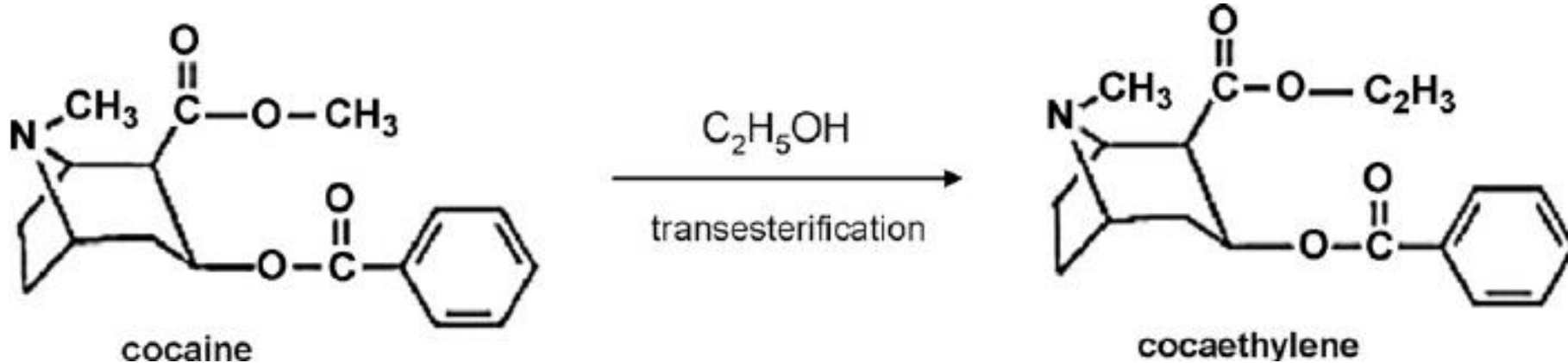


methylenedioxyamphetamine (MDMA)

- There is a popular belief that does not produce serious toxicity
- Serious complications and mortality are really lower than on cocaine and amphetamines however
- Changes in blood pressure and heart rate can be substantial (40 mm Hg, 30 beats)
- Indeed cardiac or cerebrovascular reasons (e.g. subarachnoid hemorrhage) can be the reason for fatalities together with accidents
- **Fatality rate 0.2-5 per 10 000 users**
- Commonly other drugs are employed in death (according to one AUS study – 1/3 morphine, 30% alcohol, 10% cocaine and 13% cannabinoids)

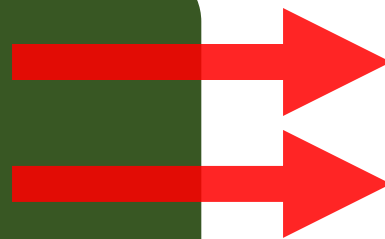
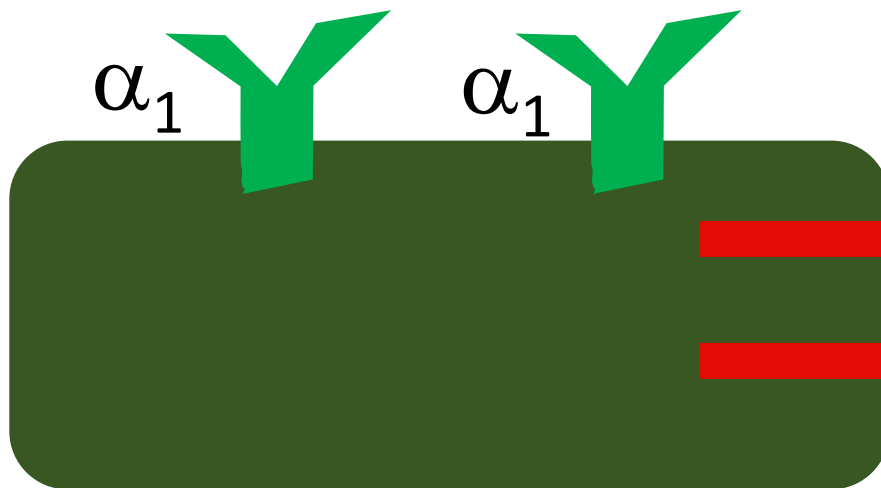
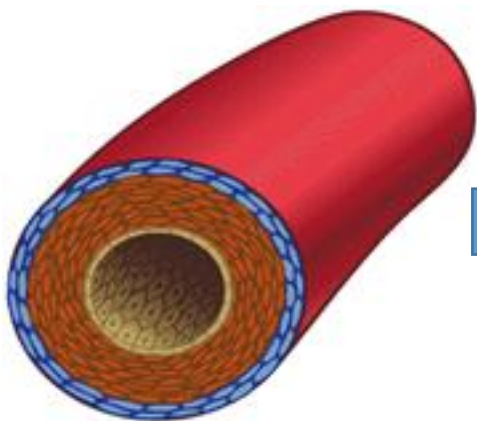
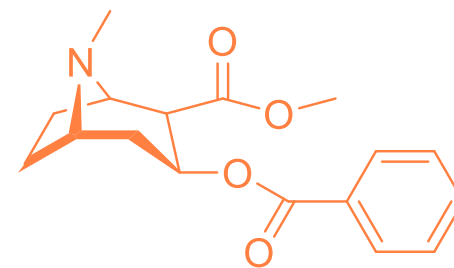
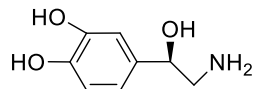
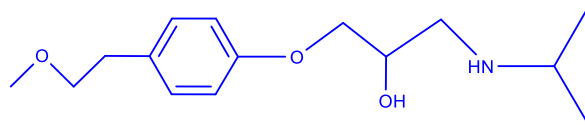
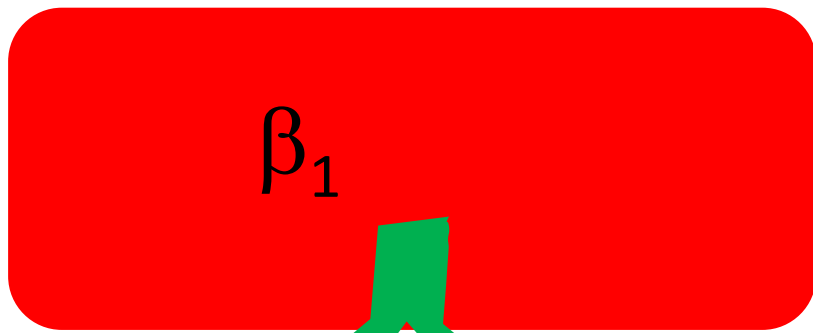
cocaine + ethanol

