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!

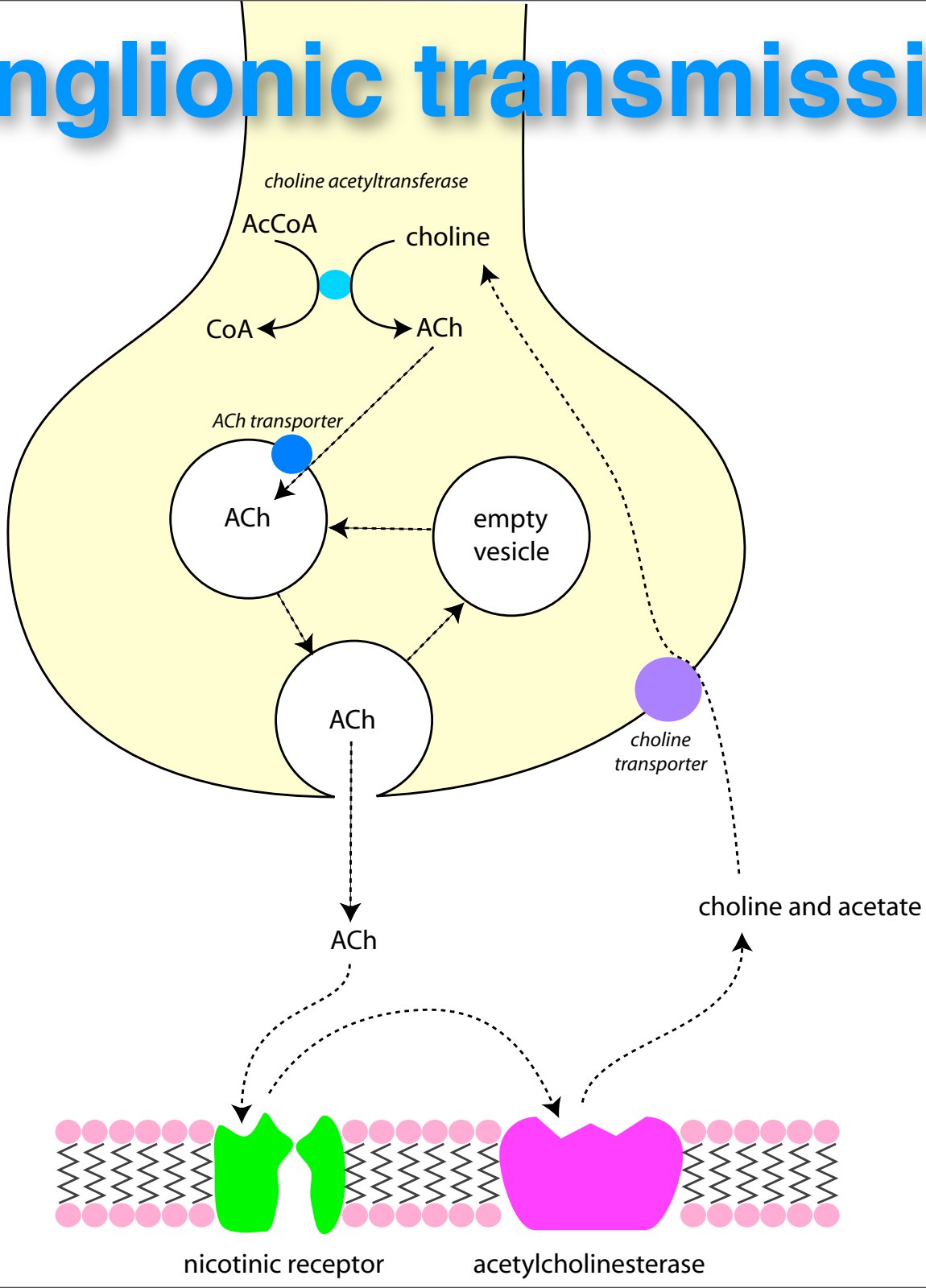
release of ACh

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

