Pharmacology of the ANS II. Sympathomimetics and Sympatholytics

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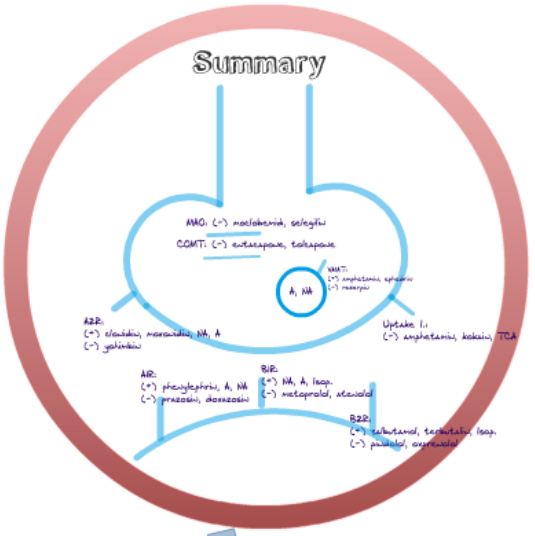

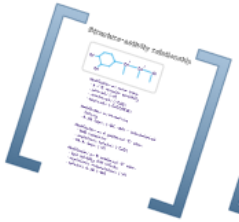

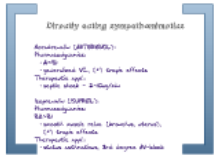

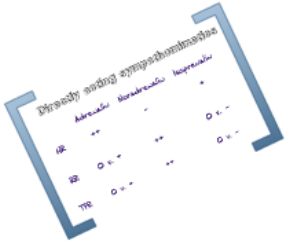

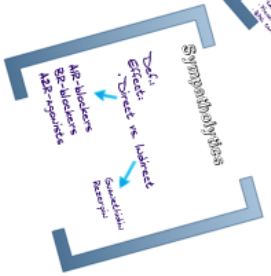

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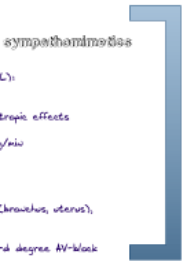
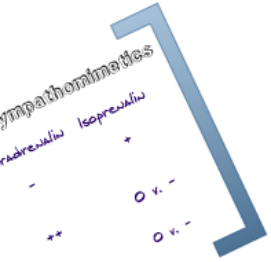
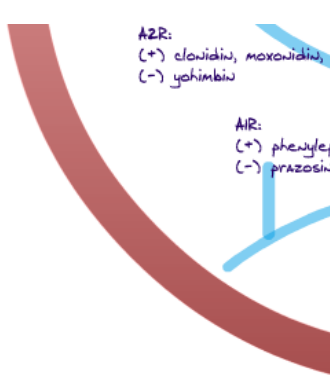
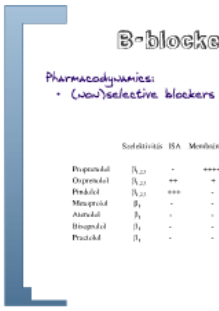
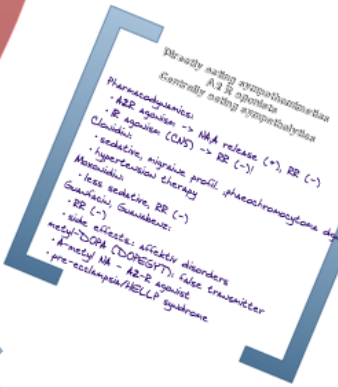










Prezi

Adrenergic transmission

Synthesis:

- Tyrosine -> DOPA -> Dopamine -> NA -> A

Uptake:

- Uptake I: high Km, spec. NA, A, Isop.,
  - (-) TCA, Amph., Kok.
- Uptake II: low Km, A>NA>Isop.,
  - (-) Phenoxybenz.
- Uptake III: vesicular monoamine transport
  - (-) rezerpin

Degradation:

- MAO-A, MAO-B, COMT

Targets of adrenergic transmission

A1R: smooth muscle (vascular!), m. dil. pup., prostata (IP3, DAG) (+) Ca2+ -> CONTRACTION
A2R: presynaptic loc., adrenergic-cholinergic terminal (cAMP) (+) K+ -> KATECHOLAMIN release (-)

