
Central Neurotransmission

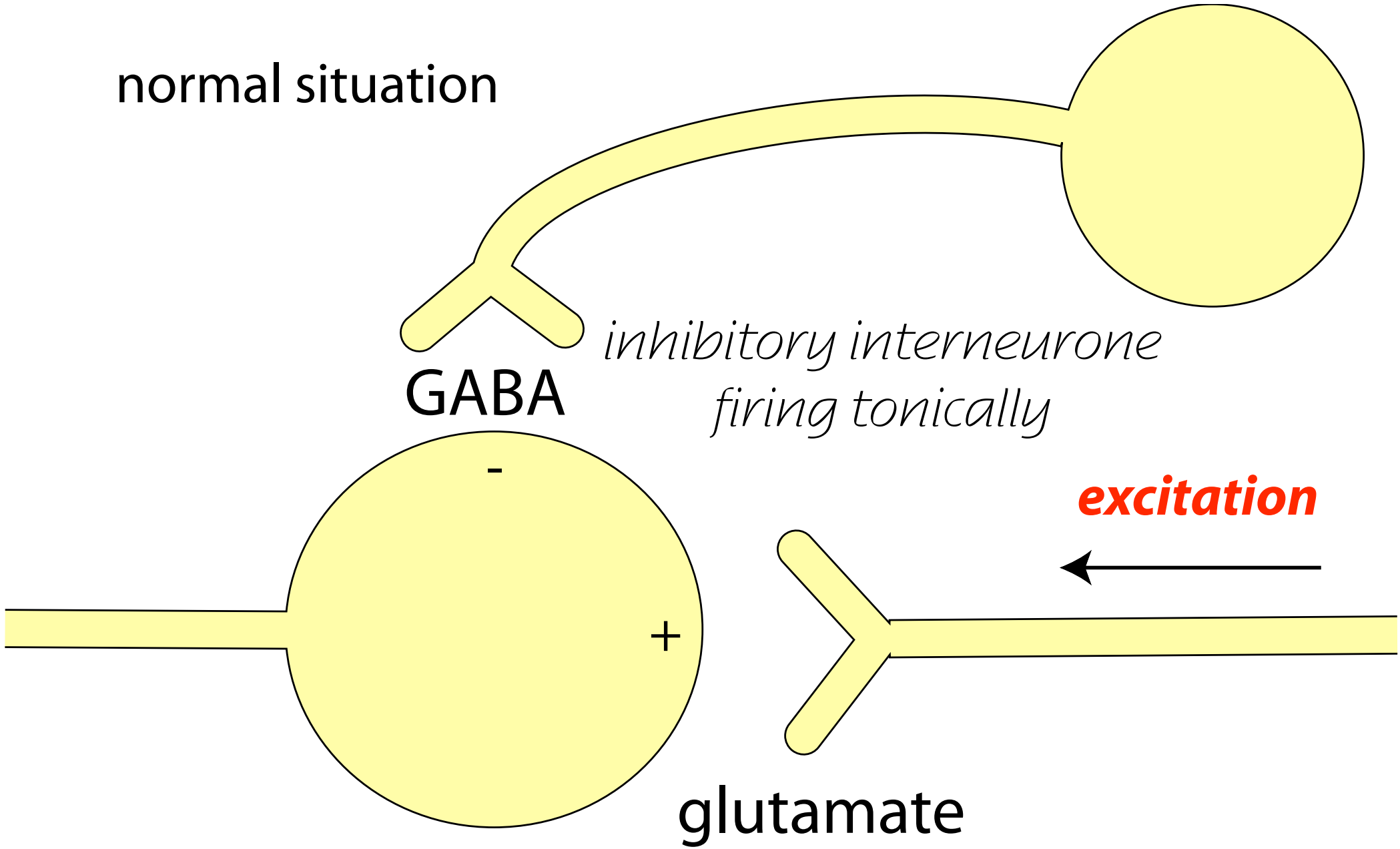
definitions

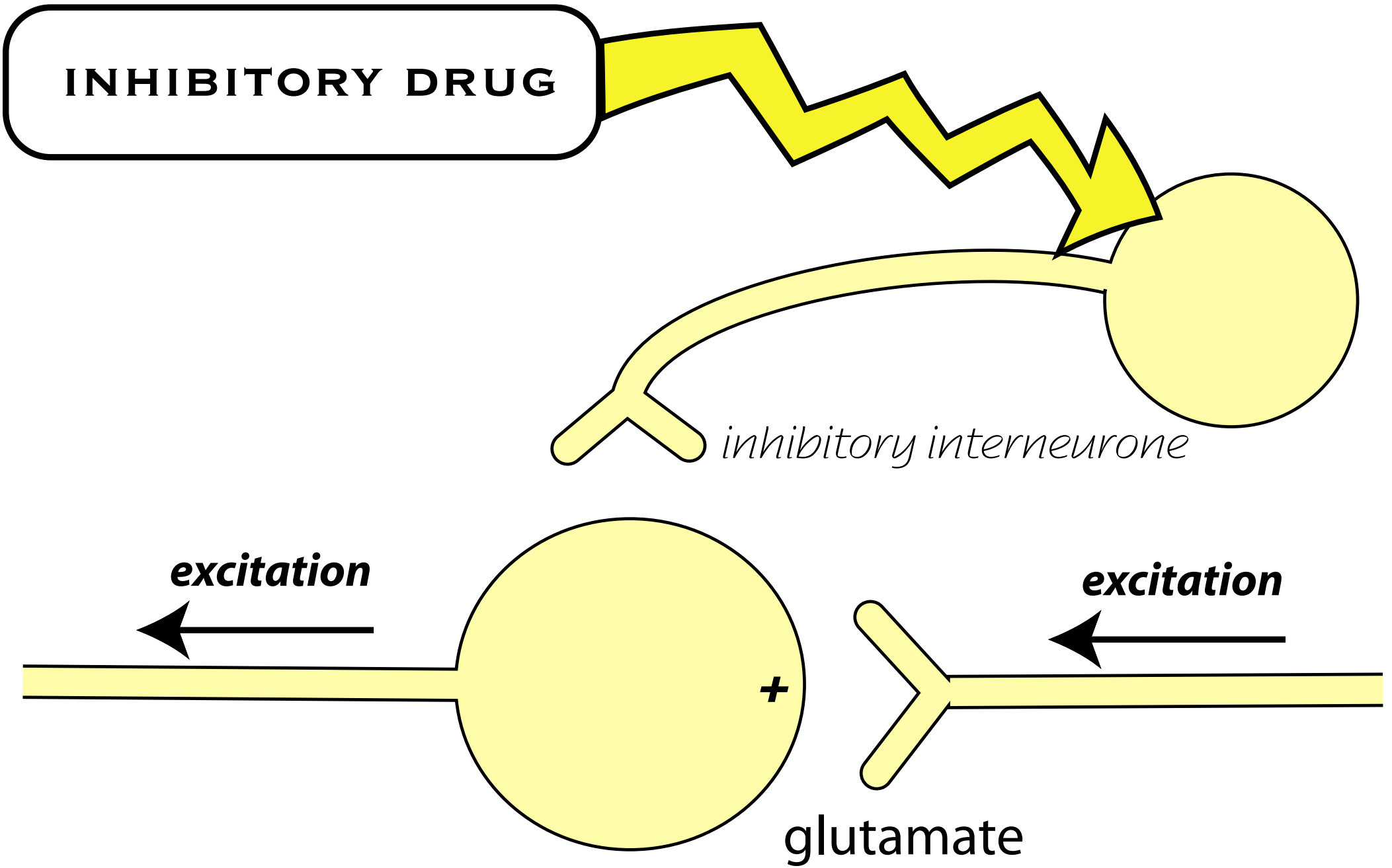
- neurotransmitter
  - acts rapidly, briefly & at short range
- neuromodulator
  - act more slowly and further away
  - responsible for most synaptic plasticity
  - not always from neurones

effects

- behavioural – ? – cellular
- depend on
  - wiring (NGF etc)
  - receptor subtypes , distribution & numbers
  - transduction mechanisms
  - neuromodulators
  - their transduction mechanisms
  - all these can change!


