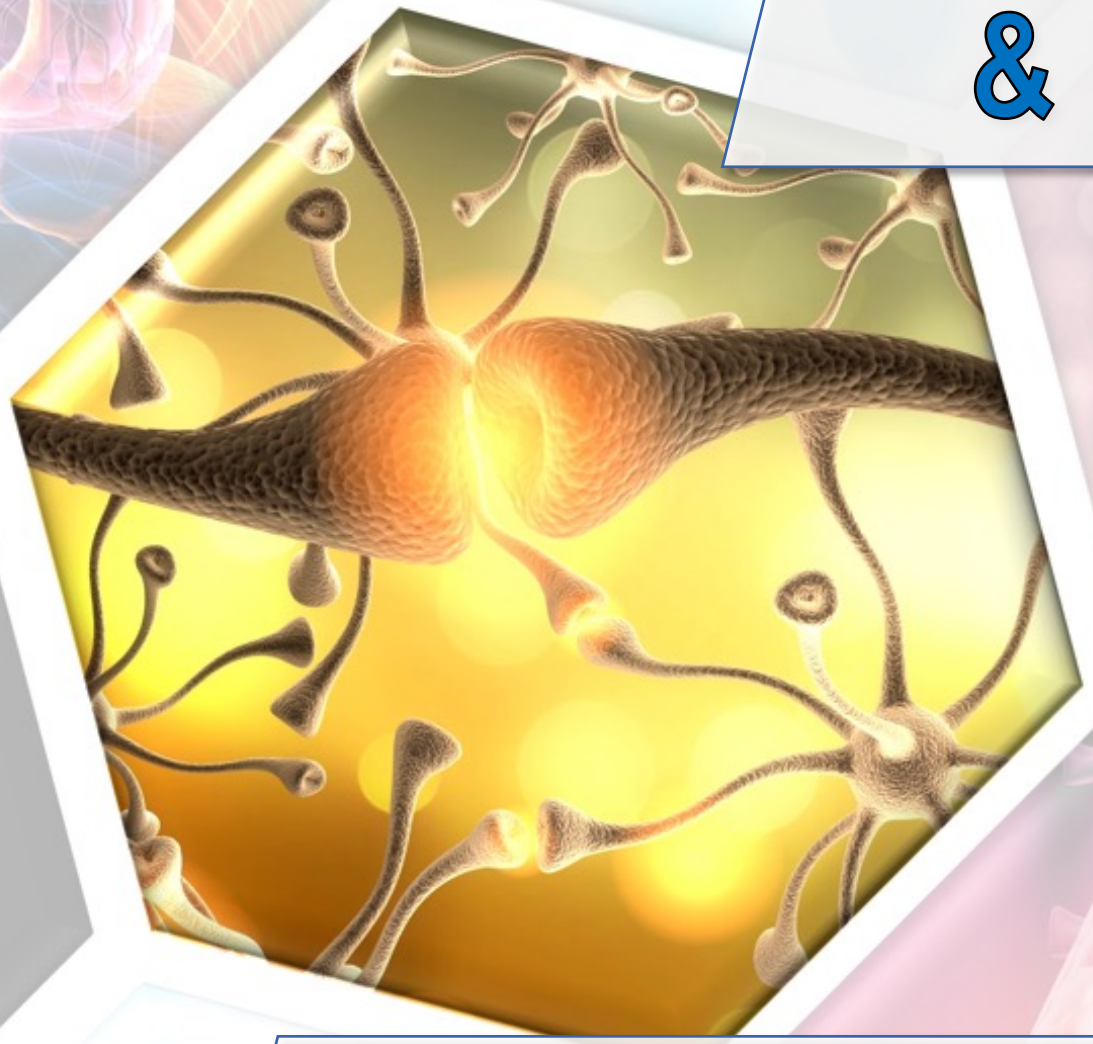
IMPERIAL

Neurotransmitters & Pharmacology



Dr Chris John c.john@imperial.ac.uk

Session Plan

QUESTIONS: Go to **www.menti.com** and use the code **8752 3753**

Synaptic Transmission

Neurotransmitters

Neurotransmitter release

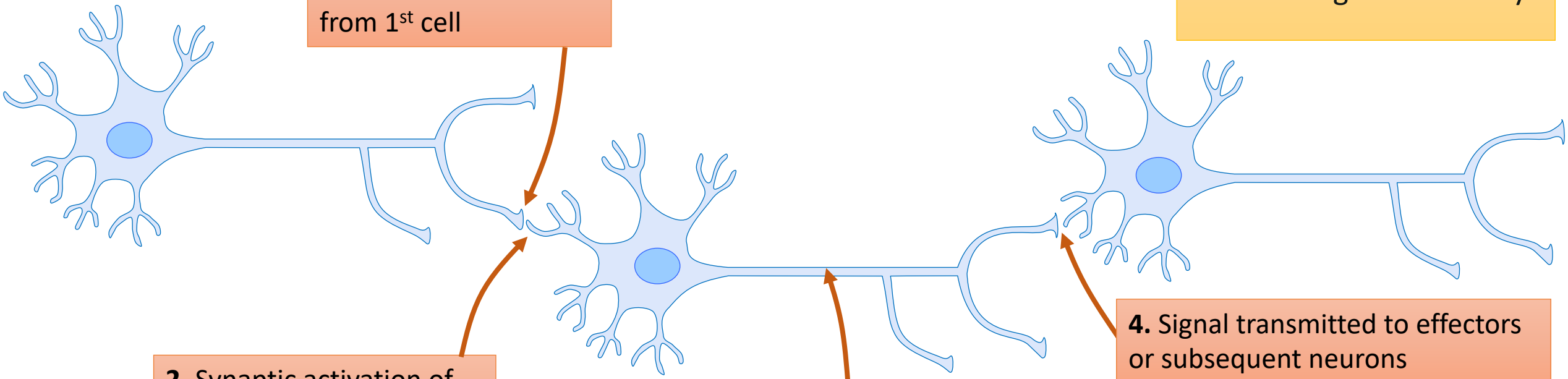
Pharmacology of Neurotransmission

Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

Synaptic Transmission

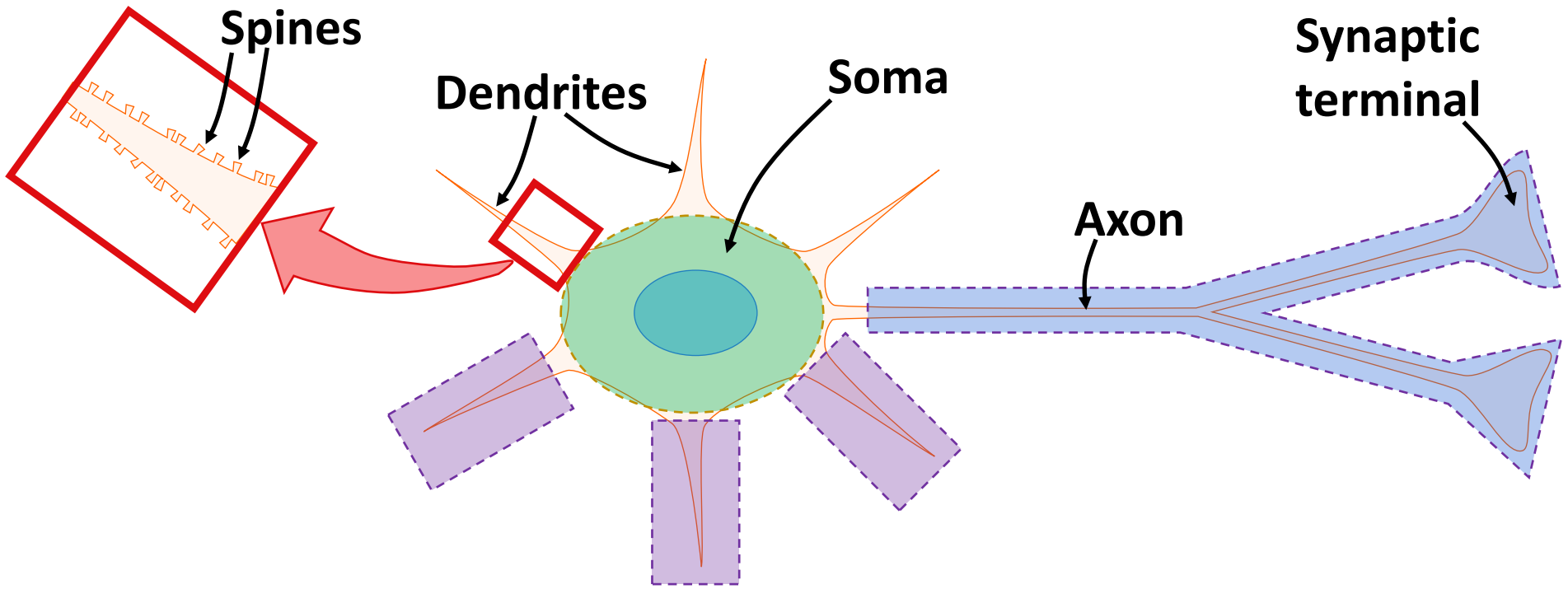