B1R: heart, (cAMP), Ca2+ (+) -> (+) TROPIC EFFECTS
B2R: smooth muscle (bronchus, uterus, urin., skeletal mucle) + heart (20%)!!! (cAMP) -> MLCK-P -> RELAXATION (N.B.: INODILATOR EFFECT)
B3R: adipose tissue, liver -> lypolysis, glycolysis, glükoneogenezis

Sympathomimetics

Def.:

Effect:

- Direct vs. Indirect

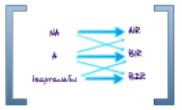
Katecholamines:

- Adrenalin
- Noradrenalin
- Isoprenalin
- Dopamin, Dobutamin

Amphetamin, metamphetamin
Ephedrin
Tiramin
TCA, Kokain

Directly acting sympathomimetics

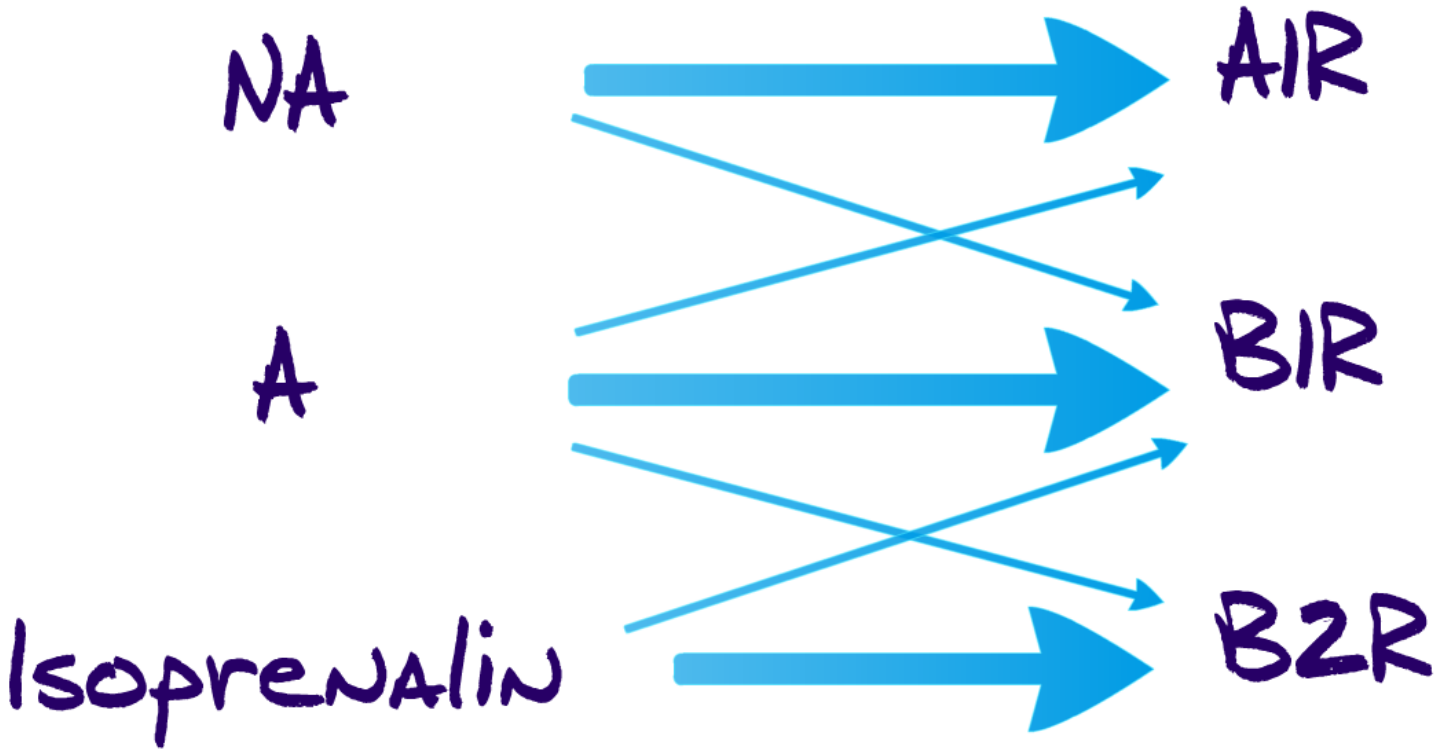
Adrenalin (TONOGEN), 1mg/1ml,



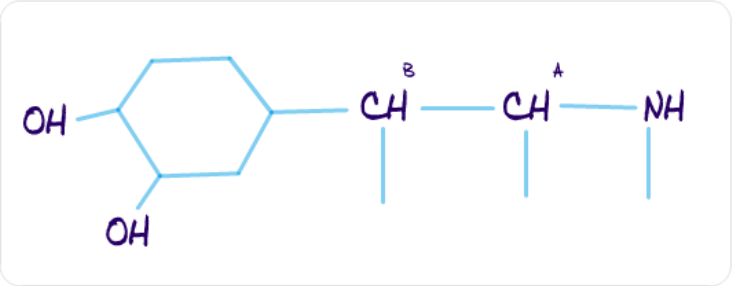
Farmacodynamics:

- B1>A1=B2
- (+) tropic effects, ineffective!!!
- redistribution of circulation!!!
- rhythm disturbances (ES, VT, VF)
- generalized VC.: ->afterload (+) ->oedema pulm.
  - dilatatio cord.- pericard. tamp.

Therapeutic appl.:



Structure-activity relationship



Modification on amino group:
- A / B receptor specificity
- adrenalin (-H)
- noradrenalin (-CH3)
- isoprenalin (-CH(CH3)2)

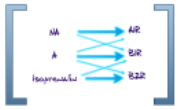
Modification on benzol-ring
Potency
- A, NA, Isopr., (-OH, -OH) - katecholaminok

Modification on A positioned "C" atom:
- "MAO resistance"
- amphetamin, ephedrin (-CH3)
- NA, A, Isopr. (-H)

Modification on B positioned "C" atom:
- lipid solubility, CNS effects
- amphetamin, metamphetamin (-H)
- ephedrin, A, NA (-OH)