acetyl choline receptors

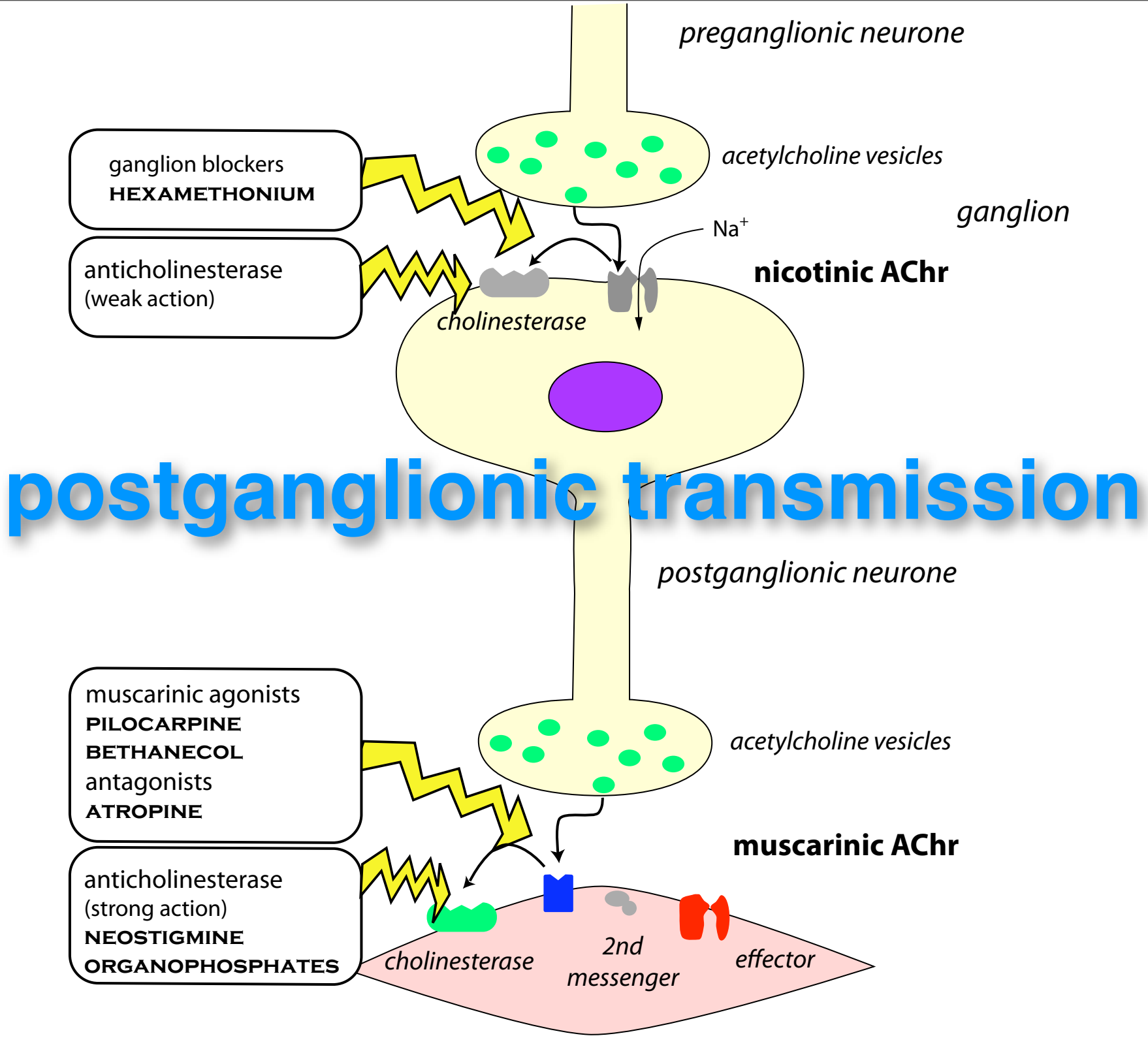
- nicotinic
  - ionotropic
- muscarinic
  - metabotropic