- A common combination – in patients presented at emergency departments about 36% also ingested alcohol
- In those who died, cocaine levels were lower on autopsy in cases of cocaine + ethanol
- Cocaethylene is formed and has Na^+/K^+ -channel blocking properties

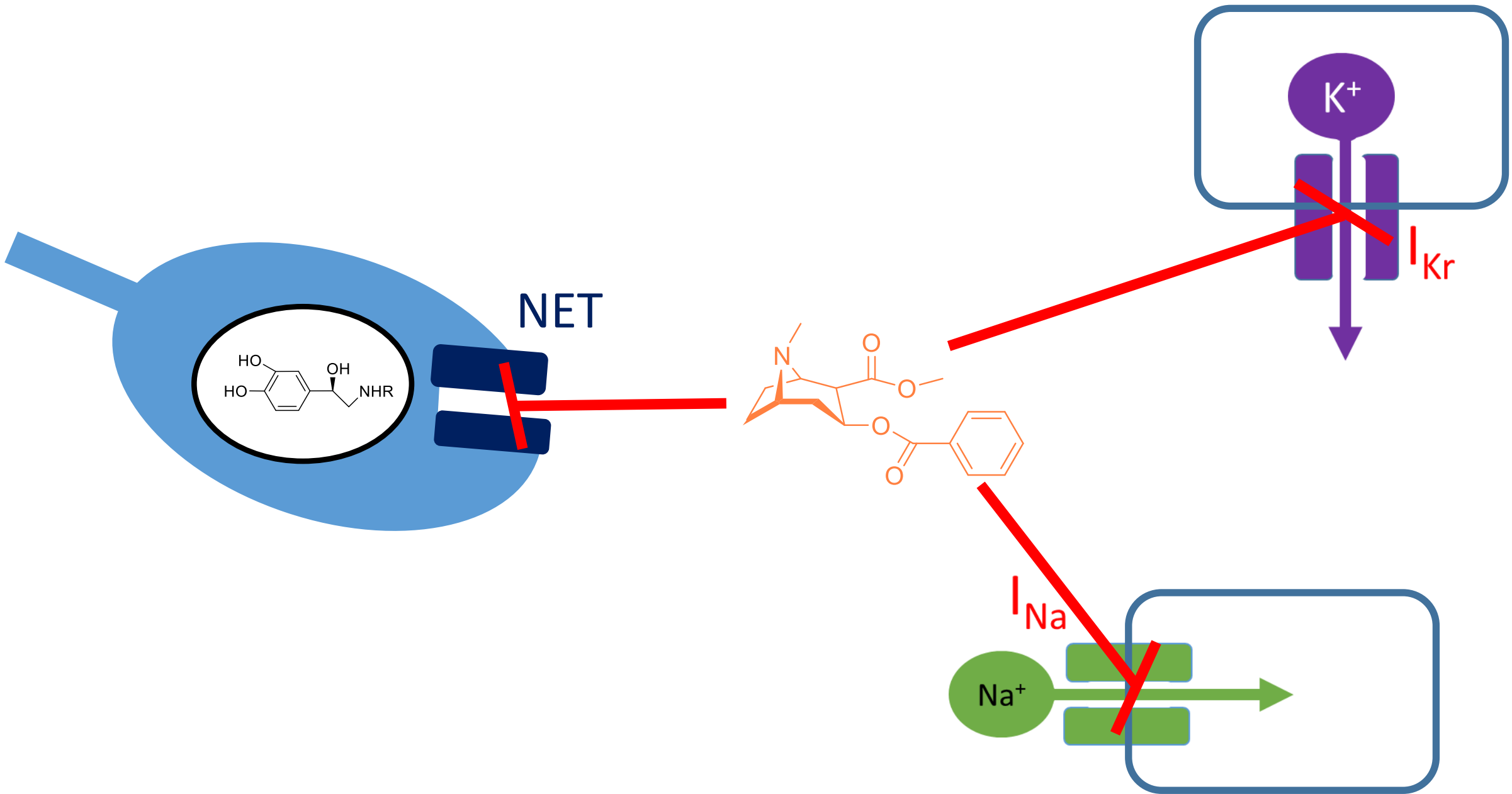


Treatment of cardiotoxicity cause by indirect sympathomimetics

- benzodiazepines as the drug of 1st choice
 - possibly dexmedetomidine, an α_2 -adrenoreceptor agonist
- no betablockers (potentially mixed α/β -blockers can be employed)
- common means of AMI and HF treatment
- dysrhythmias – cocaine the best available treatment is hypertonic sodium bicarbonate. Lidocaine for amphetamines, possibly also in the case of cocaine
- hyperthermia – cooling if needed