Information transfer across the synapse requires release of **neurotransmitters** and their interaction with **postsynaptic receptors**

- Rapid timescale
- Diversity
- Plasticity
- Learning and memory



Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

Structure



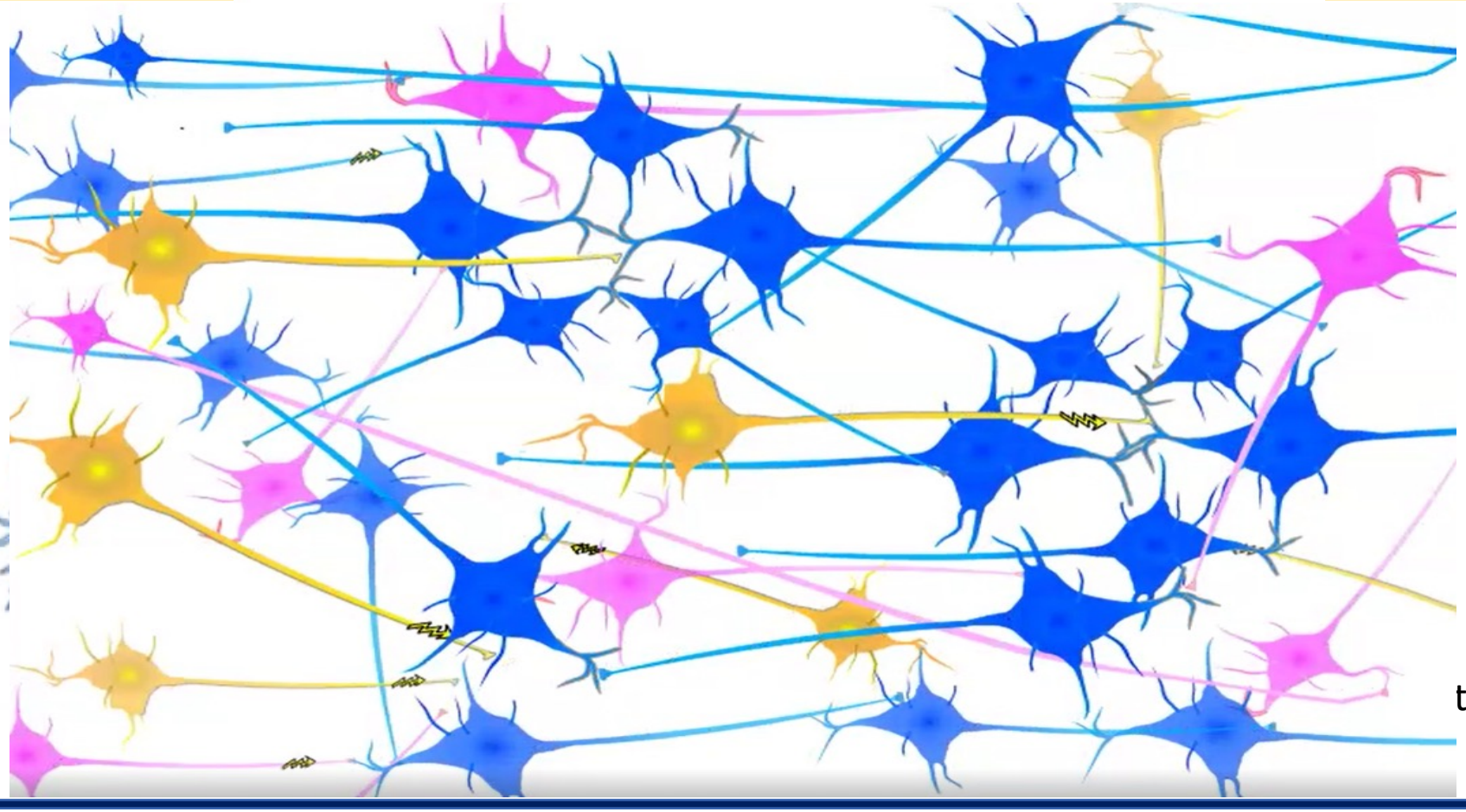
Communication between cells requires **neurotransmitter release**

Information reception → **Integration** → **Rapid transfer** (action potential)

Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

Structure

Each neuron may receive and make **several hundred or thousand** synapses



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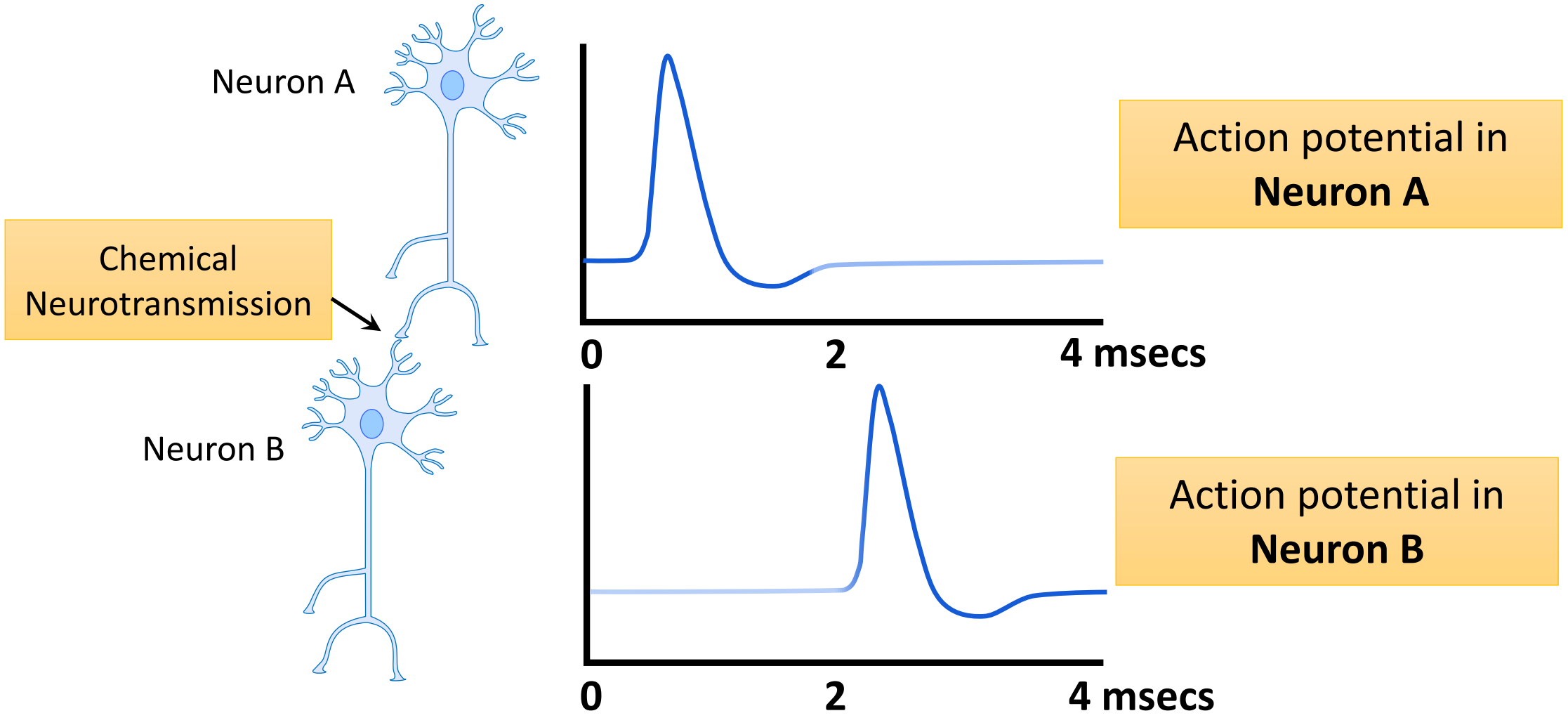
Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

