Anticonvulsant Drugs

by the end of this lecture you should be able to

- formulate a treatment plan for an animal with intermittent or continuous convulsions

What would you do?

- 3 year old collie cross
- eaten unkown amount of metaldehyde
- convulsing for 30 minutes

epilepsy

- affects 0.5% dogs & cats
- usually tonic - clonic seizures
- absence seizures not seen

causes

- primary
  - idiopathic
- secondary
  - distemper
  - head injury
  - encephalitis
  - tumours
- reactive
  - hyperthermia
  - poisoning

drugs

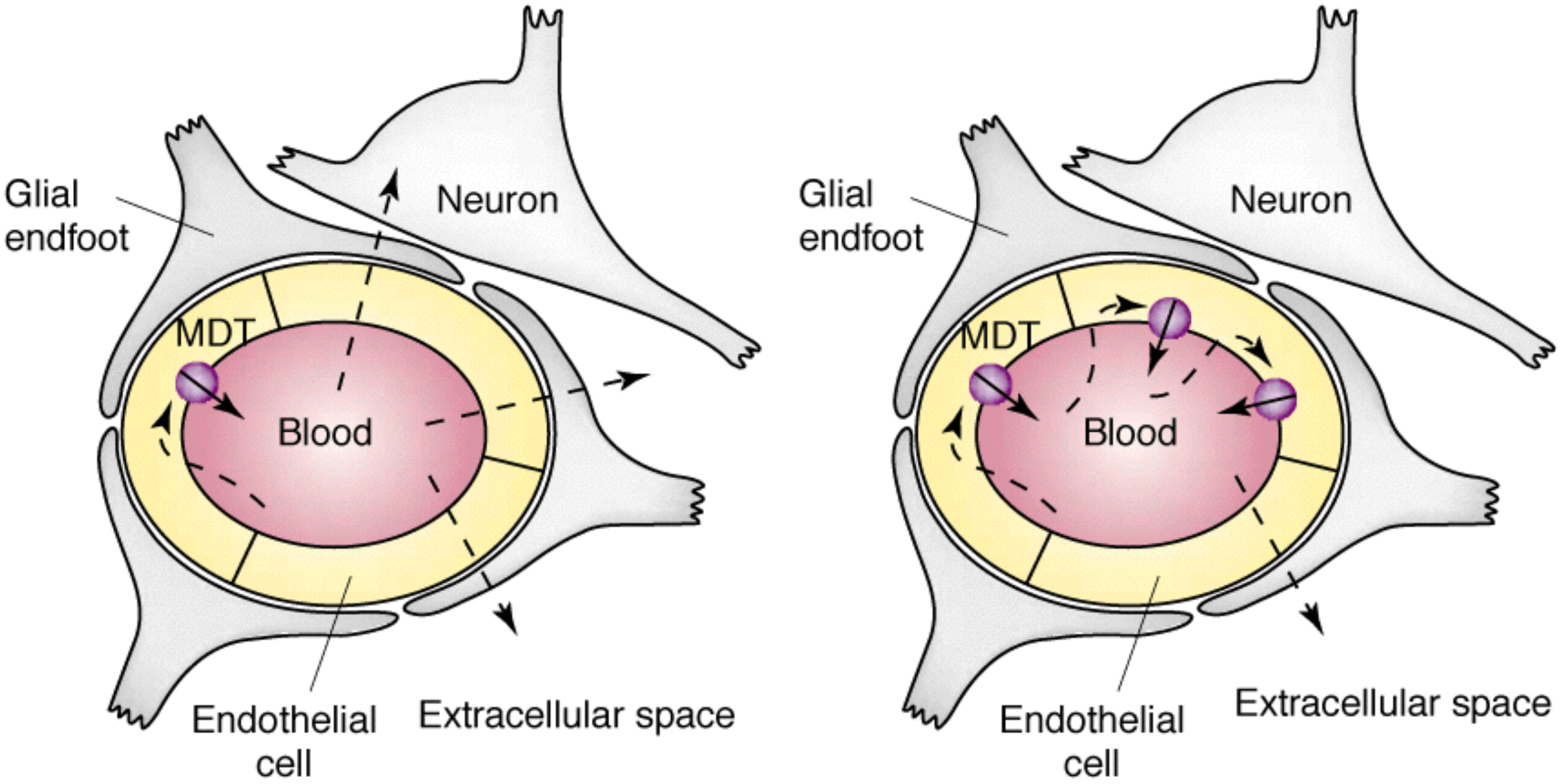
- effective in about 33%
- some control in 33%
- ineffective in the rest