disinhibition


normal situation
inhibitory interneurone
firing tonically
GABA
-
excitation
+
glutamate


INHIBITORY DRUG
inhibitory interneurone
excitation
excitation
+
glutamate

time course

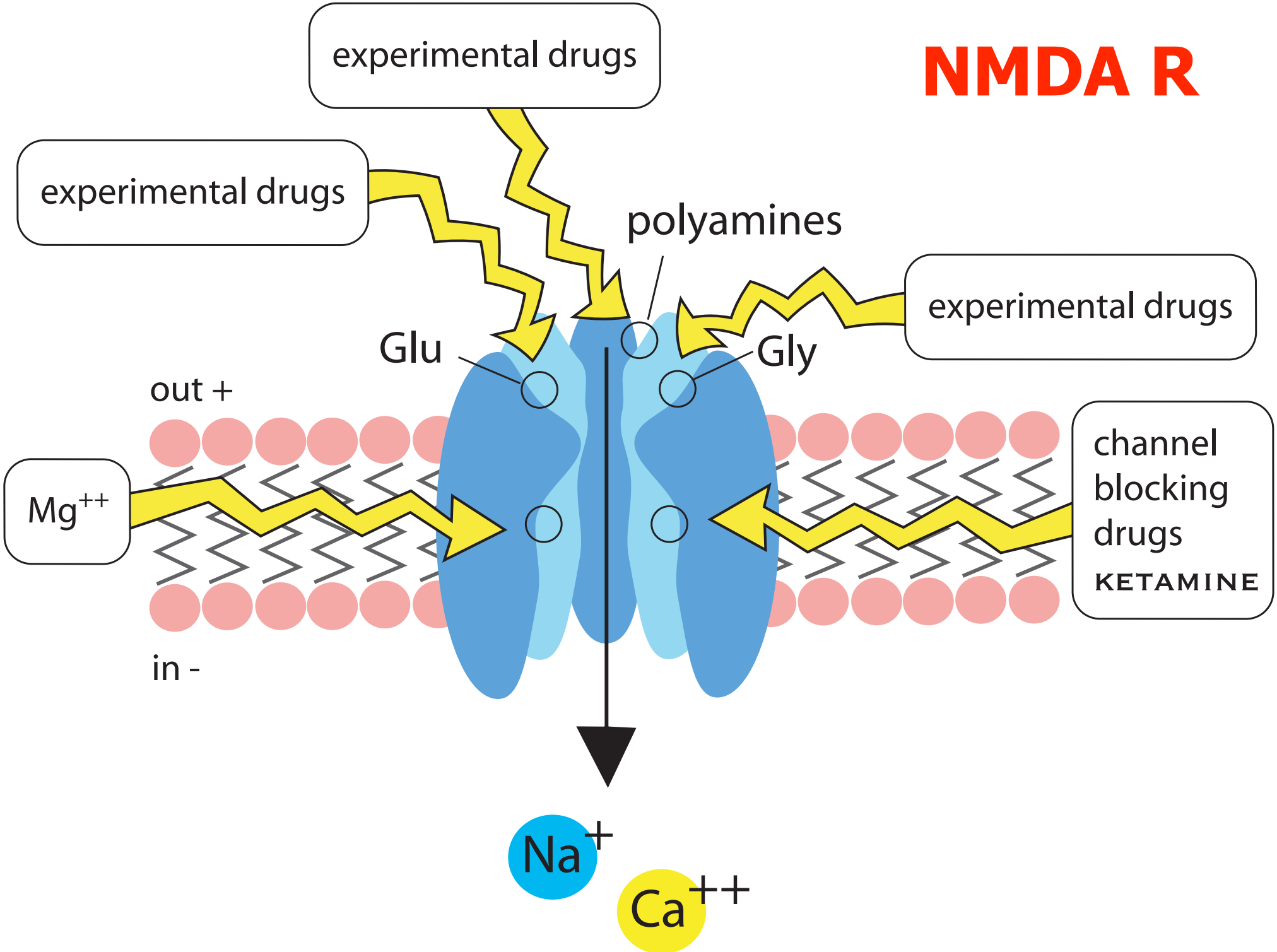
- milliseconds
  - fast transmitters
- tens of ms
  - NMDA receptors
- seconds – minutes
  - neuromodulators
- minutes – days
  - receptor up / down regulation
- days – weeks (-never)
  - neurone reconnections