Directly acting sympathomimetics

Adrenalin (TONOGEN), 1mg/1ml,



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  - dilatatio cord.- pericard. tamp.

Therapeutic appl.:

- ALS
- Bradycardia protokol - 2-10 ug/min
- Anaphylactic reaction - 500 ug i.m.
- Epistaxis-local application
- Asthma bronchiale? - Laryngitis subglottica
- NB!!! NOT RECOMMENDED in hypovolaemic shock!
- Dose: 0,05-0,1-0,2! mg i.v.

Directly acting sympathomimetics

Noradrenalin (ARTERENOL):

Pharmacodynamics:

- A1>B1
- generalized VC., (+) tropic effects

Therapeutic appl.:

- septic shock - 2-10ug/min

Isoprenalin (ISUPREL):

Pharmacodynamics:

B2>B1

- smooth muscle relax. (bronchus, uterus), (+) tropic effects

Therapeutic appl.:

- status asthmaticus, 3rd degree AV-block

Directly acting sympathomimetics

	Adrenalin	Noradrenalin	Isoprenalin
HR	++	-	+
RR	0 v. +	++	0 v. -
TPR	0 v. +	++	0 v. -

Directly acting sympathomimetics

Dopamin:
1-3 ug/kg/min - D1, D2 receptorok (kidney! art.aff.) -> GFR (+), RBF (+)
3-5 ug/kg/min - B1R, B2R (heart!) -> (+) inotropic
5-10 ug/kg/min - A1R (arteries!) RR (+)

Dobutamin:
5-20 ug/kg/min - B1R, B2R (heart) -> (+) inotropic

Selective B2 agonists:
- salbutamol (VENTOLIN), fenoterol (BEROTEC), terbutalin (BRICANYL)

Pharmacodynamics:
- smooth muscle relax. (bronchus, uterus)

Therapeutic appl.:
- asthma bronchiale, premature birth (uterus relax.)

