Autonomic Nervous System

Cholinergic Transmission

parasympathetic system

- medullary outflow
  - eye
  - lacrimal glands
  - salivary glands
  - heart
  - lung
  - upper gut
- sacral outflow
  - lower gut
  - bladder
  - genitals

sites of drug action

- CNS
- ganglia
- peripheral tissues
- everywhere!

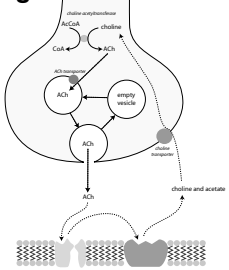
release of ACh

- arrival of action potential
- opening of Ca channels
- increase in [Ca^{++}]
- exocytosis of vesicle
- co-transmission?

acetyl choline receptors

- **nicotinic**
  - **ionotropic**
- **muscarinic**
  - **metabotropic**

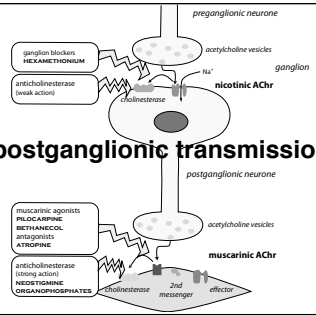
ganglionic transmission



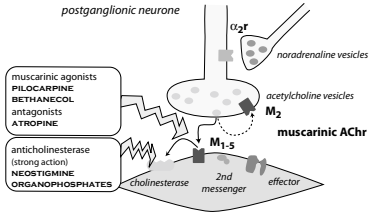
nicotinic receptor subtypes

- **ion channels with 5 subunits**
- **at least 16 different subunits cloned**
  - **ganglionic – (α3)2(β4)3**
  - **CNS – (α3)2(β4)3 & (α7)5**
  - **neuromuscular junction – (α1)2β1γϵ**

postganglionic transmission



postganglionic transmission



muscarinic receptors

- **M1 – neural**
  - **CNS excitation, gastric acid secretion, gut motility**
- **M2 – cardiac**
  - **cardiac & neural inhibition**
- **M3 – glandular**
  - **secretion, smooth muscle contraction, vasodilatation (NO)**
- **M4 – CNS / smooth muscle**
- **M5 – substantia nigra, salivary gland, iris**

muscarinic agonists

- **acetylcholine**
- **bethanecol – po**
- **pilocarpine – eye**
- **carbachol**
- **muscarine**

muscarinic antagonists

- **atropine**
- **hyoscine**
- **glycopyrrolate**
- **pirenzepine (M1 – gut only)**

muscarinic antagonists

log Ki	M1	M2	M3	M4	M5
atropine	9	8.8	9.3	8.9	9.2
oxybutynin	8.2	7.5	8.3	8.1	7.7
pirenzepine	8.2	6.5	6.9	7.4	7.2
tolterodine	8.4	8.1	8.2	7.9	8.4

atropine effects

- dries secretions
- reduces salivation
- slows gut
- tachycardia
- dilates pupil
- blurred vision
- difficulty with urination

atropine indications

- anaesthetic premedication
  - in cats (and pigs?)
  - in conjunction with irritant anaesthetics like ether
- treating gut spasm
  - not very effective
- treating bradycardia
  - depends on cause
- organophosphate poisoning

atropine contra-indications

- glaucoma
- tachycardia

atropine precautions

- care in cardiac disease
- horses
  - cycloplegia often causes panic
- ruminants
  - blocks parotid secretions but not submandibular – very sticky saliva
- rabbits
  - break atropine down rapidly

hyoscine

- very similar to atropine
- may have more CNS effects
- used for motion sickness in man
- not very effective in dogs

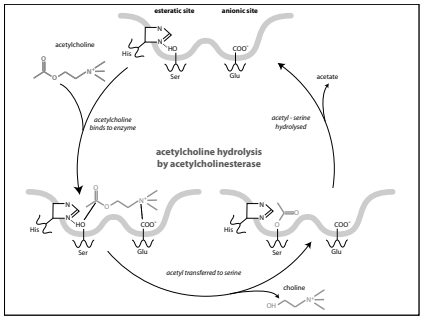
glycopyrrolate

- quaternary ammonium compound
  - does not cross blood brain barrier
- more specific for heart
- longer action than atropine
- expensive!

cholinesterases

- **acetylcholinesterase**
  - **cholinergic synapses**
- **butyrylcholinesterase**
  - **plasma and other tissues**
  - **breaks down many esters**

acetylcholinesterase



anticholinesterases

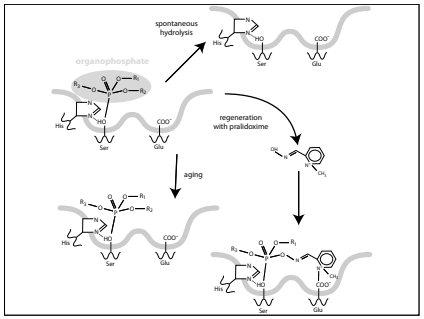
- **edrophonium**
- **neostigmine**
- **physostigmine**
- **organophosphates**
- **carbamates**

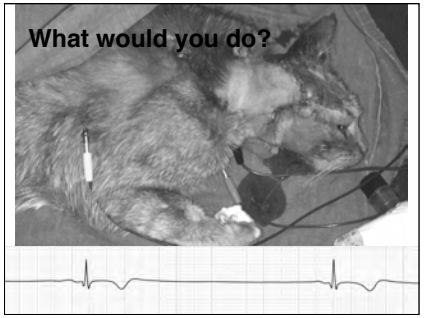
anticholinesterases

- block breakdown of ACh
- enhance cholinergic transmission
- produce signs of parasympathetic overactivity

organophosphates

- insecticides
  - not used much on animals now
  - still used on plants
- (nerve gases)





What would you do?

cholinergic transmission

- acetylcholine is released at postganglionic nerve endings to act at muscarinic receptors
- there are several subtypes of muscarinic receptors
- atropine is widely used as a non-specific muscarinic antagonist
- muscarinic agonists are not widely used because of side effects
- all autonomic system drugs have widespread side effects