(a)

Normal expression of multidrug transporters

(b)

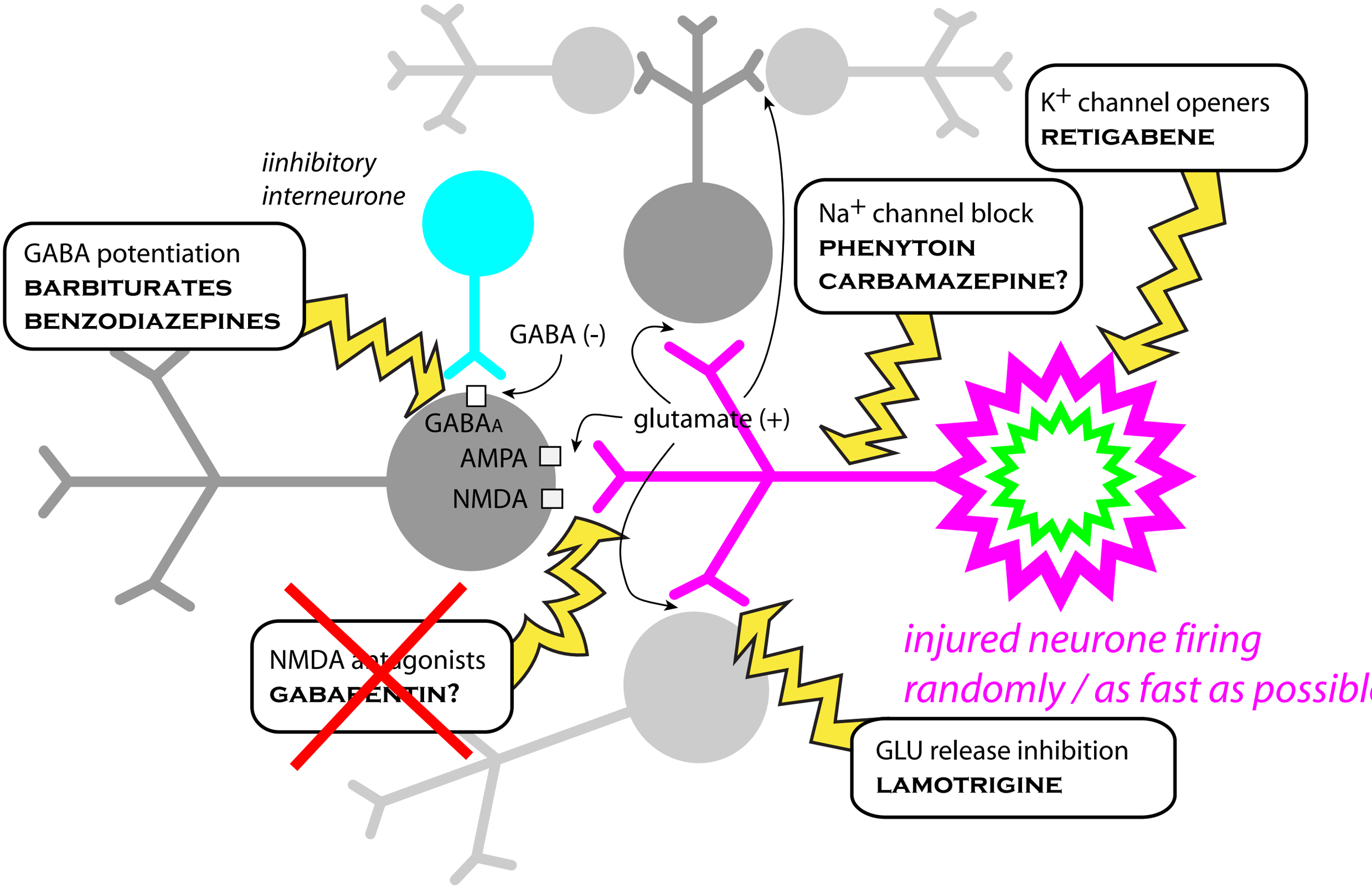
Overexpression of multidrug transporters