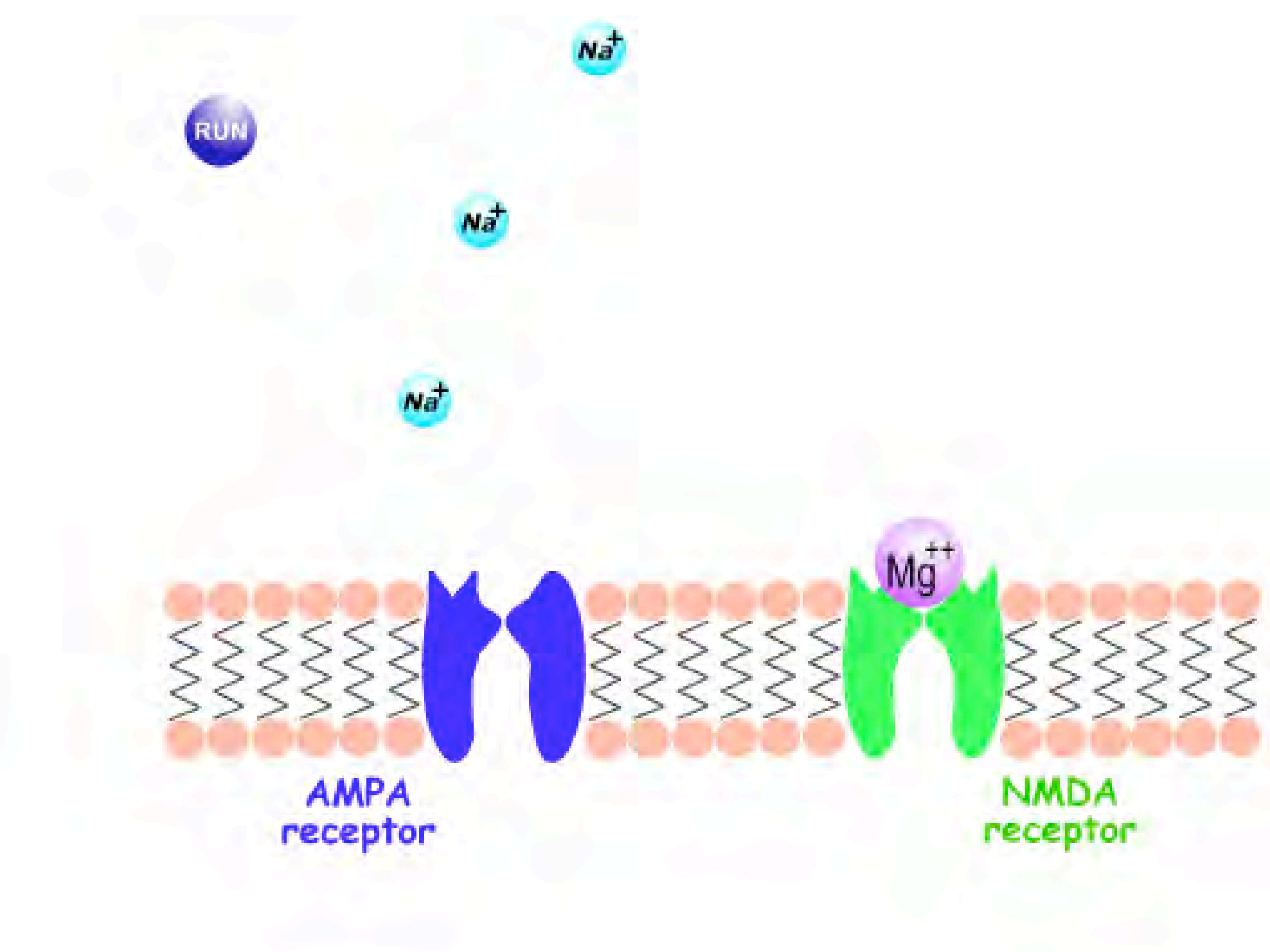
neurotransmitters

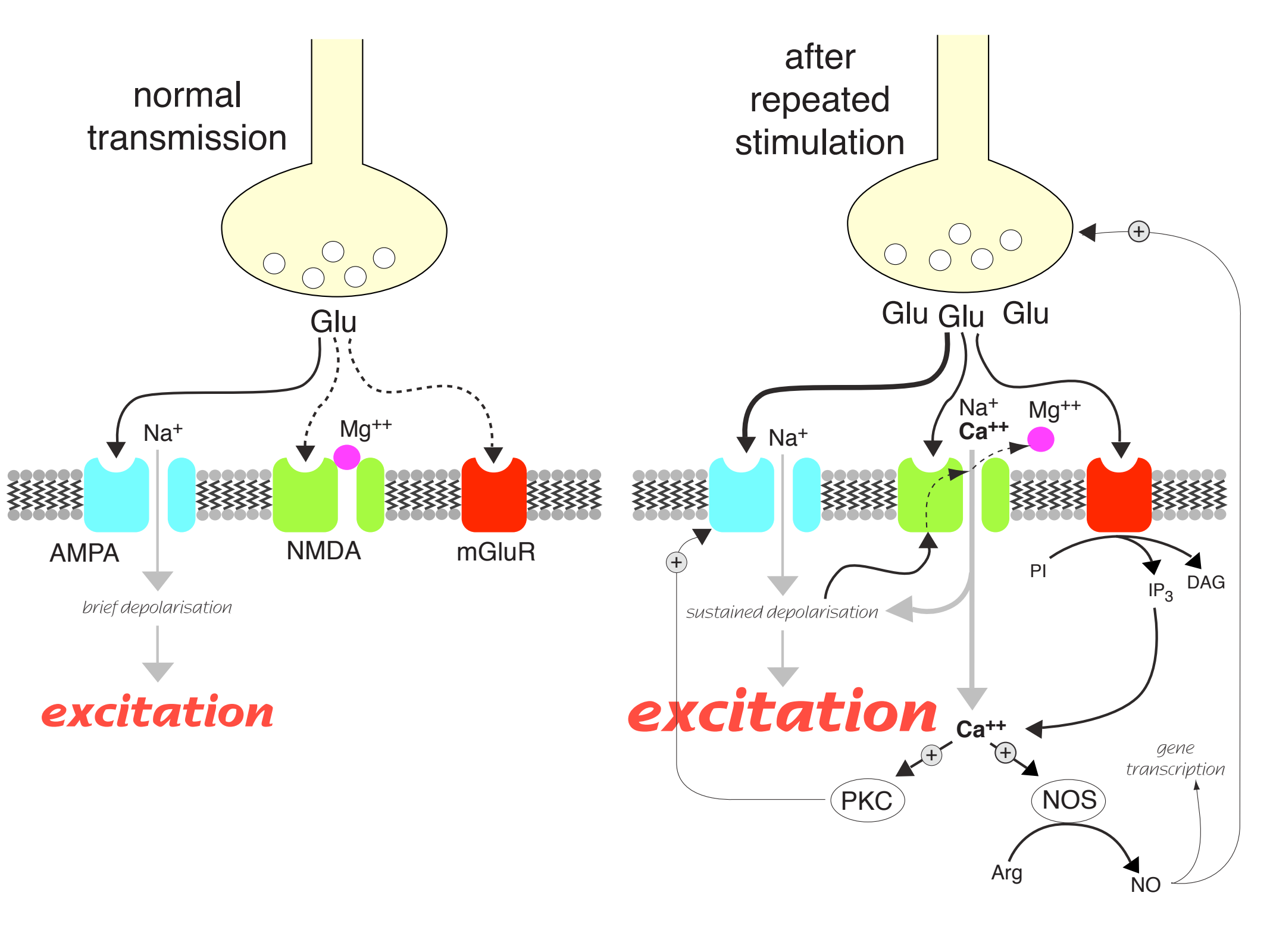
- excitatory
  - glutamate
- inhibitory
  - GABA
  - glycine
  - catecholamines
- both / either
  - 5HT
  - adenosine / ATP

glutamate receptors

- AMPA fast
  - normal transmission
- NMDA medium
  - wind up
  - pain
  - memory
- metabotropic slow (9 subtypes)
  - modulation?
- kainate fast
  - ?