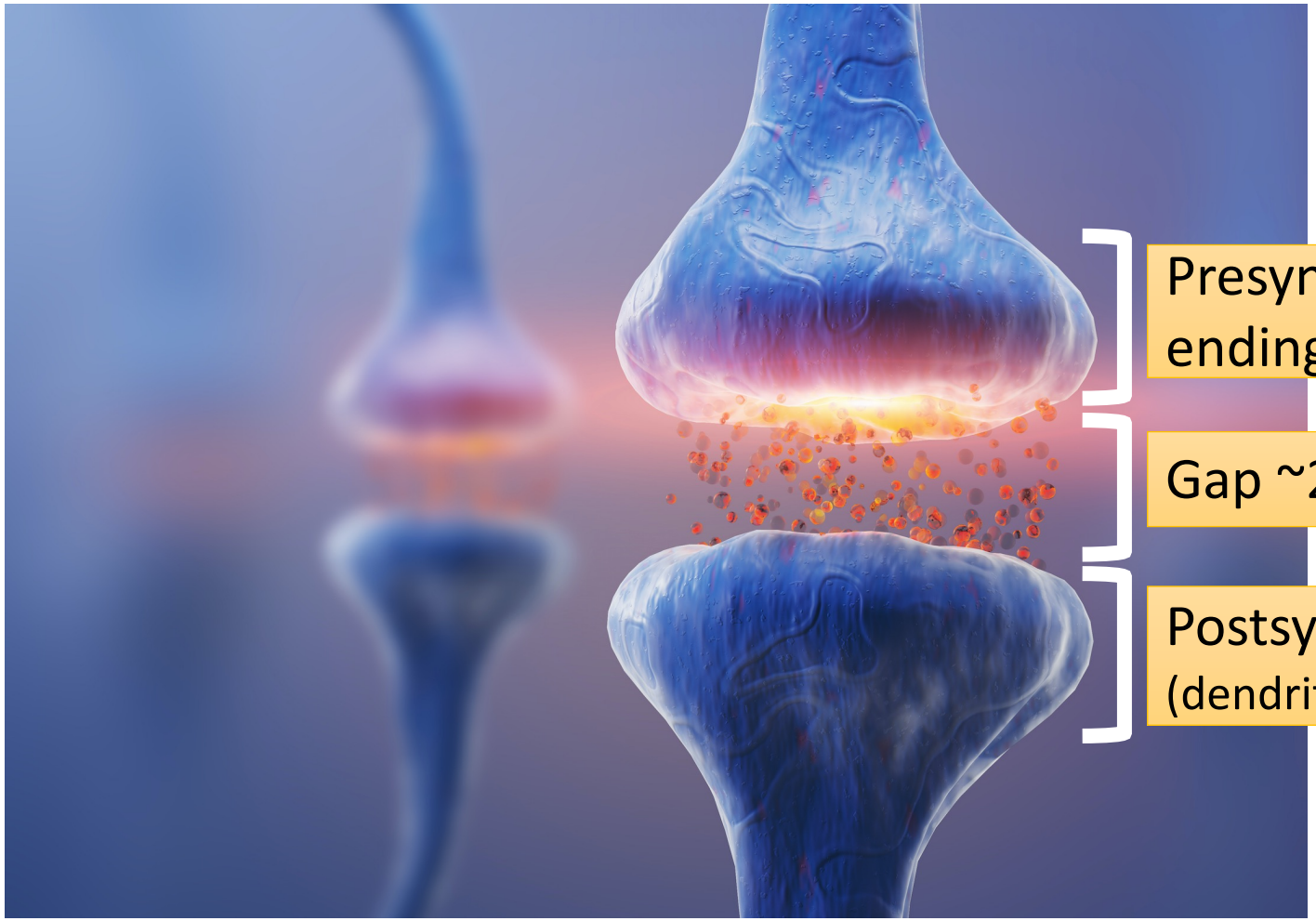
Speed & Chemical Neurotransmission



Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

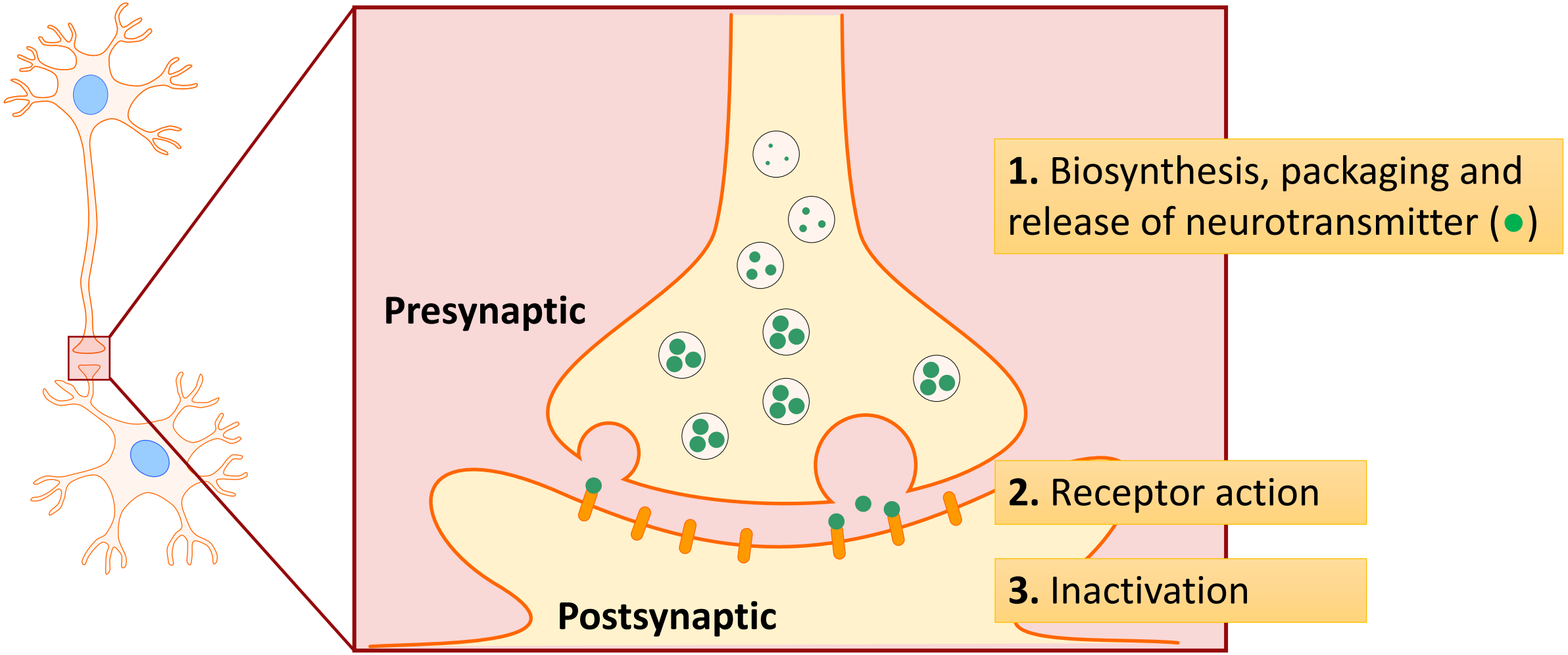
Synapses

Neurotransmission is restricted to specialised structures called **synapses**



Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

Synaptic transmission: 3 stages



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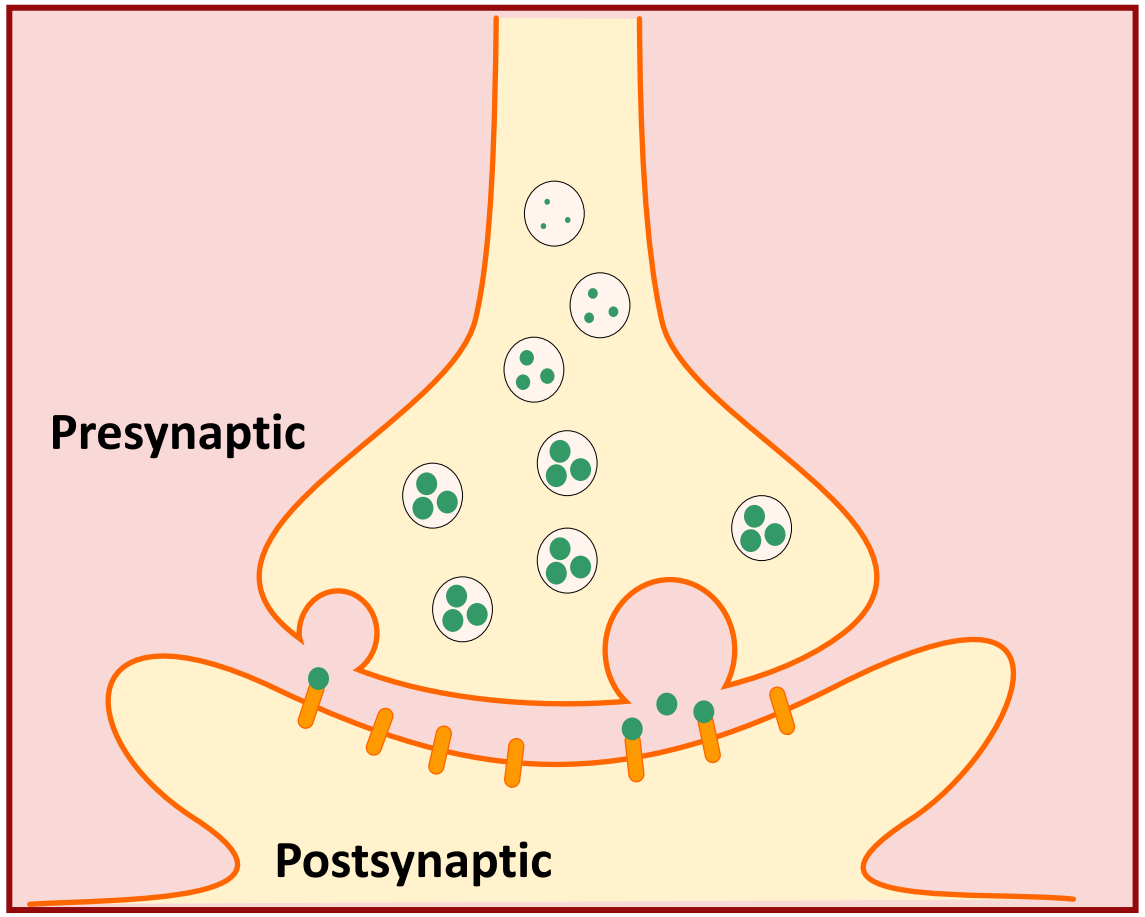
Neurotransmitters



Enormous diversity in variety of transmitters and their receptors including **Amino acids** (e.g. glutamate, γ-aminobutyric acid [GABA], glycine [Gly]), **Amines** (e.g. noradrenaline [NA] and dopamine [DA]) and **Neuropeptides** (e.g. opioid peptides)