**hypertension
and
consequences**

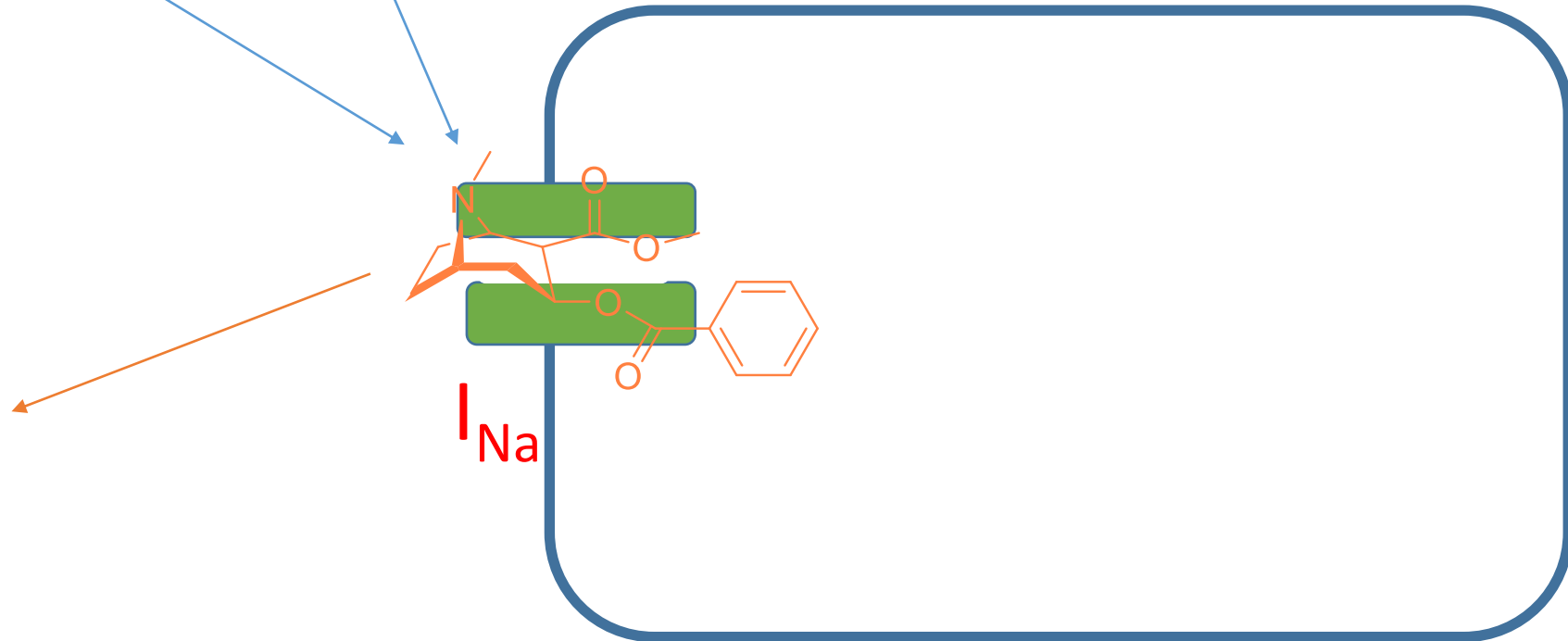


NaHCO_3

NaHCO_3

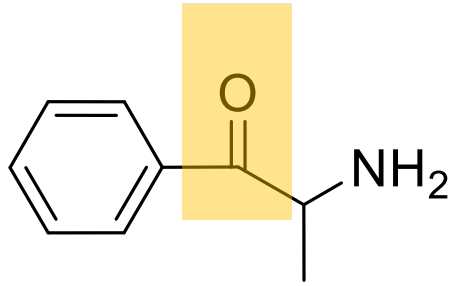
NaHCO_3

NaHCO_3

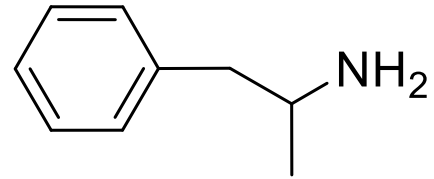


Na

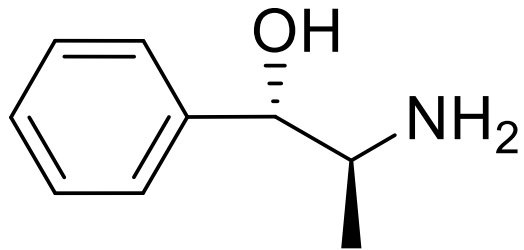
Cathinones – other sympathomimetics



cathinone



amphetamine






cathine



Review

Khat, a Cultural Chewing Drug: A Toxicokinetic and Toxicodynamic Summary

Bárbara Silva ^{1,2,*} , Jorge Soares ^{1,2}, Carolina Rocha-Pereira ^{1,2,3}, Přemysl Mladěnka ⁴ , Fernando Remião ^{1,2,*} 
and on behalf of The OEMONOM Researchers [†]

