

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!

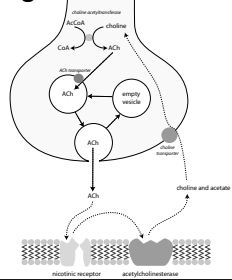
release of ACh

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

acetyl choline receptors

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

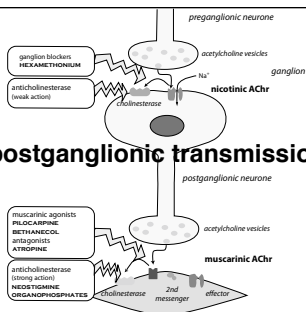
ganglionic transmission



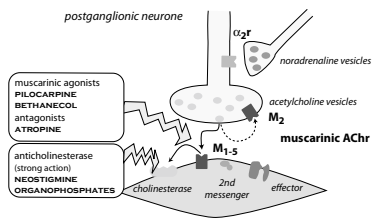
nicotinic receptor subtypes

- **ion channels with 5 subunits**
- **at least 16 different subunits cloned**
 - ganglionic – $(\alpha 3)2(\beta 4)3$
 - CNS – $(\alpha 3)2(\beta 4)3$ & $(\alpha 7)5$
 - neuromuscular junction – $(\alpha 1)2\beta 1\gamma\epsilon$

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

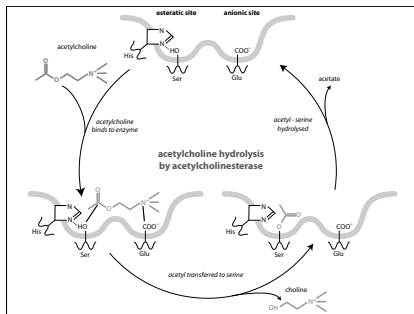
glycopyrrolate

- 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

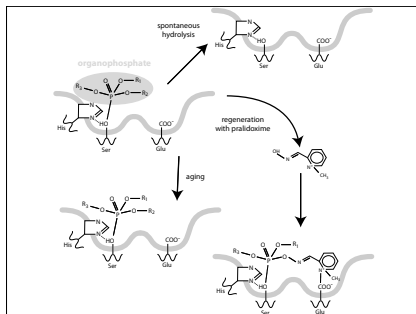
- **edrophonium**
- **neostigmine**
- **physostigmine**
- **organophosphates**
- **carbamates**

anticholinesterases

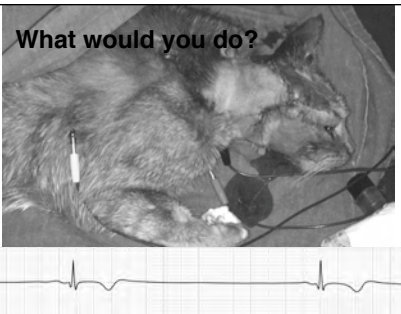
- block breakdown of ACh
- enhance cholinergic transmission
- produce signs of parasympathetic overactivity

organophosphates

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



What would you do?



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