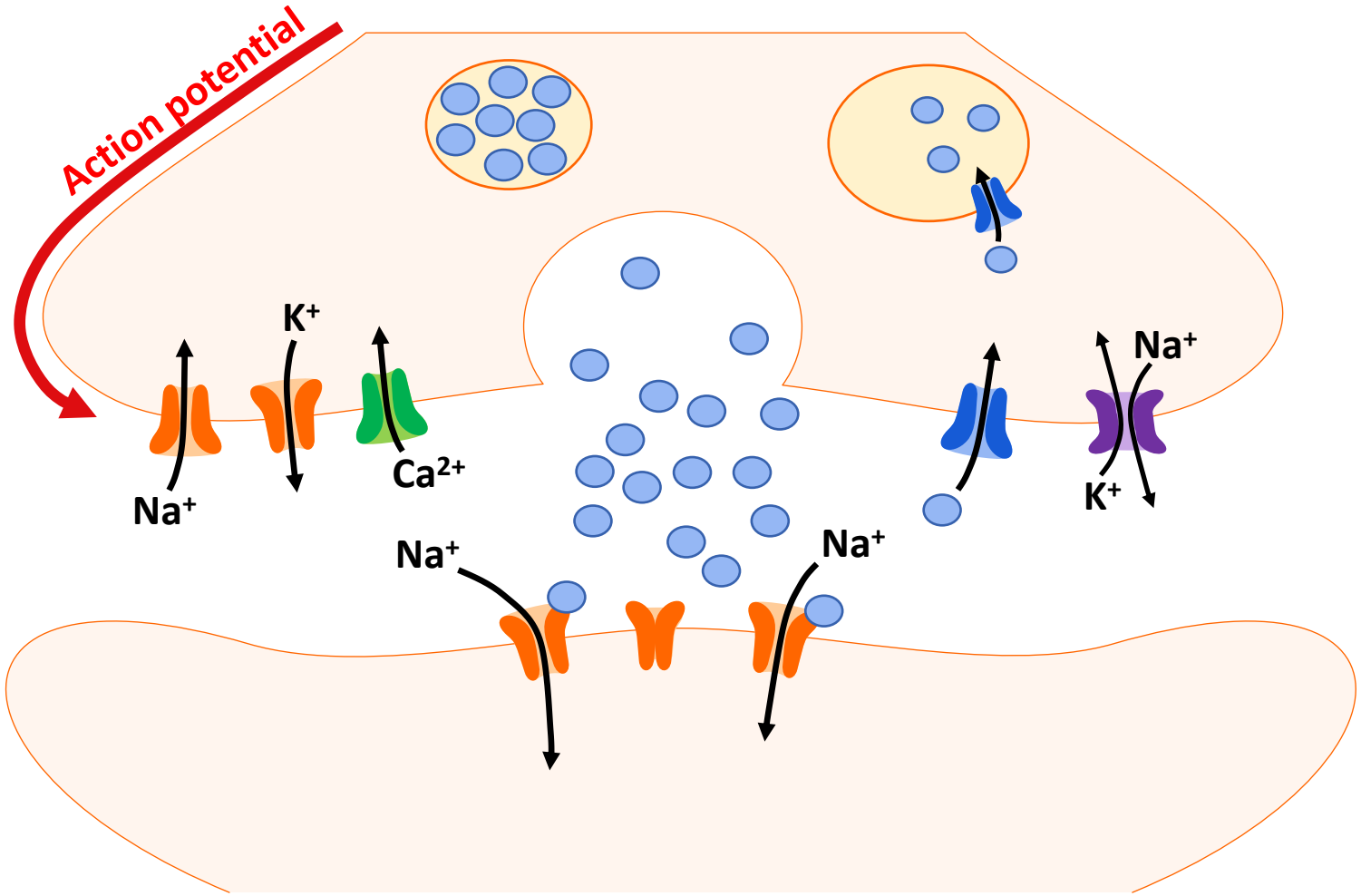
Vary in abundance from **nM** to **mM** CNS tissue concentrations

May mediate **rapid** (µs - ms) or **slower** effects (secs)

Neurons receive multiple transmitter influences which are integrated to produce diverse functional responses

Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

Activation of a CNS synapse



Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

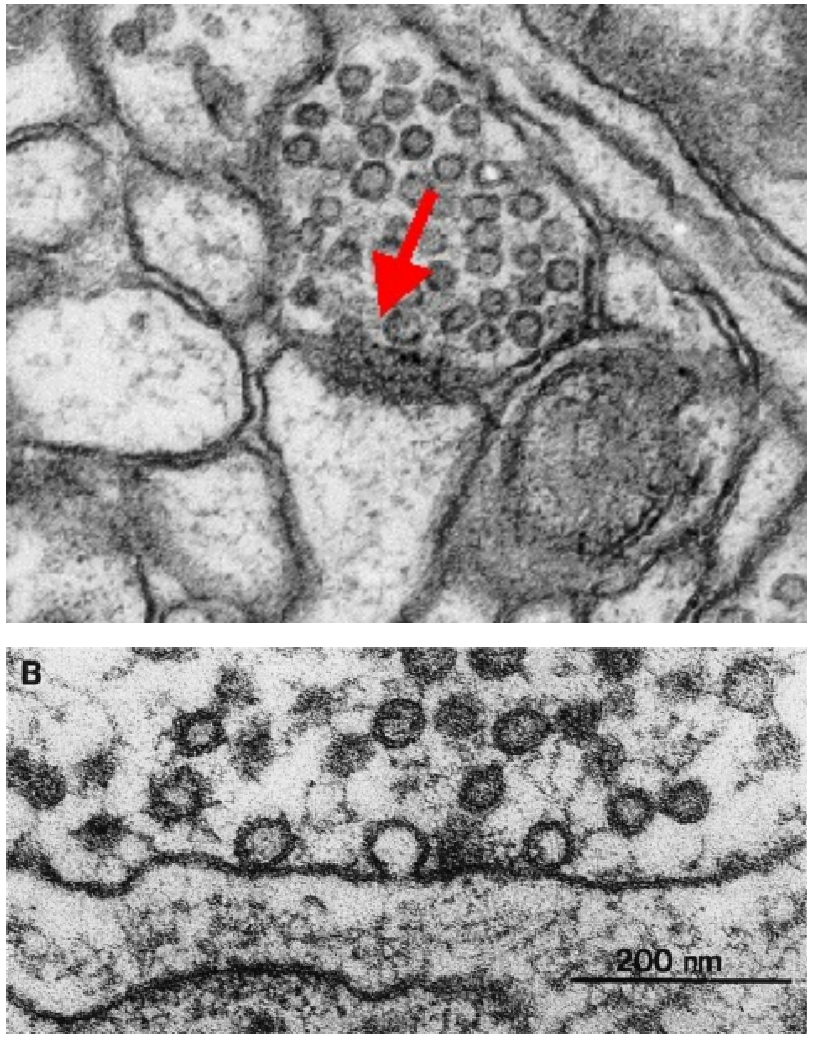
Recap: synaptic transmission – essential features

Restricted to specialised structures - the **synapses**

Calcium is essential - transmitter release requires an increase in intracellular Ca^{2+} (200 μM)

Transmission is **fast** - within ms

Synaptic vesicles (SVs) provide the source of neurotransmitter (4,000-10,000 molecules per SV)