Toxins **2022**, *14*, 71. <https://doi.org/10.3390/toxins14020071>

In East African countries, the dependence on this plant was estimated to be 5–15% of the population

khat dependence in Yemen: male subjects 49% (Yemen, 2016), similar previous reports: 51% in the UK, 52% in Saudi Arabia, and 44% in Australia

cathinones

“bath salts” in America and “plant food” in Europe

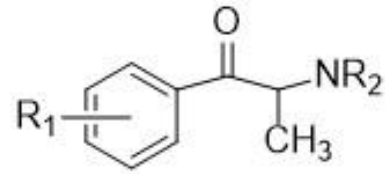
brand names such as “Ivory Wave”, “Purple Wave”, „Vanilla Sky”, “Red Dove”



alamy stock photo

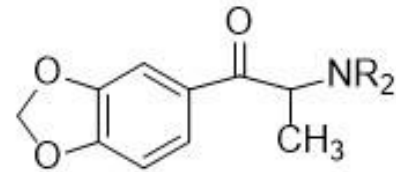
BLXPLT
www.alamy.com

cathinones



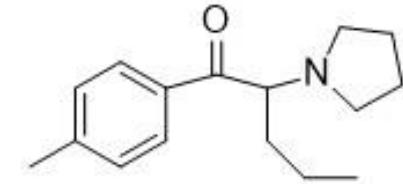
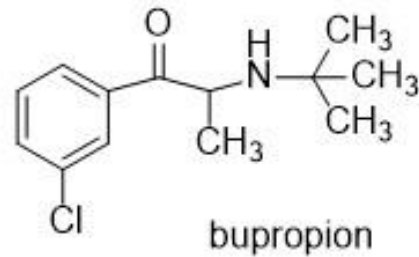
close cathinone derivatives

	R ₁	R ₂
cathinone	-	-H ₂
dimethylcathinone	-	-(CH ₃) ₂
ethcathinone	-	-C ₂ H ₅
3-fluoromethcathinone	3-F	-CH ₃
4-fluoromethcathinone	4-F	-CH ₃
mephedrone	4-CH ₃	-CH ₃
methcathinone	-	-CH ₃
methedrone	4-OCH ₃	-CH ₃

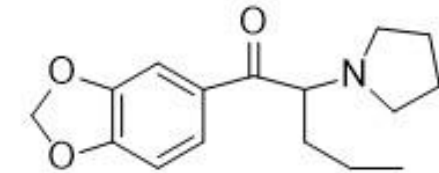


methylenedioxcathinone derivatives

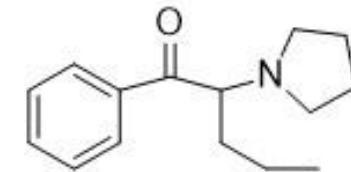
	R ₂
ethylone	-C ₂ H ₅
methylone	-CH ₃



pyrovalerone



methylenedioxyvalerone



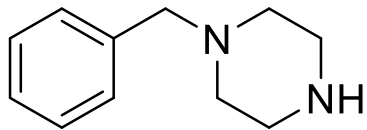
flakka (α -pyrrolidinovalerophenone, α -PVP)

Cardiovascular toxicity of cathinones

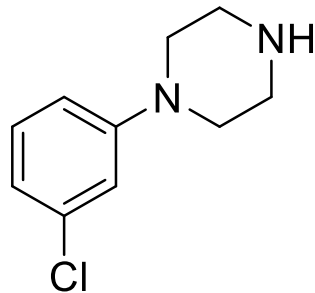
- Considered, in general, less potent than amphetamines
- Similar mechanism of action, similar cardiovascular side effect and similar treatment possibilities

piperazines

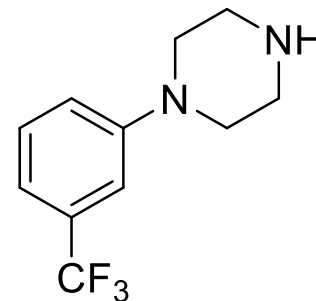
- “legal Ecstasy”, their abuse started in 90s
- also α_2 -receptors can be involved
- about 10% potency of amphetamines, quite long effect (6-8 hours)
- sometimes even calm environment can normalize tachycardia and hypertension, in severe cases clonidine



1-benzylpiperazine



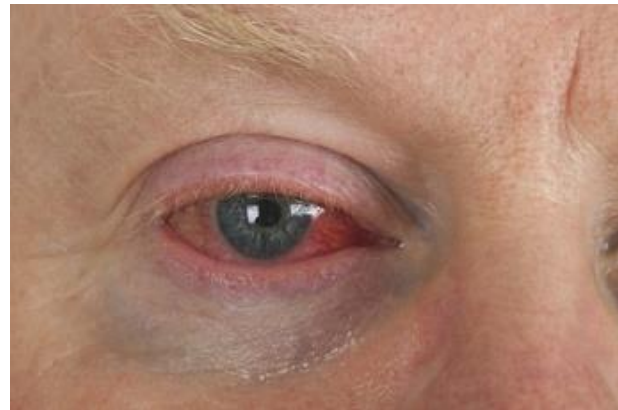
1-(3-chlorophenyl)piperazine



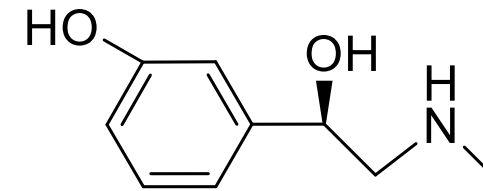
1-(3-trifluoromethyl)piperazine

α_1 -agonists

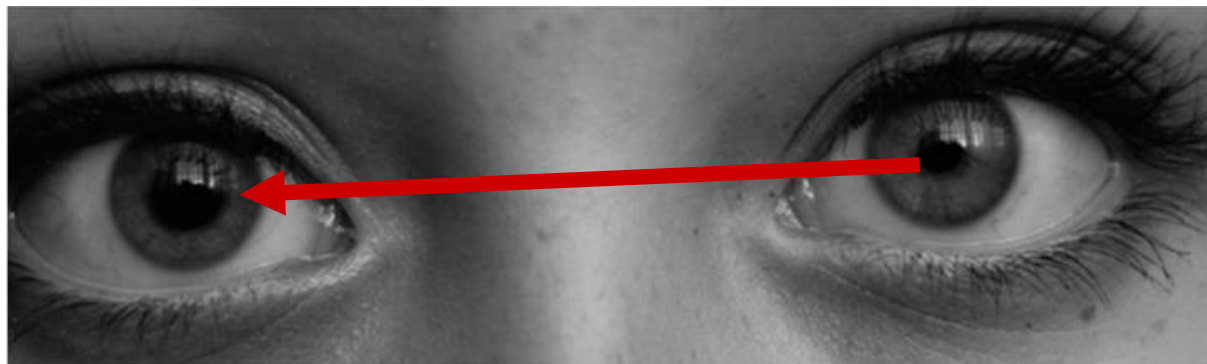
Therapeutic use:



orally for common cold



phenylephrine /m-synephrine/



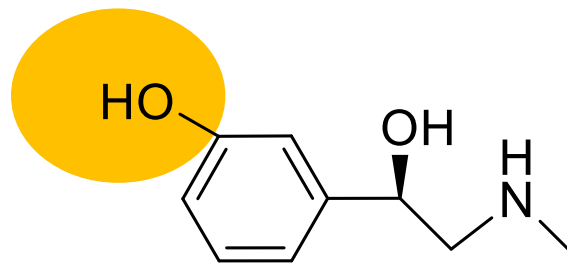
α_1 -agonists - p-synephrine



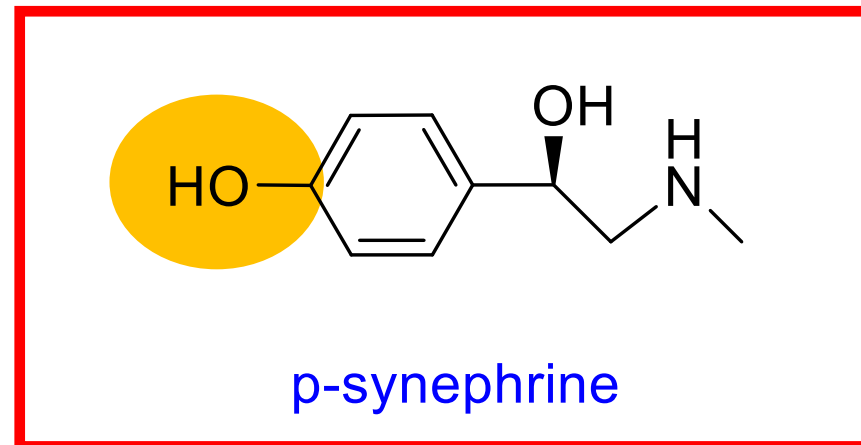
- isomer of phenylephrine

Claimed use: increase in athletic performance and/or promote body weight loss

Phenylephrine 6x less affinity than noradrenaline on α_1 -receptors while p-synephrine 1000x



phenylephrine /m-synephrine/



p-synephrine



cardiovascular side effects of α_1 -agonists

- increase in blood pressure
 - possibly with reflex bradycardia
- rarely hemorrhagic or ischemic stroke
- side effects can follow also local administration

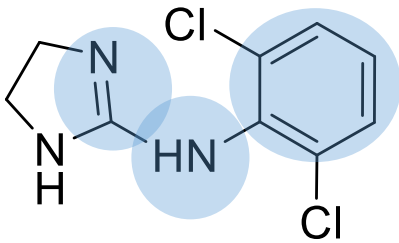
α_1 -antagonists

Therapeutic use: hypertension and BPH – low risk of hypotension

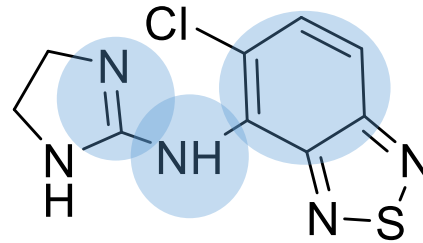
But there are drugs used for other purposes which also block α_1 -receptors:

- TCA
- Antipsychotic drugs – basal and MARTA
- Risk of hypotension (also orthostatic hypotension) with possible
 - Fractures and lacerations
 - Myocardial infarction and sudden cardiac death