ganglionic transmission

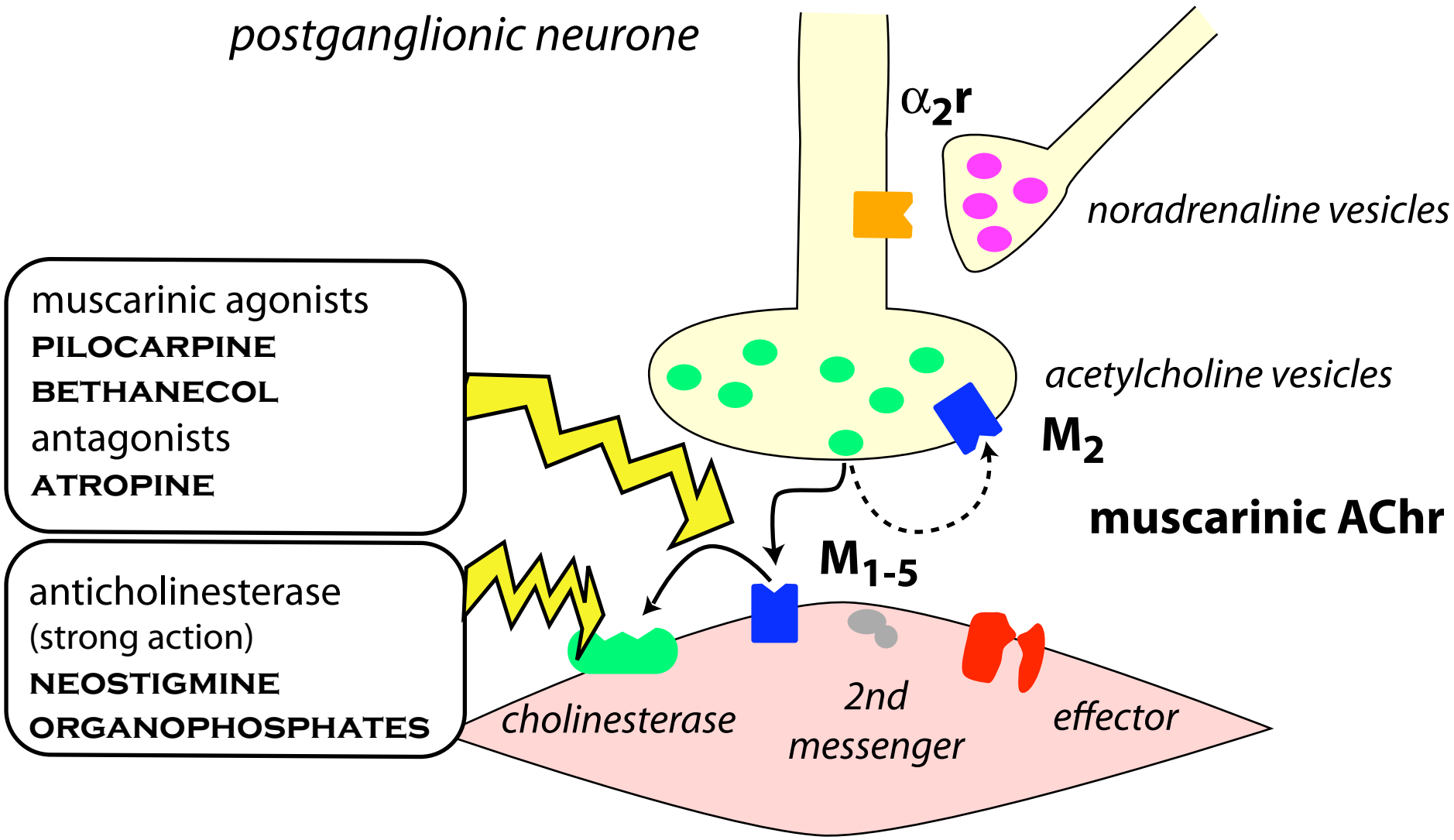


nicotinic receptor subtypes

- 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 – $(\alpha 1)2\beta 1\gamma\epsilon$


preganglionic neurone
ganglion blockers
HEXAMETHONIUM
acetylcholine vesicles
ganglion
Na+
anticholinesterase
(weak action)
nicotinic AChr
cholinesterase
postganglionic transmission
postganglionic neurone
muscarinic agonists
PILOCARPINE
BETHANECOL
antagonists
ATROPINE
acetylcholine vesicles
muscarinic AChr
anticholinesterase
(strong action)
NEOSTIGMINE
ORGANOPHOSPHATES
cholinesterase
2nd
messenger
effector

