Pharmacology of the ANS I.
Parasympathomimetics/-lytics

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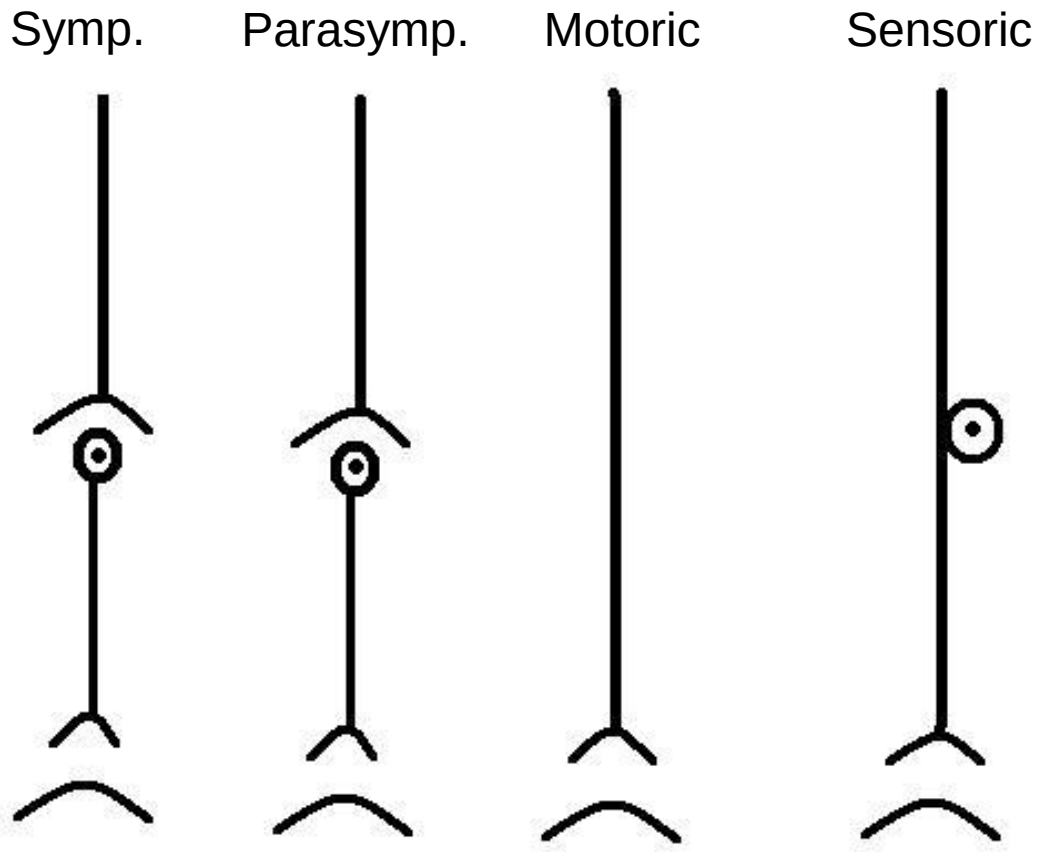
The autonomic nervous system

- sympathetic (thoracolumbar)
- parasympathetic (brainstem, craniosacral, cranial-nerves!!!)
- enteric – GIT -plexus submucosus (Meissner)
  -plexus myentericus (Auerbach) (NANC!!!)

- independent – autonomous
- to secure homeostasis
- manage vital functions (cardiac output, blood pressure, etc.)