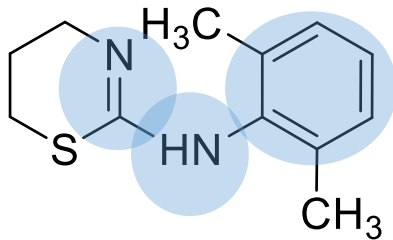
α_2 -agonists



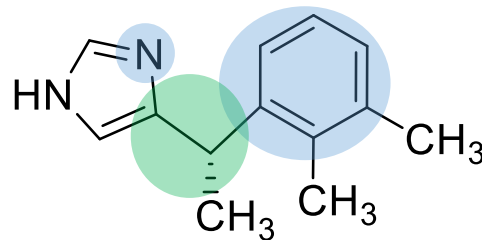
clonidine – hypertension



tizanidine – muscle relaxation

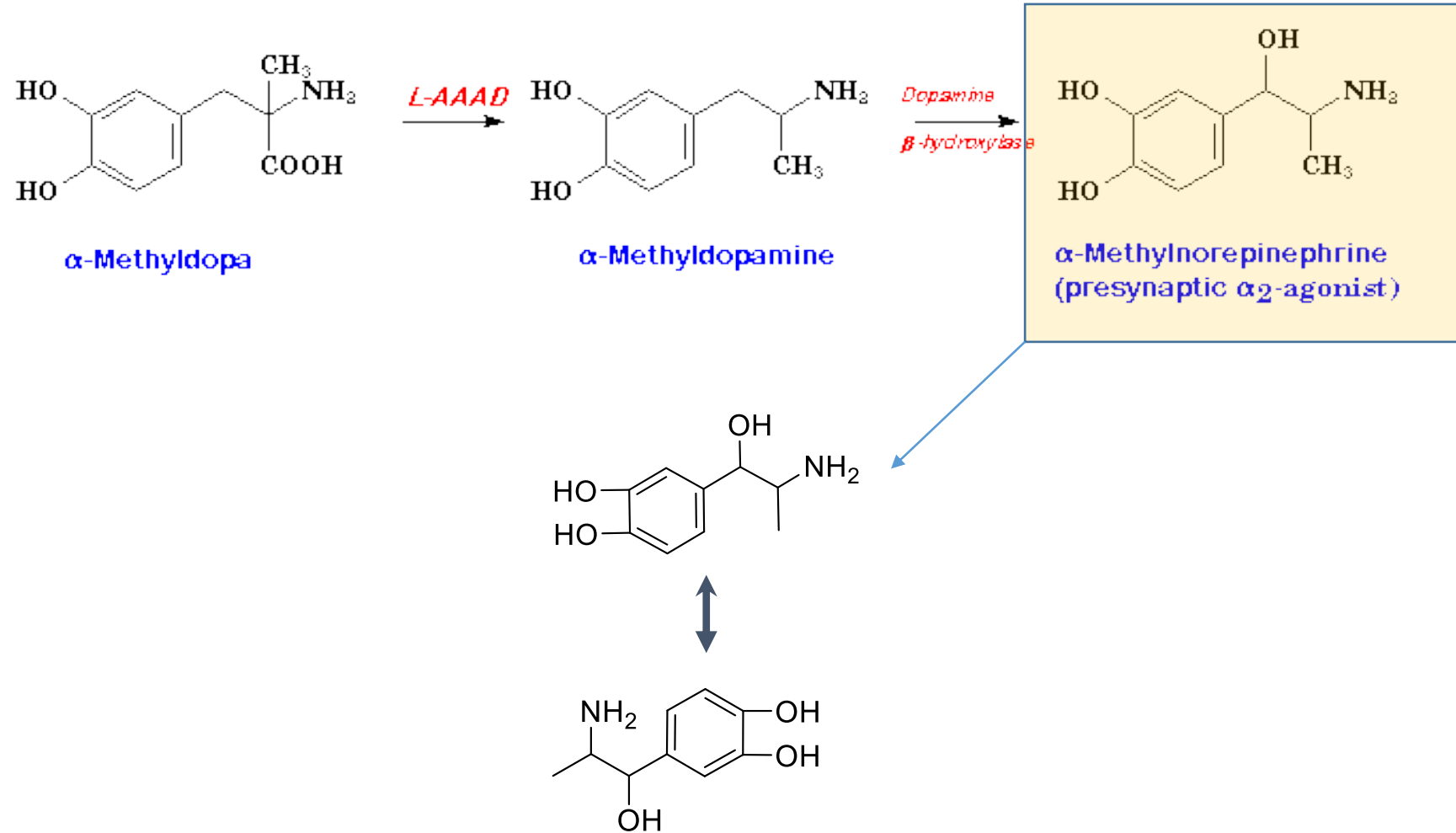


xylazine – anesthesia in animals

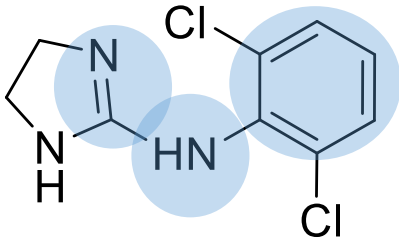


dexmedetomidine – sedation/anesthesia in humans

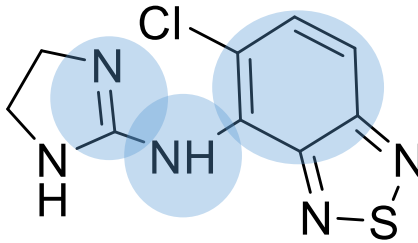
methyldopa



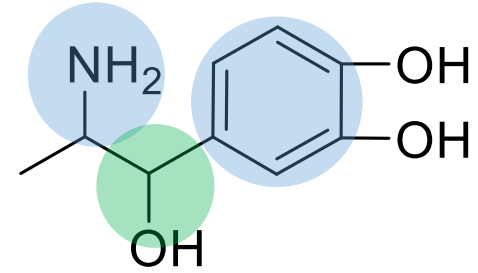
α_2 -agonists



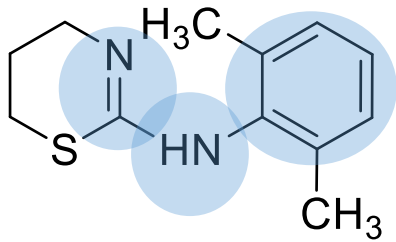
clonidine



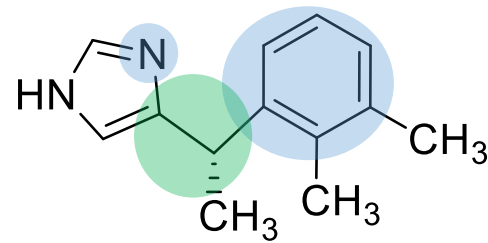
tizanidine



active metabolite of methyldopa



xylazine



dexmedetomidine

α_2 -agonists CARDIOVASCULAR EFFECTS

- **α_2 -agonists** used for hypertension (methyldopa, clonidine)
 - low risk – a decrease in blood pressure is anticipated and positive effect
 - There can be bradydysrhythmias (bradycardia or AV blocks)
- Other **α_2 -agonists**
 - CV effect are not primarily expected from the patient point of view, moreover, some of them are frankly misused as adulterants in illicit drugs – higher risk of toxicity