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

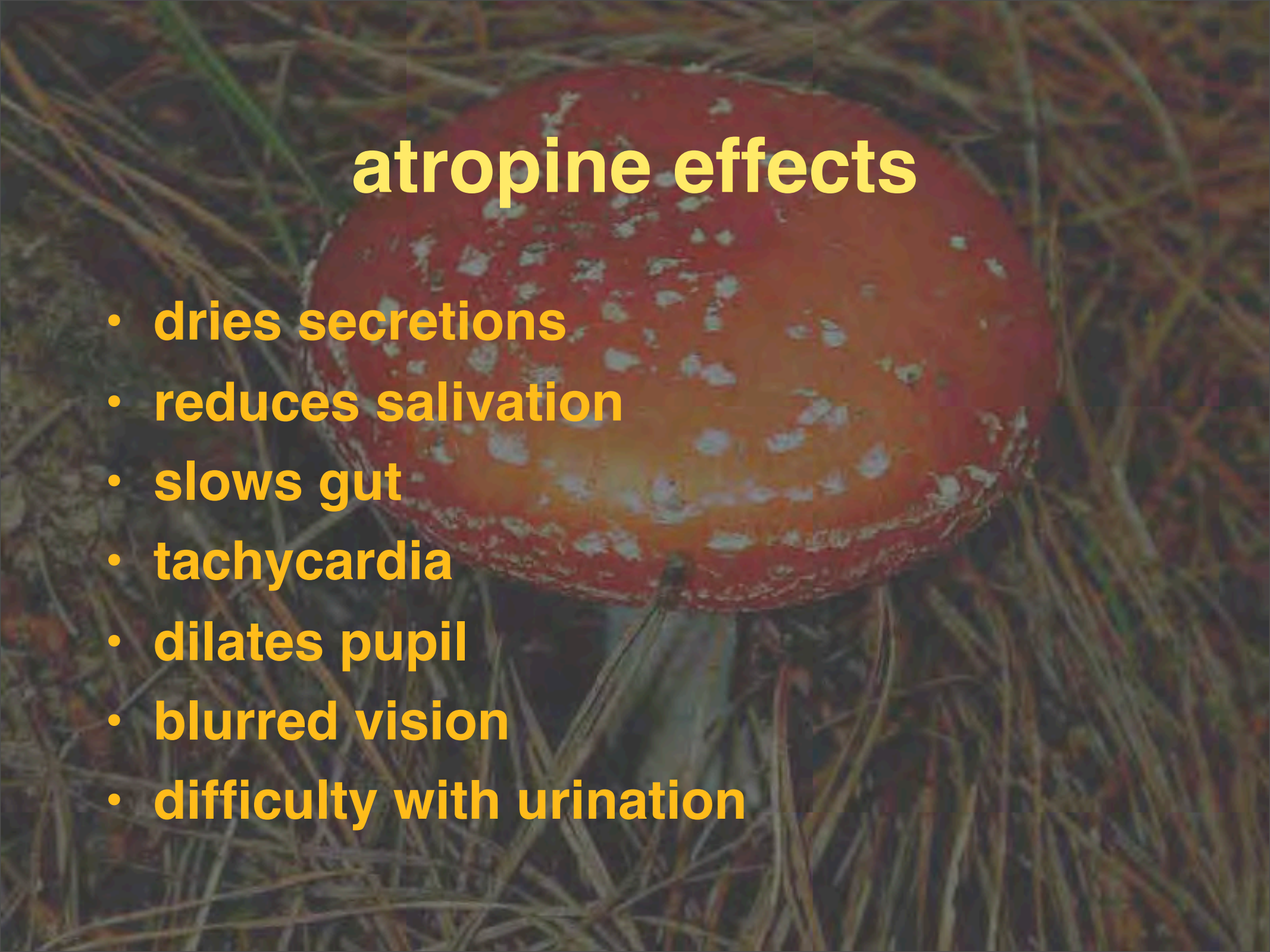
muscarinic antagonists

- 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


deadly nightshade
Atropa belladonna