Indirectly acting sympathomimetics

Amphetamin, metamphetamin
Pharmacodynamics:
- VMAT (amph.-NA exchange)
- Uptake I. block
- MAO block

Effects:
- RR (+), HR (+), resp. stim., psychostim., appetite (+)
- mood, concentration (+)

Ephedrine:
Pharmacodynamics:
- NA, A release (+)

Therapeutic appl.:
- anaesthesiol., RR (+)
- nose drop, "running nose"

Tyramine:
Pharmacodyanmiic:
- NA, A release (+)
  "cheese reaction"

TCA, Kokain
Pharmacodynamics:
- uptake I. inhibition

Sympatholytics

Def.:

Effect:

- Direct vs. Indirect

AlR-blockers
BR-blockers
A2R-agonists

Guanethidin
Rezerpin

Directly acting sympatholytics (AR blockers)

Haloalkilamines:

- Phenoxibenzamin: A1, A2 R block., mAch, 5-HT - irreversible
- Dibenzamine

Indol derivatives:

- Yohimbin: A2R blokk.

Imidazol derivatives:

- Phentolamin: A1, A2 R blokk - reversible
- Tolazolin

others (selective AIR blockers):

- Prazosin (MINIPRESS), Doxazosin, Terazosin, Tamzulosin, Urapidil (EBRANTIL)

Therapeutic appl.:

- Hypertension: prazosin
- N.B.! first pill effect! (Schellong tünet(+)) = postural hypotension, reflex tachyc.
- Pheochromocytoma: phenoxybenzamin, phentolamin
- BPH: tamzulosin prostata stroma - A1AR block.!

Directly acting sympathomimetics
A2 R agonists
Centrally acting sympatholytics

Pharmacodynamics:

- A2R agonism -> NA,A release (+), RR (-)
- IR agonism (CNS) -> RR (-)!

Clonidin:

- sedative, migraine profil. ,phaeochromocytoma dgn.
- hypertension therapy

Moxonidin:

- less sedative, RR (-)

Guanfacin, Guanabenz:

- RR (-)
- side effects.: affektív disorders

metyl-DOPA (DOPEGYT): false transmitter

- A-metyl NA - A2-R agonist
- pre-ecclampsia/HELLP syndrome

B-blockers

Pharmacodynamics:

- (non)selective blockers of adrenerg BR

	Szelektivitás	ISA	Membránstab.	Lipidold.
Propranolol	$\beta_{1,2,3}$	-	++++	
Oxprenolol	$\beta_{1,2,3}$	++	+	
Pindolol	$\beta_{1,2,3}$	+++	-	
Metoprolol	β_1	-	-	
Atenolol	β_1	-	-	
Bisoprolol	β_1	-	-	
Practolol	β_1	-	-	

B-blockers

Therapeutic appl.:

- SV rhythm disturbances (PSVT, atrial fibrill.)
- Hypertension (SV (-), JGA (-))
- Angina pectoris, ACS (Instable AP, AMI)
- Chr. card. decomp. - never in acute!!!
- Pheochromocytoma, thyreotoxic crisis- carvedilol/labetolol
- migraine prophyl.

Kontraindications:

- Asthma bronchiale
- Bradycardia - AV block
- Cardio Ca^{2+} blocker (verapamil) NEVER!!!
- DM - hypoglycaemia

Indirectly acting sympatholytics

Guanethidin:
Pharmacodynamics:
- occupance of synaptic vesicles.
- prim. eff.: RR (+), then RR (-)

Therapeutic application.:
old-fashioned antihypertensive drug
- similar effect: bethanydin, debrisoquin