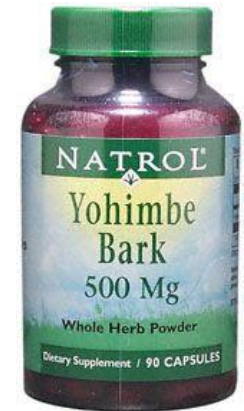
α_2 -agonists INTOXICATION TREATMENT

- There are no well established protocols since the intoxication is rather rare
- Possibly activated charcoal
- i.v administration of atropine, possibly dopamine
- Formerly yohimbine, currently atipamezol
- Initial hypertension after α_2 -agonists administration does not require treatment in the majority of cases (possibly nitroprusside can be used)



Yohimbine (also known as quebrachine)

- Isolated from *Pausinystalia yohimbe*
- an antagonist at α_2 -receptors

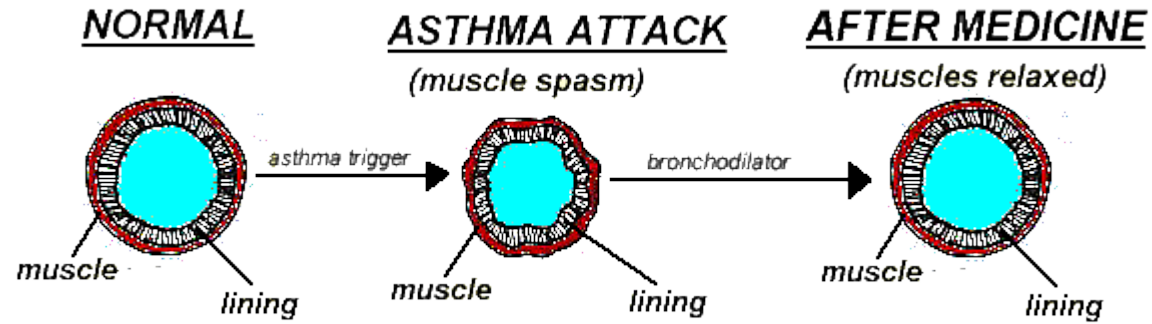




yohimbine

- antagonism at α_2 -receptors in the periphery – vasodilation of pelvic area – erectile dysfunction treatment
- Other claims – improvement in athletic performance, bodybuilding and weight loss
- Central effect - dose-dependent increase in blood pressure and heart rate
- Short half-life → short duration of the effect
- Treatment is not needed in most patients
- Cardiovascular effects resolve mostly spontaneously within several hours
- Fatal cases are extremely rare

β_2 -agonists



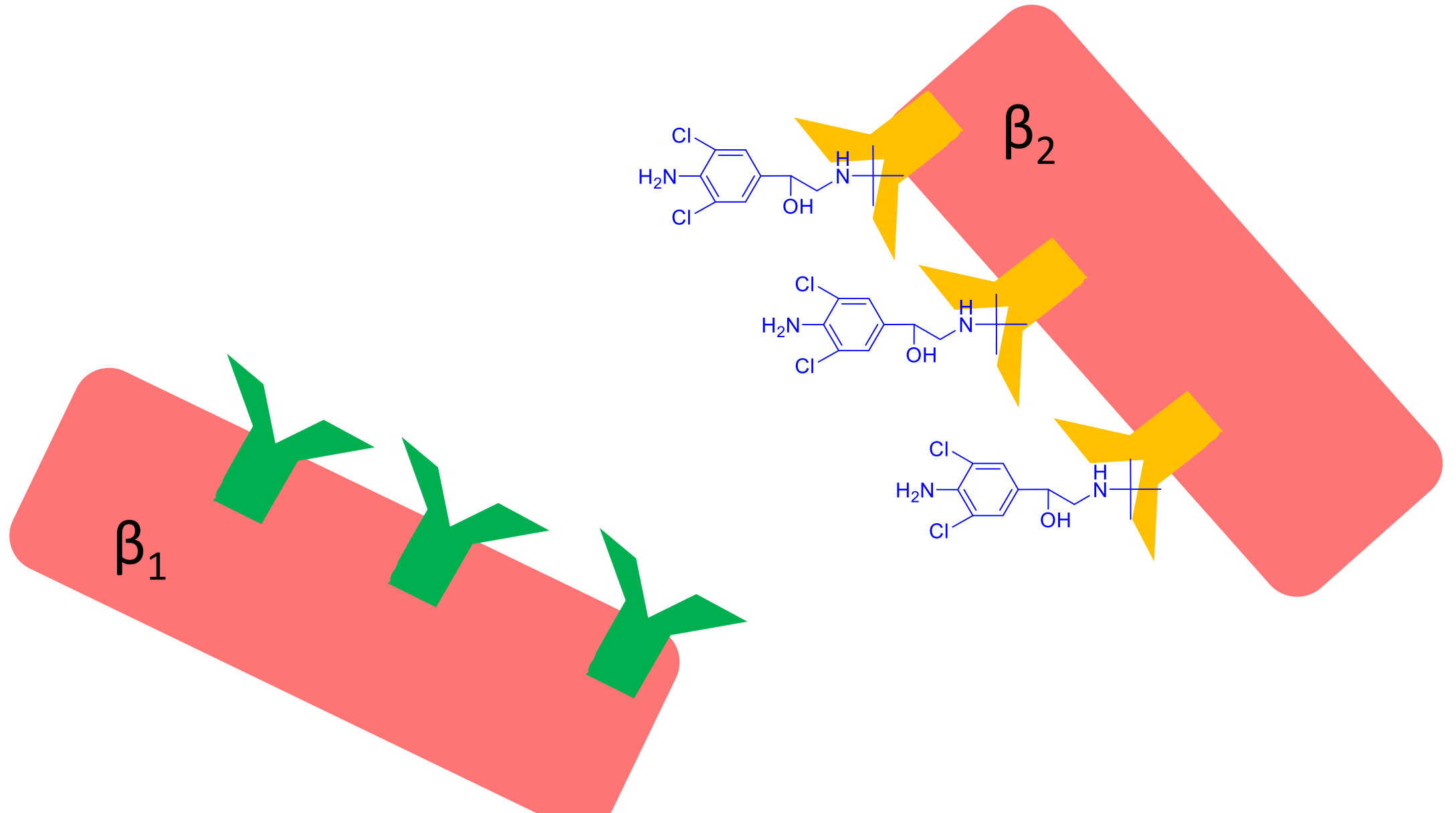
- Asthma and COPN
- Tocolytics
- (ab)used in the sport