sympathetic vs. parasympathetic

Fibres



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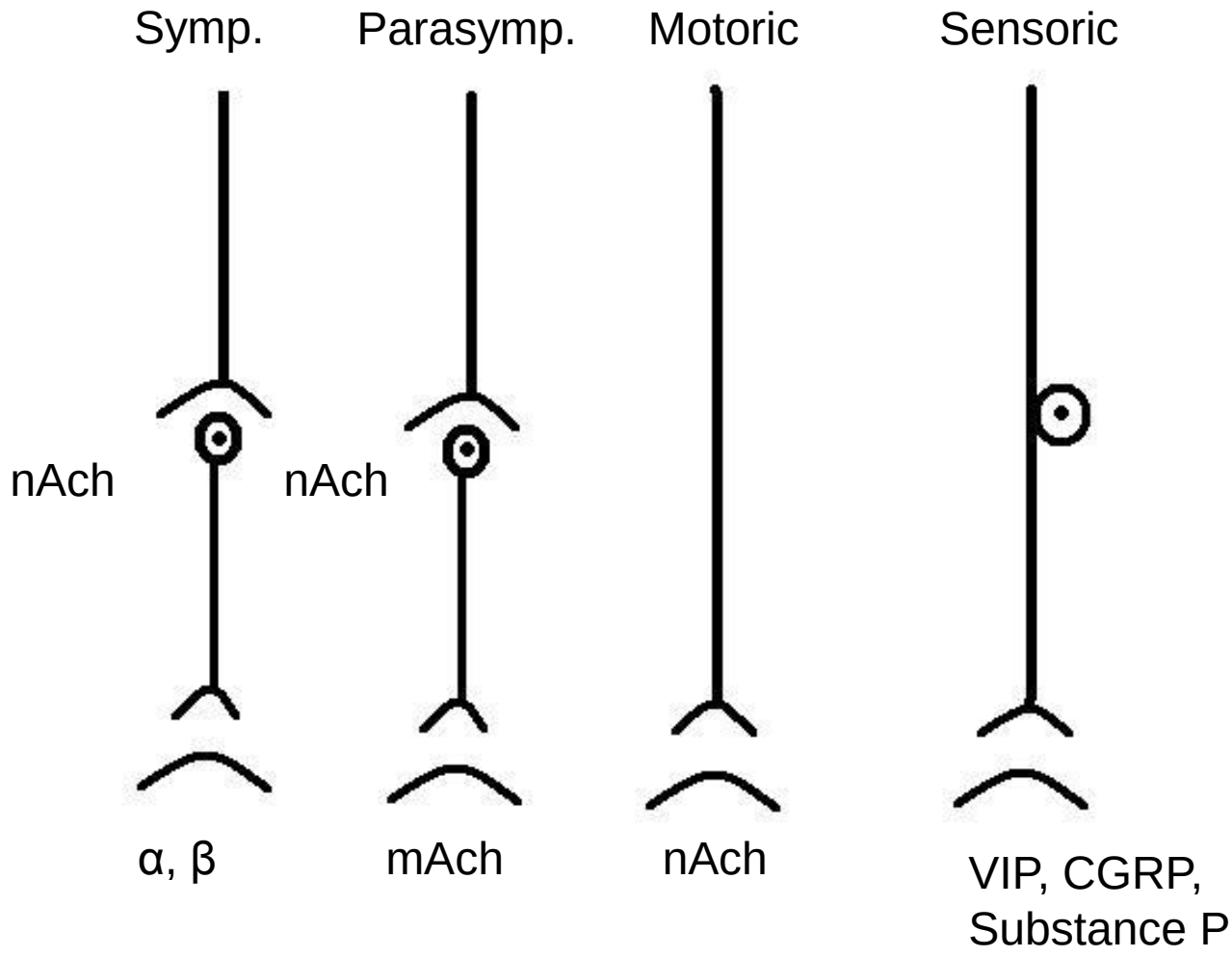
Symp.
Parasymp.
Motoric
Sensoric
nAch
nAch
α, β
mAch
nAch
VIP, CGRP,
Substance P

Cholinergic transmission I.

Neurotransmitter - Receptor

Ach – AcCoA + choline (phosphatydyle-etanol-amin) - ChAT

Synthesis-Transport-Storage - TARGET!

- Hemicholinium-3 - ChAT!!!
- colchicin (RA) – vinblastin (chemotherapeutic drugs)
- vesamicol - vesicular transport

Cholinergic transmission II.

m Ach - metabotropic:

- M_1 - neural, IP_3, DAG, Ca^{2+}
- M_2 - cardial, cAMP ↓, K^+
- M_3 - glandular-endothelial, IP_3, DAG, Ca^{2+}
- M_4 - CNS, cAMP ↓, K^+
- M_5 - CNS, IP_3, DAG, Ca^{2+}

n Ach - ionotropic:

- N_m - NMJ, Na^+, K^+
- N_n – autonomic ganglia, Na^+, K^+

Cholinergic transmission III.

Degradation/Hydorlysis:

- AchE: - 2ms, RBC, synaptic cleft, spec. for Ach,
  active sides! N.B.! Cholinesterase inhibiting drugs
- ButchE, (PchE): - not spec. (muscle relaxant), liver

Cholinergic transmission:

- Parasympathetic postggl. fibres
- NMJ
- Autonomic preggl. fibres
- CNS

Cholinomimetic agents

- Def.:!
- Direct (Cholinoceptor activating drugs) vs. Indirect (ChE-inhibiting drugs)

Cholinoceptor activating drugs: Alkaloids – Choline esters

Alkaloids: - muscarine: Amanita muscaria, mACh
- pilocarpine: Pilocarpinium chloratum, glaucoma th., hypersalivation
-lobeline, arecoline: euphoriac effect

Cholinoceptor activating drugs

Choline esters: -metacholine: th. of urinary retention

-carbachol: GIT, eye-drop 3%

-betanechol: GIT, prokinetic effect

Effects:

- heart:- (-) chronotropic, (-) inotropic M_2R
- vessels:- intact endothel: M_3 -IP_3, DAG, Ca^{2+}- NO (EDRF)(endothel) - cGMP(smooth muscle)- vazodilation!
  - injured endothel: M_3 -IP_3, DAG, Ca^{2+} (smooth muscle) - vazoconstriction!