NMDA R
experimental drugs
experimental drugs
polyamines
experimental drugs
Glu
Gly
out +
Mg++
channel blocking drugs
KETAMINE
in -
Na+
Ca++


Na+
RUN
Na+
Na+
Mg++
AMPA
receptor
NMDA
receptor


normal transmission
Glu
Na+
Mg++
AMPA
NMDA
mGluR
brief depolarisation
excitation
after repeated stimulation
Glu Glu Glu
Na+
Na+
Ca++
Mg++
PI
IP3
DAG
sustained depolarisation
excitation
Ca++
PKC
NOS
Arg
NO
gene transcription

glutamate

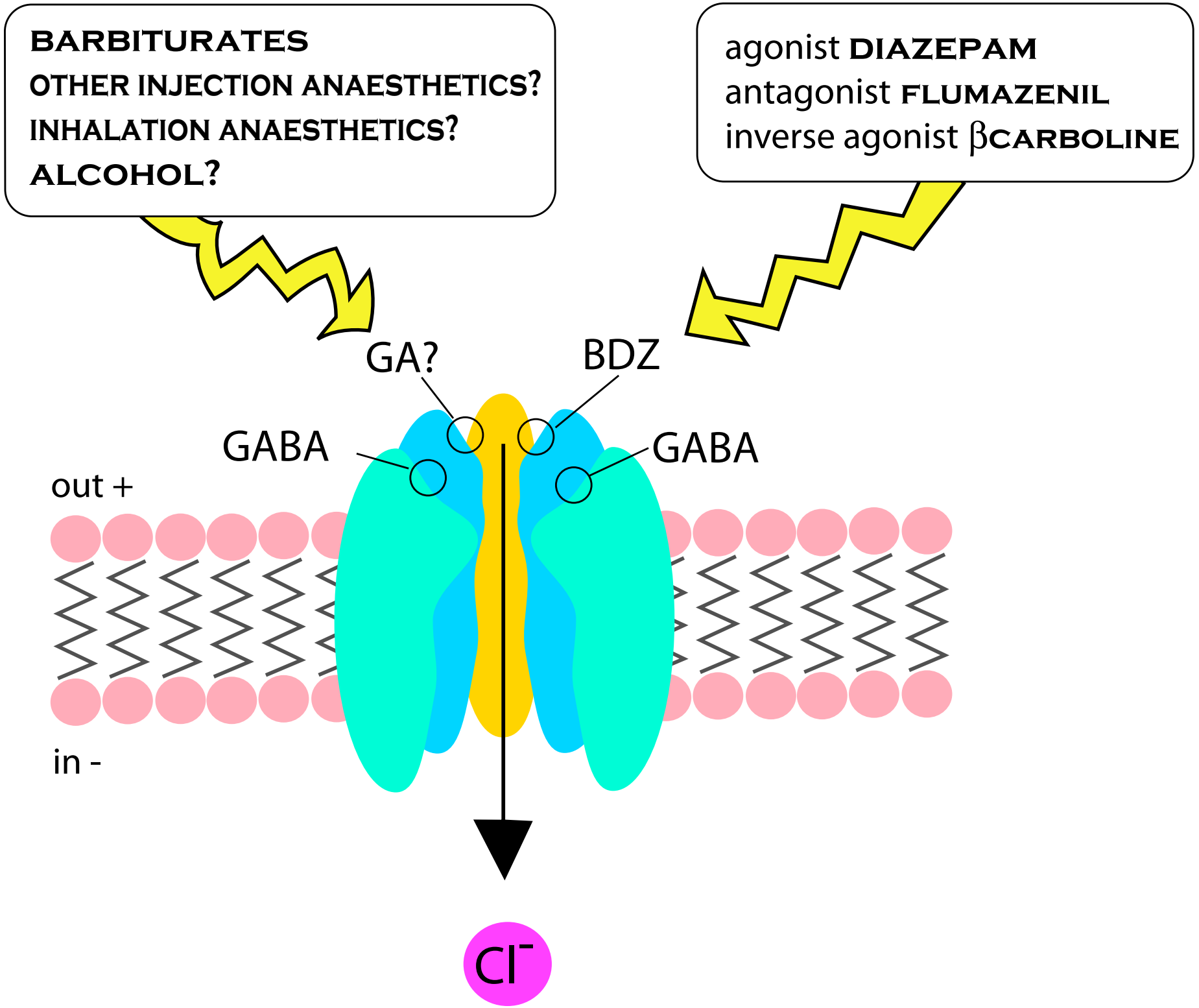
- energy metabolism
- excitotoxicity

neurotransmitters

- excitatory
  - glutamate
- inhibitory
  - GABA
  - glycine
  - catecholamines
- both / either
  - 5HT
  - adenosine / ATP

GABA / glycine receptors