TRENDS in Pharmacological Sciences

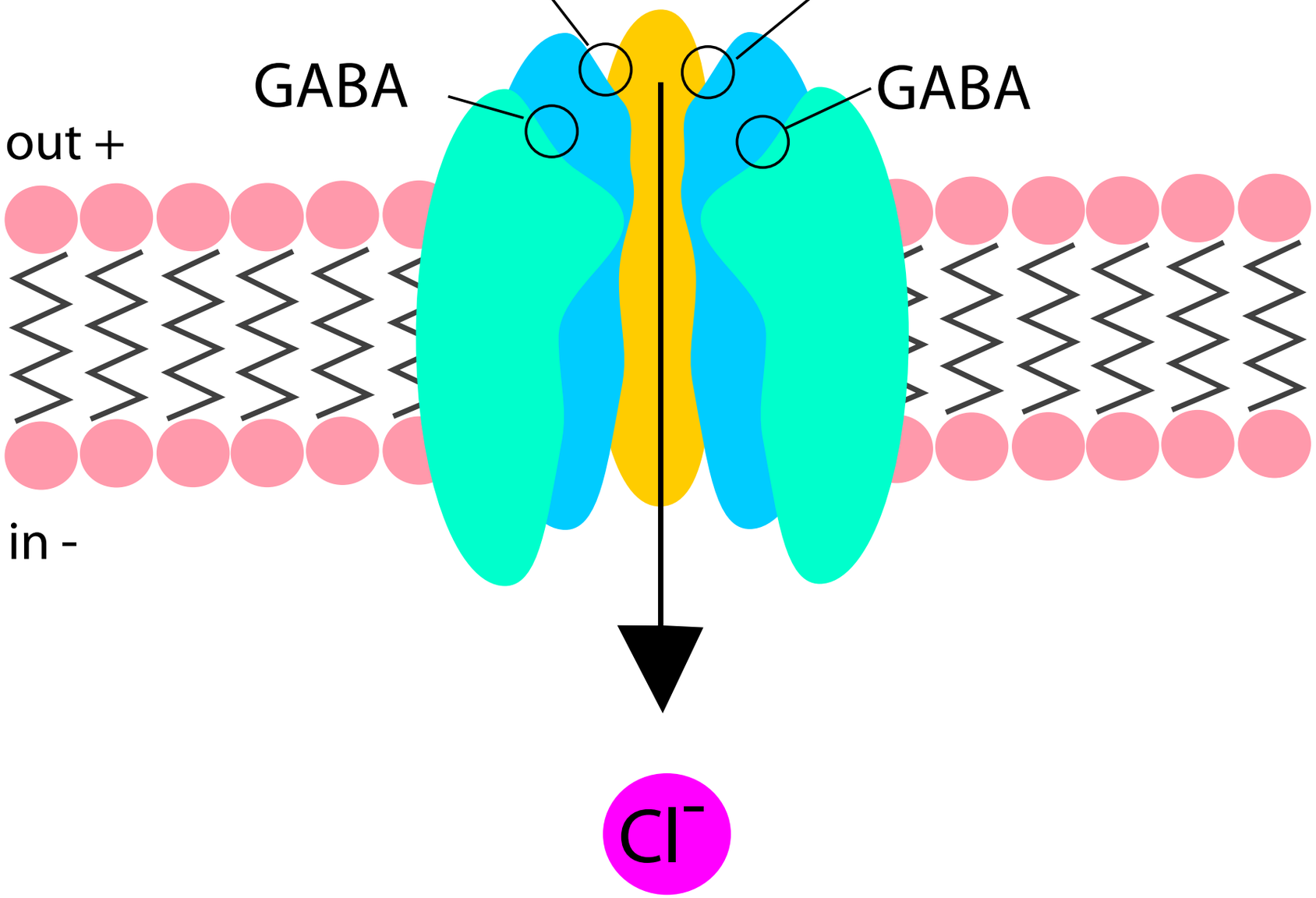
drugs

- given for life
  - side effects
  - cost
  - effects of other illness / procedures
- suppress signs rather than cure disease


iinhibitory
interneurone
GABA potentiation
BARBITURATES
BENZODIAZEPINES
GABA (-)
GABAA
AMPA
NMDA
glutamate (+)
K+ channel openers
RETIGABENE
Na+ channel block
PHENYTOIN
CARBAMAZEPINE?
injured neurone firing
randomly / as fast as possible
NMDA antagonists
GABAPENTIN?
GLU release inhibition
LAMOTRIGINE