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

atropine contra-indications

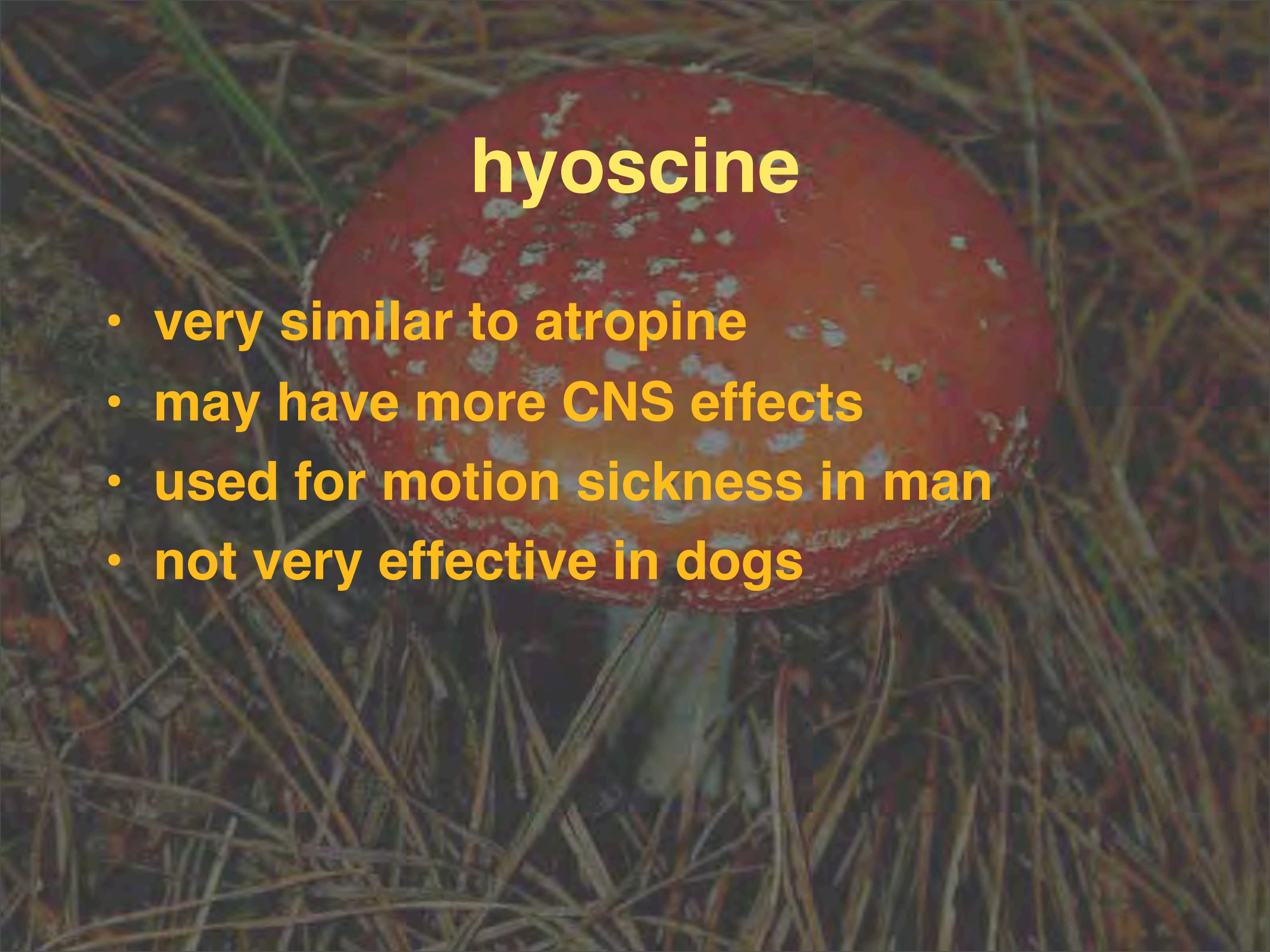
- glaucoma

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

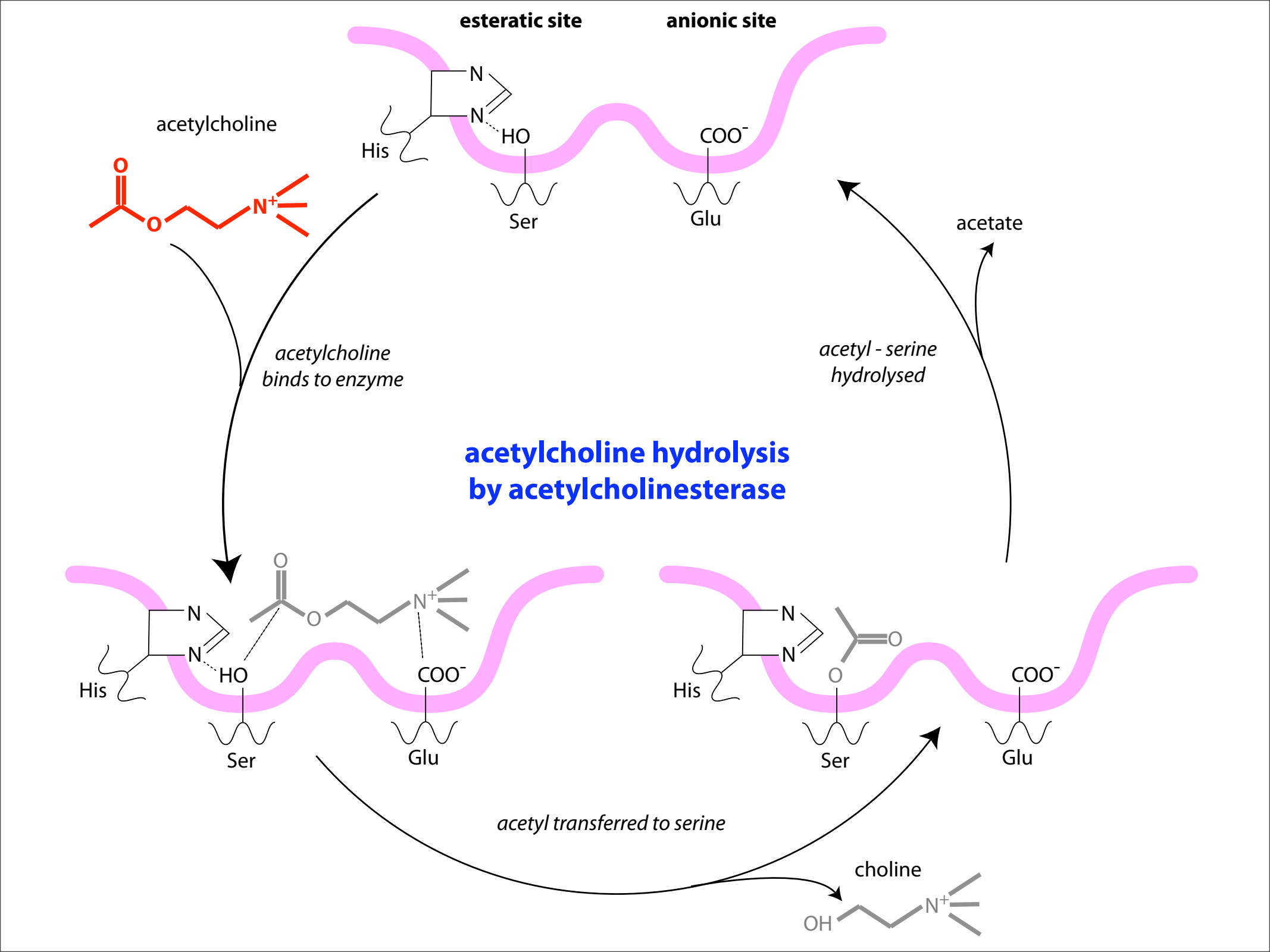
glycopyrrolate