- $GABA_A$
- glycine
  - postsynaptic chloride channels
- $GABA_B$
  - presynaptic, G protein coupled
- glycine / NMDA
  - on NMDA receptor
- glutamate (nematodes)


BARBITURATES
OTHER INJECTION ANAESTHETICS?
INHALATION ANAESTHETICS?
ALCOHOL?
agonist DIAZEPAM
antagonist FLUMAZENIL
inverse agonist βCARBOLINE
GA?
BDZ
GABA
GABA
out +
in -
Cl-

GABA / glycine receptors

- $GABA_A$
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  - postsynaptic chloride channels
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- glycine / NMDA
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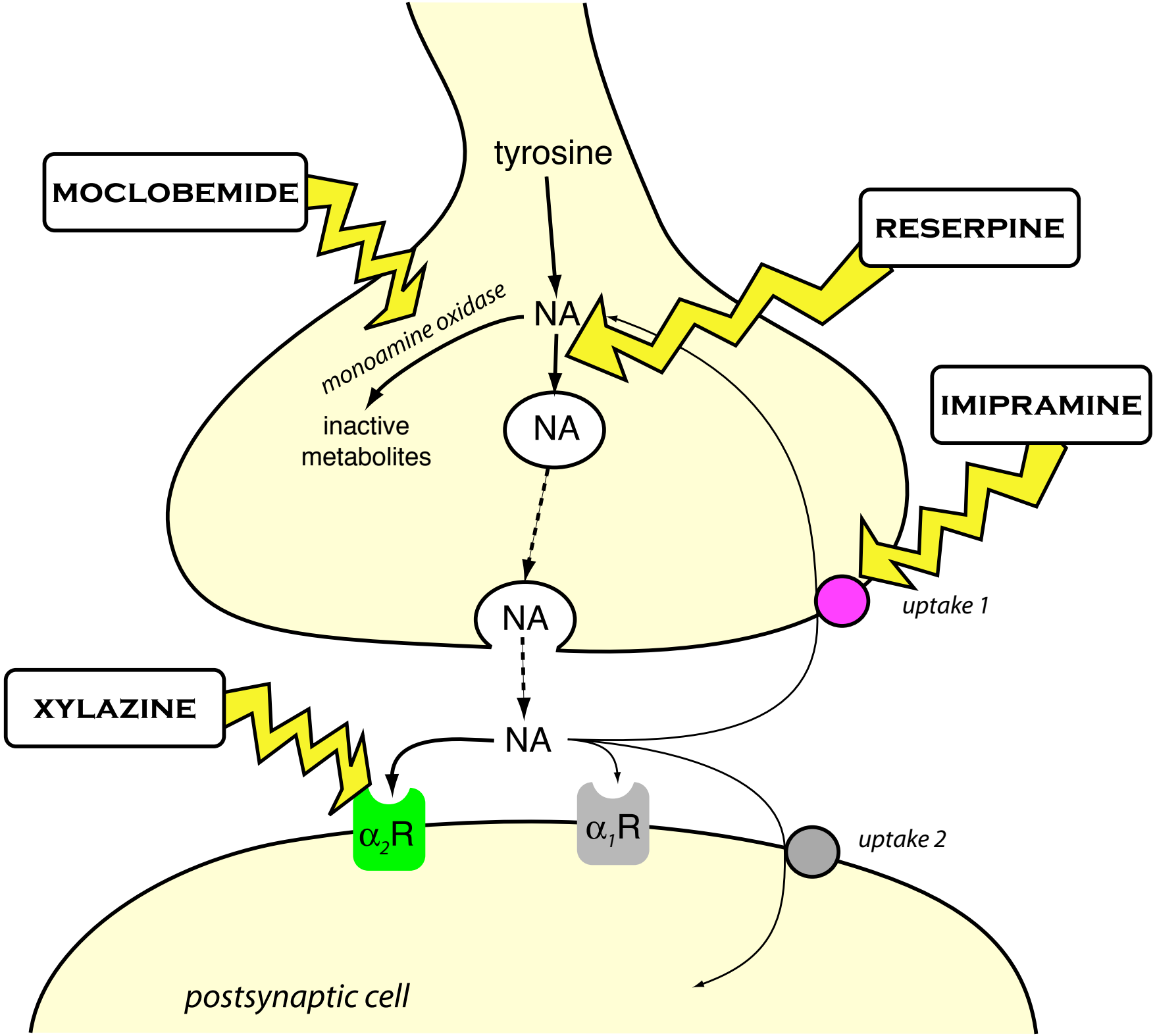
monoamine receptors