Heuser, 1977

Neurotransmitter release

Activation of transmitter release is calcium dependent and requires RAPID transduction

Membrane depolarisation

Ca^{2+} channels open

Ca^{2+} influx

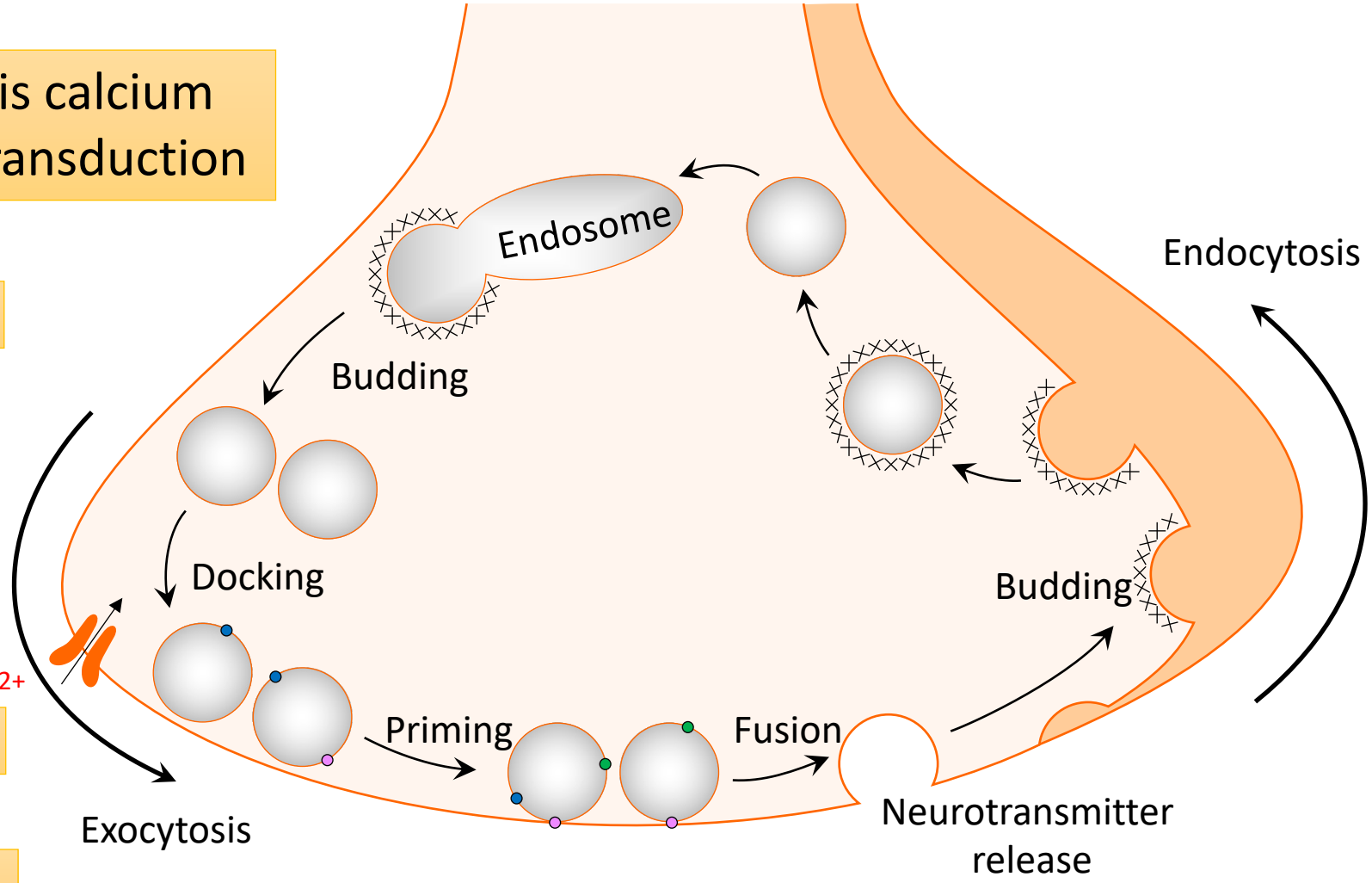
Vesicle fusion

Vesicle exocytosis

Transmitter release

Electromechanical transduction

200 µs

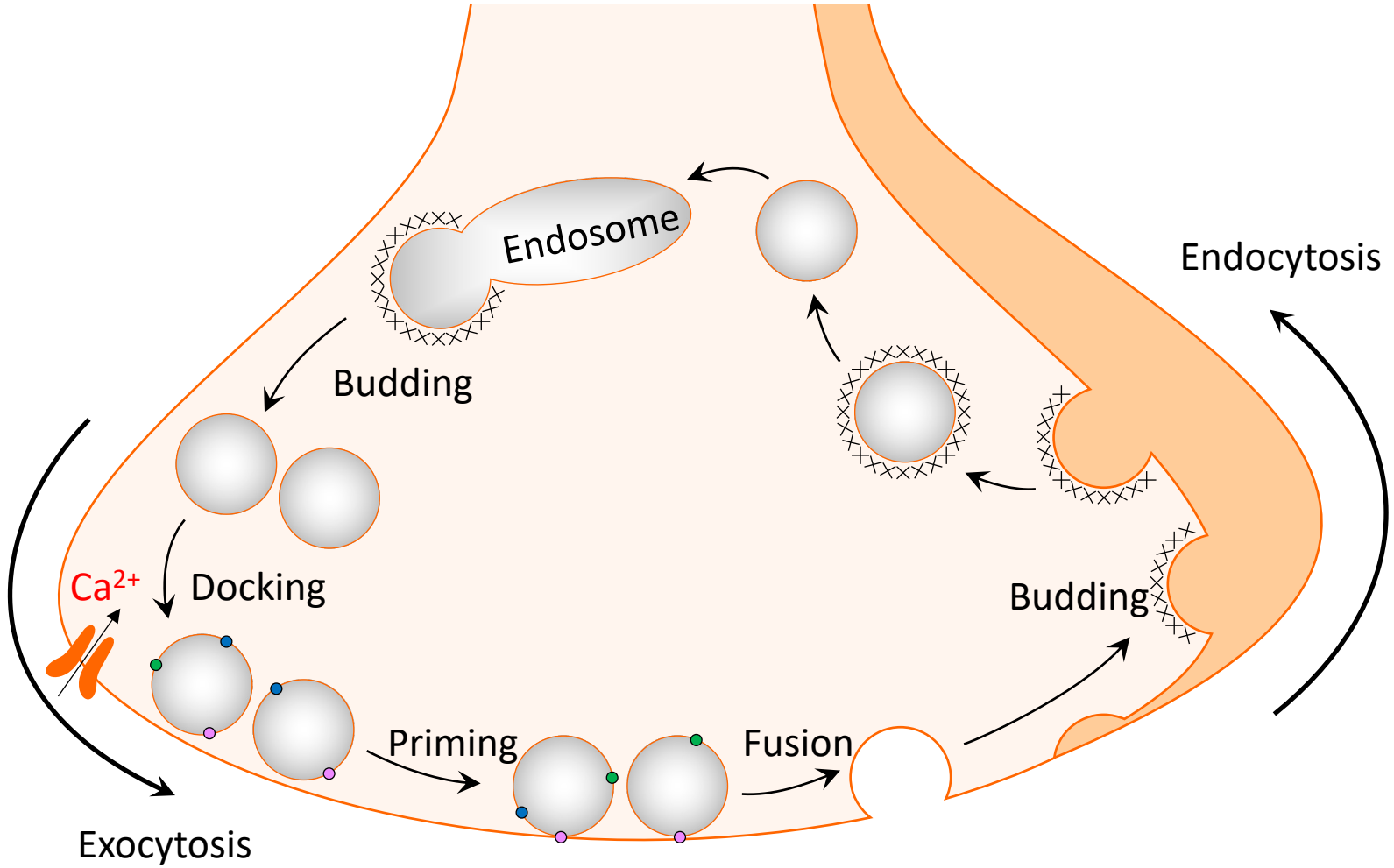


How do rapid release rates occur?