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

cholinesterases

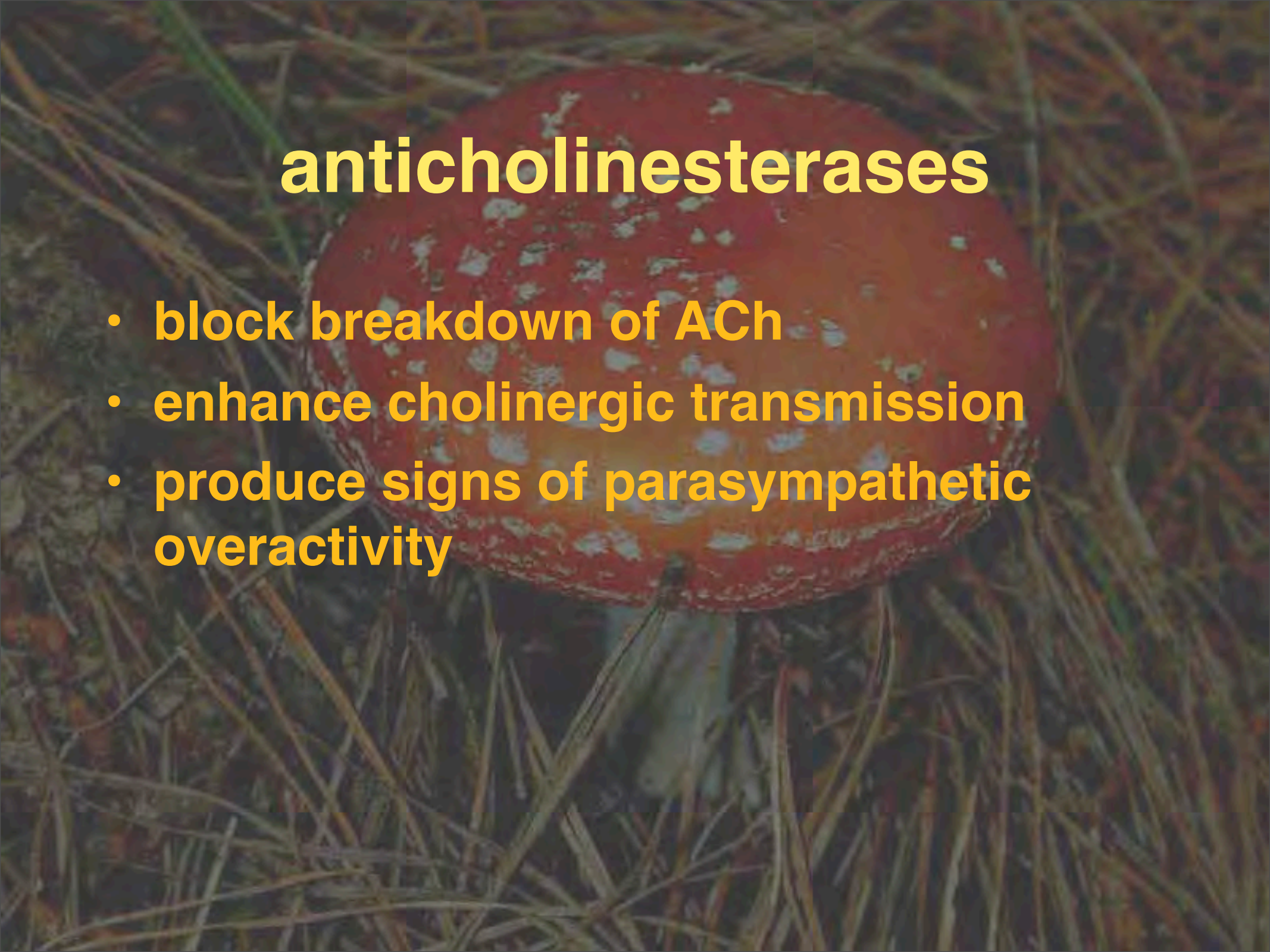
- acetylcholinesterase
  - cholinergic synapses
- butyrylcholinesterase
  - plasma and other tissues
  - breaks down many esters