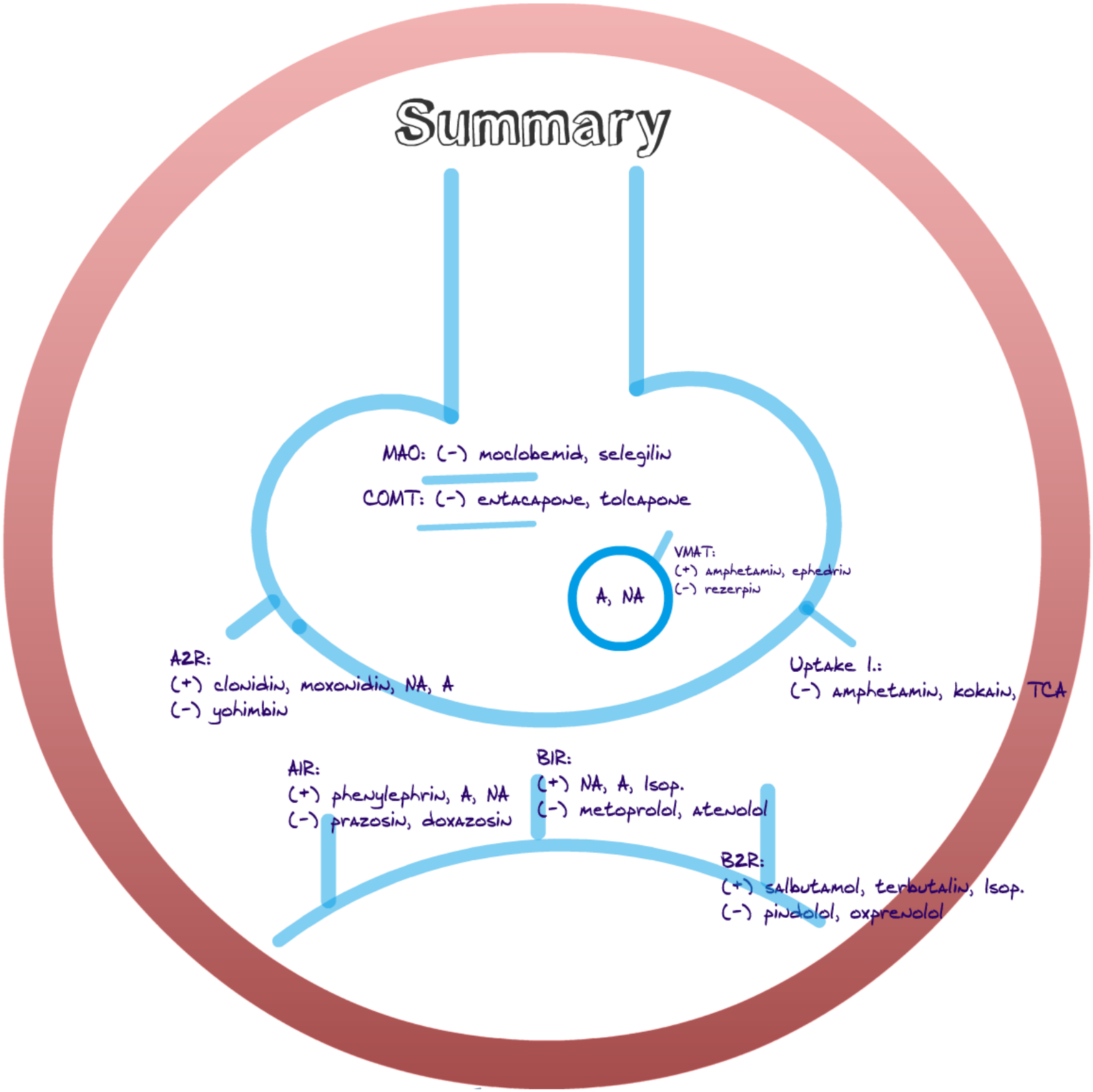
Rezerpin
Pharmacodynamics:
- VMAT blockade

Therapeutic appl.:
- old-fashioned antihypertensive drug

carbidopa, benserazid
Pharmacodynamics:
peripheral DOPA decarboxylase inhibitor
(see.: Parkinson's disease)

alfa-metil Tyr:
Pharmacodynamics:
- Tyr-hidroxiláz block.

Summary


MAO: (-) moclobemid, selegilin
COMT: (-) entacapone, tolcapone
VMAT:
(+) amphetamin, ephedrin
(-) rezerpin
A, NA
A2R:
(+) clonidin, moxonidin, NA, A
(-) yohimbin
Uptake I.:
(-) amphetamin, kokain, TCA
A1R:
(+) phenylephrin, A, NA
(-) prazosin, doxazosin
B1R:
(+) NA, A, Isop.
(-) metoprolol, atenolol
B2R:
(+) salbutamol, terbutalin, Isop.
(-) pindolol, oxprenolol