Synaptic vesicles are filled with neurotransmitter (T) and docked in the **synaptic zone**

Special proteins on the vesicle and presynaptic membrane enable fusion & exocytosis

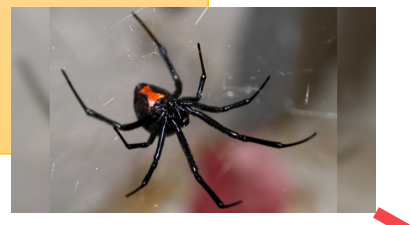
Thomas Sudhof: Nobel Prize for Physiology or Medicine, 2013



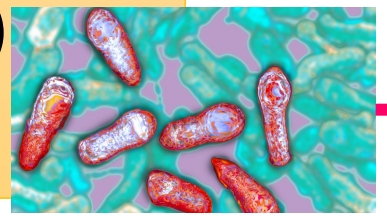
Neurotoxins

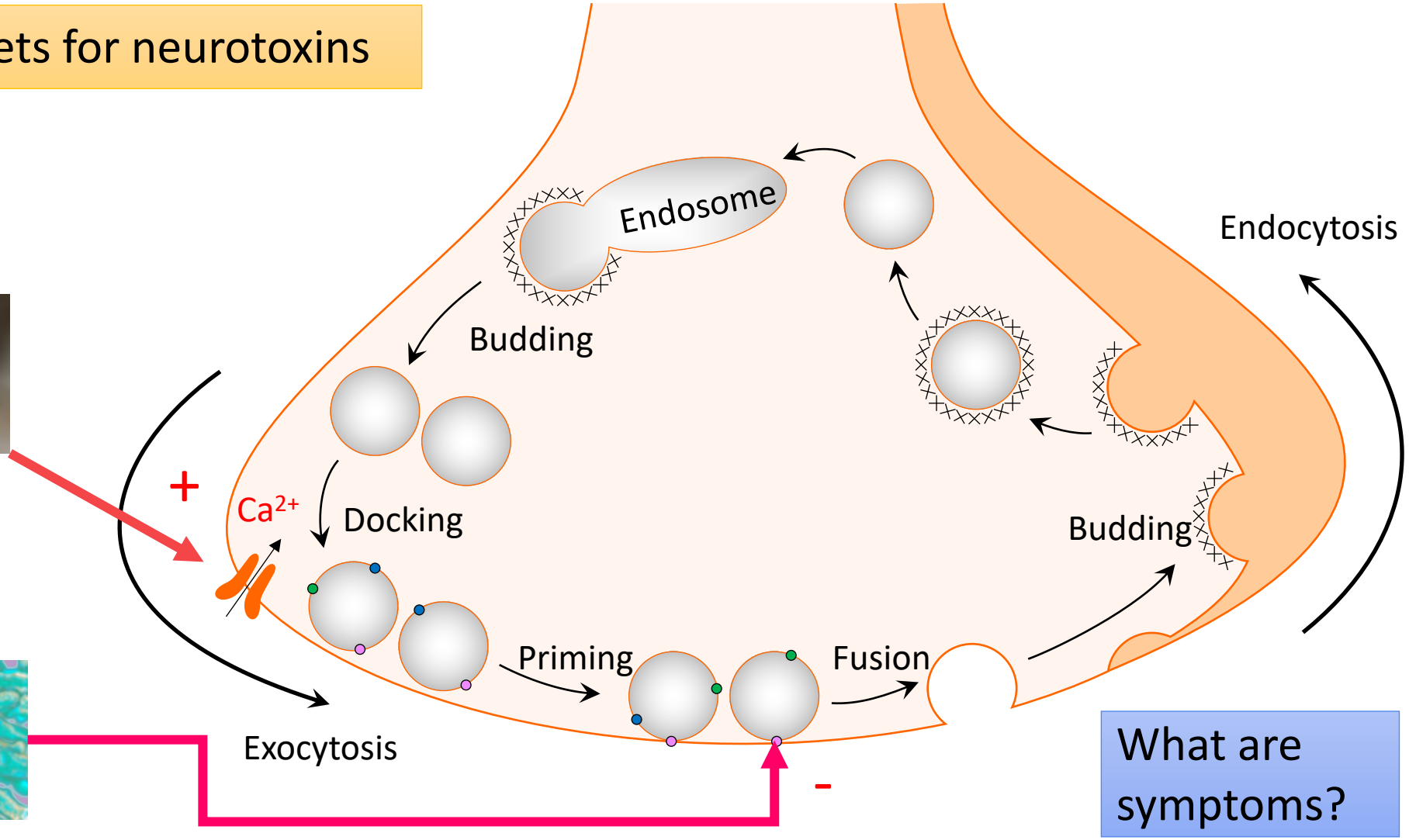
Vesicular proteins are targets for neurotoxins

Alpha latrotoxin



BOTULINUM TOXIN
(C botulinum)





What are symptoms?