acetylcholinesterase


esteratic site
anionic site
acetylcholine
His
HO
Ser
COO⁻
Glu
acetylcholine
binds to enzyme
acetyl - serine
hydrolysed
acetate
acetylcholine hydrolysis
by acetylcholinesterase
His
HO
Ser
COO⁻
Glu
His
Ser
COO⁻
Glu
acetyl transferred to serine
choline
OH

anticholinesterases

- edrophonium
- neostigmine
- physostigmine
- organophosphates
- carbamates

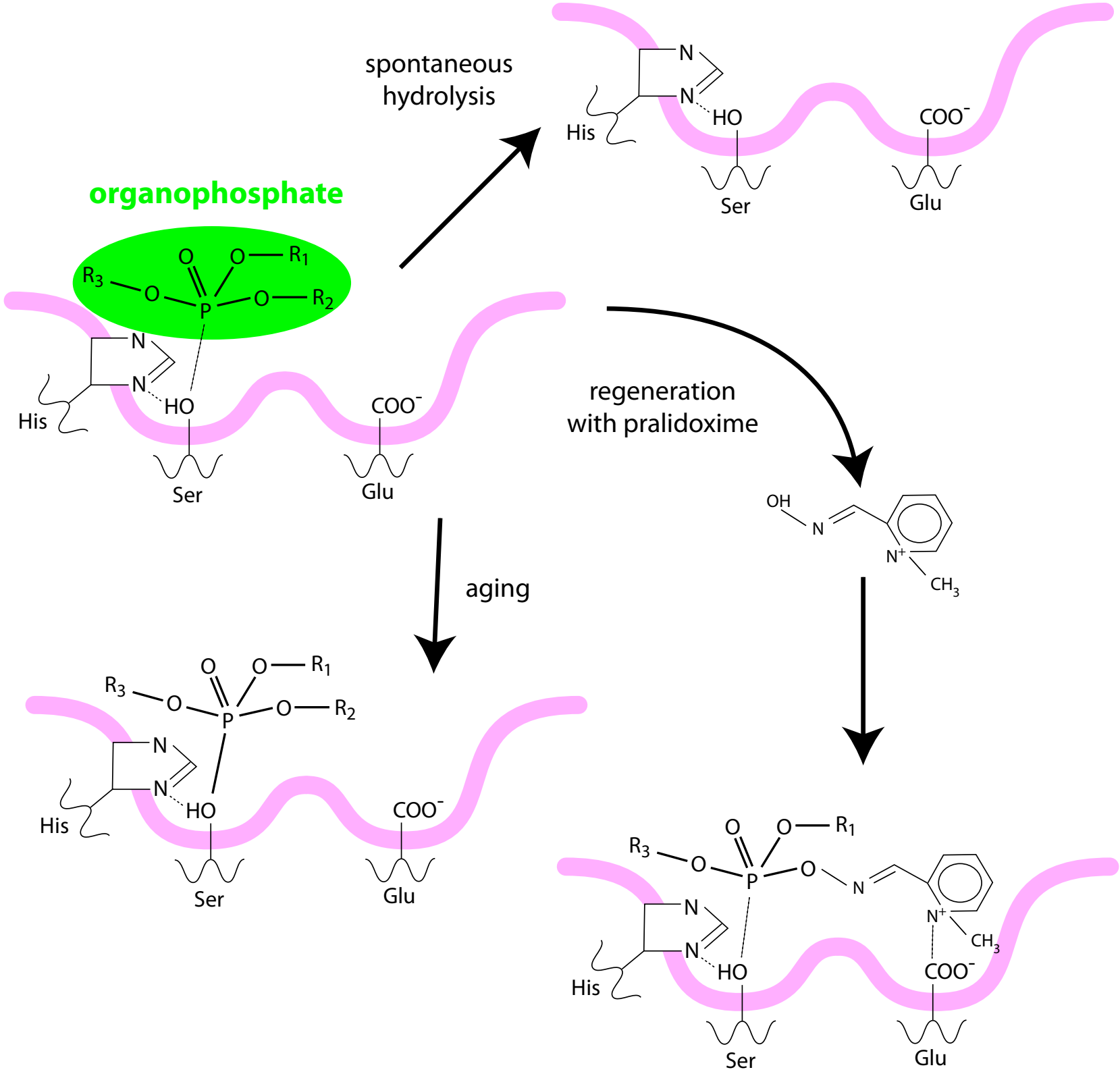