BARBITURATES
OTHER INJECTION ANAESTHETICS?
INHALATION ANAESTHETICS?
ALCOHOL?

agonist **DIAZEPAM**
antagonist **FLUMAZENIL**
inverse agonist β**CARBOLINE**



status epilepticus

- continuous seizures
- rapidly causes brain damage
  - excitotoxicity
- respiratory failure?

status epilepticus

- priorites
  - stop seizures
  - treat cause
  - prevent further brain damage?

status epilepticus

- diazepam
  - iv
  - im, per rectum
- (iv phenobarbitone)
- (iv pentobarbitone)

prevention

- phenobarbitone
- primidone
- phenytoin
- valproate
- bromide

phenobarbitone

- works reliably
- suitable half life
- cheap
- more anticonvulsant than other barbiturates

side effects

- sedation ± ataxia
- cytochrome P450 induction
  - initial half life in dog about 100 h
  - half life after induction about 24 h
- polyuria / polydipsia
- raised liver enzymes
- very rarely liver failure

start phenobarb when

- more than 1 fit / month
- a fit within 1 week of head injury
- brain lesion identified

primidone

- metabolised to phenobarbitone
- more likely to cause liver damage
- more expensive

phenytoin

- does not work reliably
- zero order kinetics at high doses
- short half life
- induces P450
- liver damage
- (teratogenic)
- newer analogues better (not in NZ)
  - fosphenytoin

valproate

- short half life in dogs
- useful in cats?

new drugs

- gabapentin
  - unknown mechanism - Na+ channel blocker??
- lamotrigine
  - sodium channel blocker
- vigabatrin
  - GABA transaminase inhibitor
- felbamate ?
  - not available in NZ

useless drugs

- carbamazepine
- ethosuxamide
- benzodiazepines
  - except possibly in cats

half lives

	dog	cat	man
phenobarbitone	42 - 100 (24 - 30)	34 - 43	70 - 100
primidone	9 - 12		6 - 12
phenytoin	2 - 4	24 - 108	15 - 24
carbamazepine	1		24 - 48
valproate	1.5 - 3	8.5	8 - 15
ethosuxamide	17		16 - 70
diazepam	2 - 5	2	24 - 72
clonazepam	1 - 5		24 - 36
felbamate	12		23
bromide	25 - 46 days!		11 days

bromide

- toxic and obselete
  - subjective unpleasant side effects
  - very long half life
- cheap
- a drug of very last resort

combinations

- phenobarbitone & bromide
  - worth trying if phenobarb alone does not work
  - an alternative to euthanasia
- phenobarbitone & phenytoin
  - not usually any more effective
- phenobarbitone & gabapentin ?
  - no data in dogs

drugs to avoid

- acepromazine
- butyrophenones

if drugs fail

- check owner compliance
- plasma levels
  - check every 6 - 12 months
- increase dose
- try combinations
  - bromide
  - gabapentin
- avoid precipitating factors

interactions with other drugs

- protein binding
- faster metabolism
- potentiation of sedatives / anaesthetics

stopping anticonvulsants

- no fits for 1 year
  - gradually reduce phenobarb
  - 2 weeks between dose changes
  - stop when plasma conc falls to ineffective levels
- start again if more than 3 fits / year

the future?

- P glycoprotein inhibitors?
- high fat diets?
  - ketones prevent fits
- nerve stimulation?
  - vagus / implanted brain electrodes
- K^+ channels?
- surgery???

What would you do?

- 3 year old collie cross
- eaten unkown amount of metaldehyde
- convulsing for 30 minutes

priorities

- ABC
- control seizures
- assess
- decontaminate
- longer term control

anticonvulsants

- anticonvulsants control seizures: they do not cure epilepsy
- phenobarbitone works best for prevention of fits in most cases but induces cytochrome P450
- diazepam is used for status epilepticus
- anticonvulsants potentiate anaesthetics & sedatives