- noradrenaline
- dopamine
- 5HT
- octopamine


MOCLOBEMIDE
tyrosine
RESERPINE
monoamine oxidase
NA
inactive
metabolites
NA
IMIPRAMINE
NA
uptake 1
XYLAZINE
NA
α2R
α1R
uptake 2
postsynaptic cell

noradrenaline

- mostly postsynaptic α2
- mostly inhibitory
- alertness, pain, blood pressure

imidazolines

- I1
  - blood pressure
- I2
  - depression?? MAO
- I3
  - insulin release

dopamine

- currently 5 receptors
- D2
  - reward pathway
  - pituitary hormone release
  - nigrostriatal pathway
  - vomiting

5HT receptors in brain

- $5HT_{1A}$ – mood / emotion, pain?
- $5HT_{1C}$ – CSF secretion, motor function
- $5HT_{1D}$ – motor function
- $5HT_{2}$ – stereotypy, mood / emotion, hallucinations
- $5HT_{3}$ – anxiety, emesis, pain?
- + 9 other subtypes!

reuptake inhibitors

- human antidepressants
- used to alter animal behaviour

other fast transmitters

- acetylcholine
  - nAChR, mAChR
- histamine
  - H1, H2, H3
- adenosine, ATP, AMP

purinergic receptors

- adenosine
  - A1 and A2 R – G protein coupled
  - presynaptic inhibition
- ATP
  - P2x (ionotropic) P2y (metabotropic)
  - co-transmission in periphery, nociception

neuromodulators

- excitatory
  - substance P
  - neurokinins A & B
  - cholecystokinin
  - nitric oxide, carbon monoxide
  - arachidonic acid / prostaglandins
  - etc, etc

neuromodulators

- inhibitory
  - encephalins, morphine – μ, δ R
  - some dynorphins – κ R
  - cannabinoids – CB1, CB2 R
  - magnesium?
  - zinc??

adaptive processes

- cfos, cjun
- growth factors


•blood sampled
2d ago
•now licking leg

central neurotransmitters

- glutamate is the main excitatory transmitter
- glutamate acts at AMPA (fast), NMDA (medium) and mglu (slow)
- GABA is the main inhibitory transmitter, acting at $GABA_A$ receptors
- neuromodulators act slowly to amplify or reduce transmission
- noradrenaline, acting a α_2 receptors, causes CNS depression