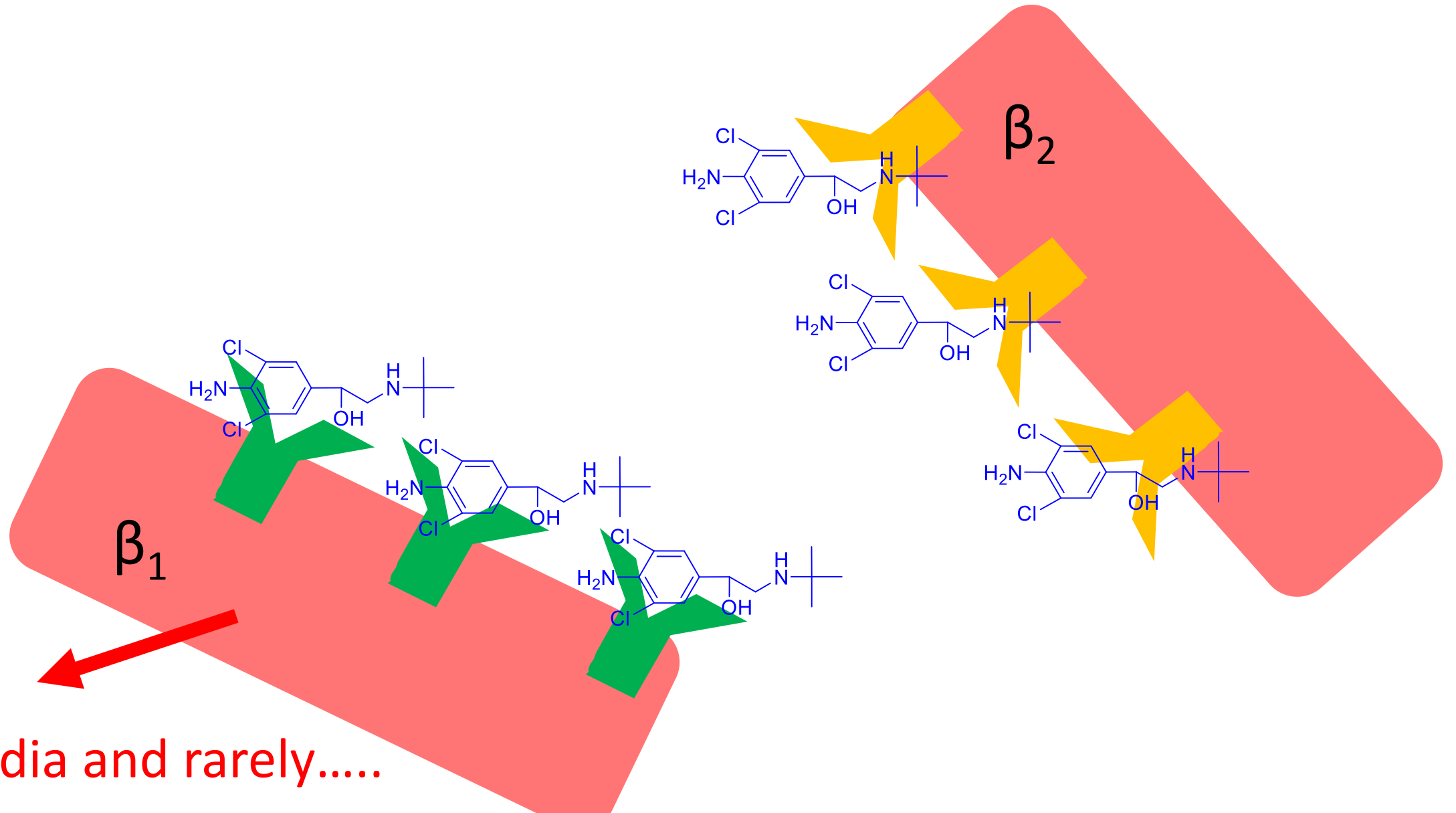
β_2 -agonists

- CV effect - dilation of blood vessels in the striated muscles.
- CV toxic effects:
 - Generally not present
 - hypotension can be observed
 - tachycardia and rarely acute myocardial infarction or dysrhythmias

β_2 -receptors agonists **LOW DOSE**



β_2 -receptors agonists **HIGH DOSE**



β -blockers (β -antagonists)

- Keydrugs in the treatment of many cardiovascular diseases
- However, in overdose, they are important cause of morbidity and mortality
- membrane-stabilizing effect, which manifests as inhibition of myocardial fast sodium channels, contributes to the toxicity