Cholinoceptor activating drugs

Respiratory tract: -bronchial constriction, secretion↑

GIT: -motility↑, peristaltic effect↑, secretion↑,
kolinokinetic effect

Urinary tract.: - motility↑

Miscellaneous glands: -secretion↑

Eye: -pupil↓, miosis

-m. ciliaris constriction, near - vision, macropsia

-th. of glaucoma - Schlemm canals, Fontana canals, outflow of humour aquosus

Choline esterase-inhibiting drugs

Reversible vs. Irreversible

Alcohols (kvaterner) – Carbamates - Organophosphates

- edrophonium (Tensilon), galantamin
- neostigmin (N^+), physostigmin (eserine), pyridostigmin (MG)
- DFP, Soman

Mech. of action.: active sides!!! revers.-irrevers.

Th.: - Glaucoma

- GIT retention – ileus (neostigmin)

-Atropin intox. (physostigmin)

-Myasthenia gravis (Tensilon)

Intoxication of organophosphates

Nerve gases: Soman, Tabun, Sarin

Pesticides/Insecticides: Diclorvos, Bi58, DFP

Cholinomimetics effects:

- hypersalivation, sweating
- miosis
- HR↓- BP↓
- Bronchial constriction - asphyxia
- GIT↑ - vomitus, diarrhea
- CNS – somnolentia, coma
- convulsions

Intoxication of organophosphates

Th.: -Decontamination, CPR, vital signs/parameters!!!

- Antidotum!

-Spec. th.: Oxims

Pralidoxim-chlorid, Obidoxim-iodid

- (nucleophil agents)

Parasympatholytic/cholinolytic drugs

Def.:!

nAch: - hexamethonium (ggl. blocking dru)

- curare (NMJ-muscle relaxant drugs)

mAch: - atropine, scopolamine, etc.

Atropos –mytology

NB.!-poison!

Parasympatholytic/cholinolytic drugs

Atropa belladonna - atropine
Belladonnae folium extractum siccum normatum

Hyoscyamus niger - scopolamin

Synthetic – ipratropium - bromid

Atropine: -D,L hyoscyamine
- Atropinium sulfuricum
- Atropinum sulfuricum®, Atropin®

Mechanism of action:
- competitive antagonist on mAchR

Parasympatholytic/cholinolytic drugs

Effects:

- Heart:- (+) chronotropic, tachycardia but! primarily bradycardia (stimulate central nuclei of n. X.) – not effect on denervated heart!
- Vessels:- RR↑, but! high dose-toxic!
- Bronchial tract: -bronchodilatation, secretion↓
- GIT: -motility↓, secretion ↓, -atonic obstipation (NB.: morfin)
- Genitourinary.: - motility ↓
- Miscellaneous tract: secretion ↓, sweat glands!!! S.Ch.!!! – atropine fever!!!
- Eye: -pupil↑, mydriasis – m. dilatator pupillae, -fotophobia
  -cycloplegia, unable to accomodate, micropsia

- CNS: -sedative
  - vestibular disturbances↓
  - extrapyr. system

Parasympatholytic/cholinolytic drugs

- Ipratropium-bromide: - N^+ - no effect in CNS
  -aerosol – inhalation route
  -anti-asthmatic drug
- Scopolamine: -TTS
  - vestibular disturbances-motion sickness
  - mydriatic in the cc. 0,5%
- Benzatropine: - N, therapy of Parkinson disease
- Pirenzepine: -gastric ulcus

Parasympatholytic/cholinolytic drugs

Therapeutic applications:

- anaesthesia, premedication:-protect against bradycardia
  -secretion↓
- Parkinson disease
- diarrhea, hypermotility (Reasec®)
- motion sickness
- colica abd. (Troparinum Combinatum®)
- intoxication of organophosphates
- bradycardia

Max. dose! 0,3 mg-1mg Σ:3mg

Parasympatholytic/cholinolytic drugs

Intoxication of atropine:

- mydriasis
- dry skin
- tachycardia
- extrapyramidal movement disorders
- agitility, agressivity
- atropin fever

Th.: -ChE blocking drug – CNS - physostigmine (N)!!!

-sedatohipnotics