anticholinesterases

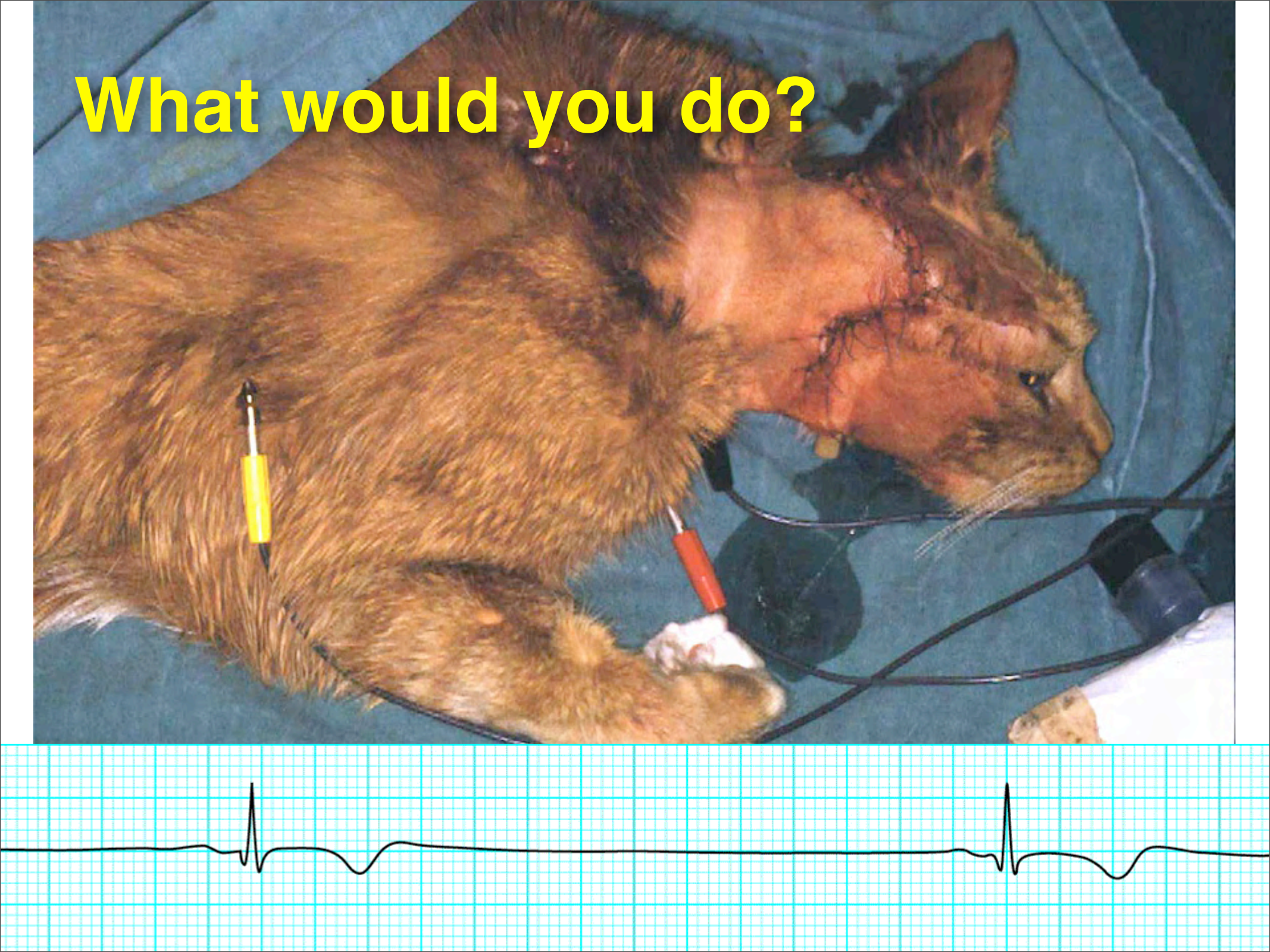
- block breakdown of ACh
- enhance cholinergic transmission
- produce signs of parasympathetic overactivity

organophosphates

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


spontaneous
hydrolysis
organophosphate
regeneration
with pralidoxime
aging
His
Ser
Glu
HO
COO⁻
OH
N
N⁺
CH₃
O
P
R₁
R₂
R₃

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