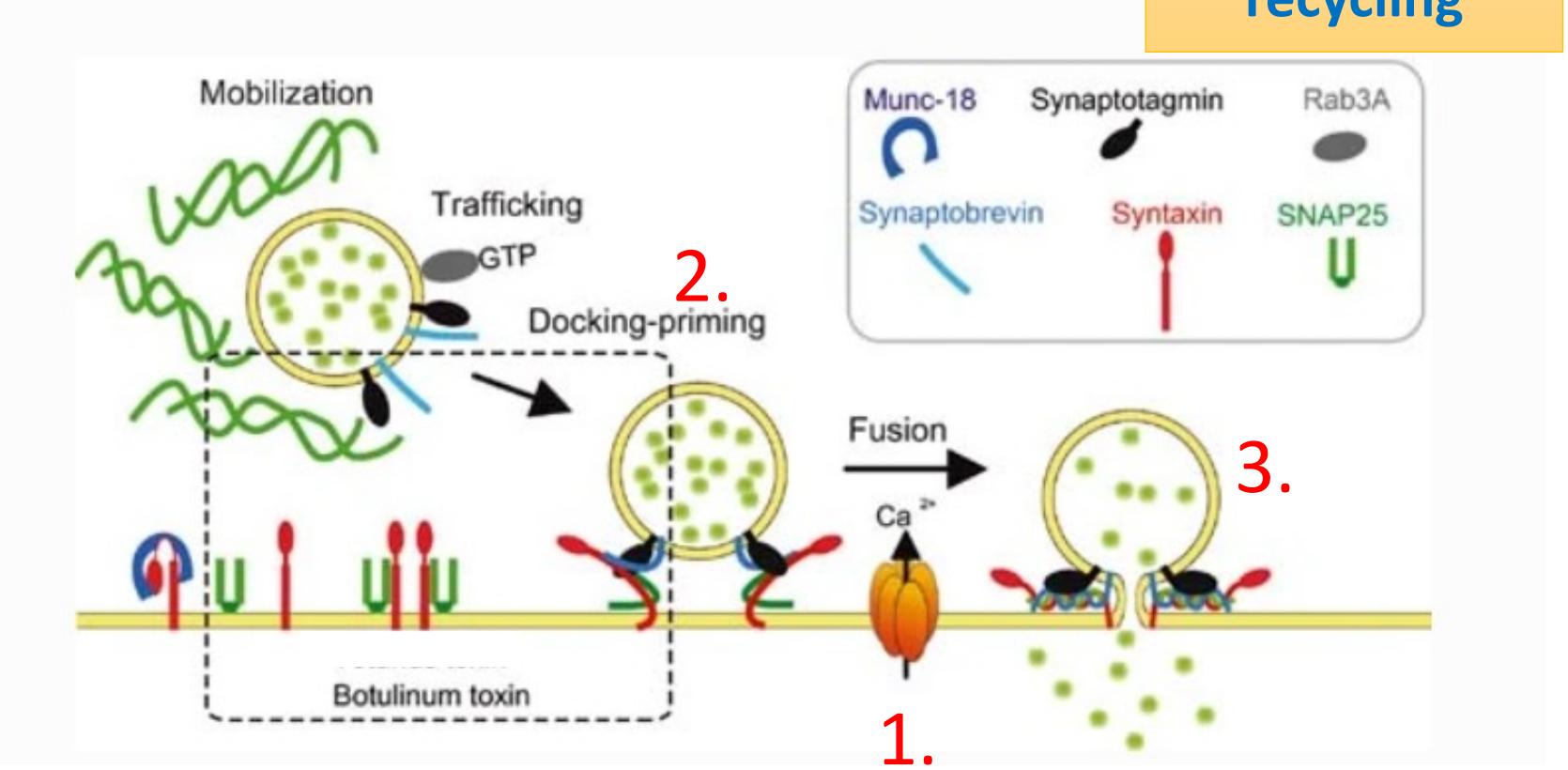
Recap: Transmitter release requirements

1. Calcium-dependent (Ca^{2+})

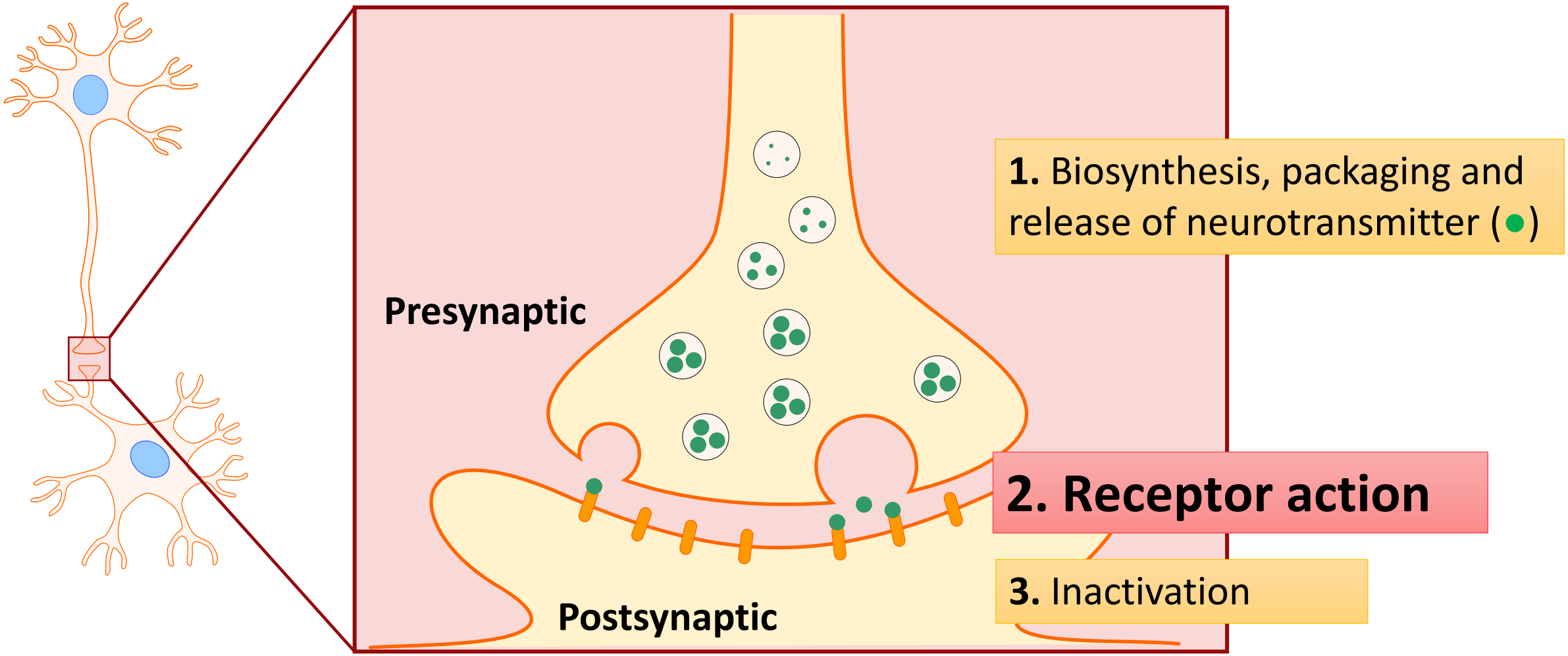
2. Transmitter-containing **vesicles** to be **docked** on the presynaptic membrane

3. Protein complex formation between vesicle, membrane and cytoplasmic proteins to enable both vesicle docking and a **rapid response to Ca^{2+} entry** leading to membrane **fusion and exocytosis**

ATP and **vesicle recycling**



Chemical transmission



Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

Session review

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Synaptic Transmission

- Is responsible for information transfer across neuronal synapses
- Requires the release of neurotransmitters and their interaction with postsynaptic receptors
- Occurs very rapidly - within msecs
- Synaptic vesicles (SVs) provide the source of neurotransmitter

Neurotransmitter release

- Is Ca^{2+} and ATP-dependent
- Requires transmitter containing vesicles to be docked on the presynaptic membrane
- Involves protein complex formation between vesicle, membrane and cytoplasmic proteins to enable vesicle docking and a rapid response to Ca^{2+} entry leading to membrane fusion and exocytosis

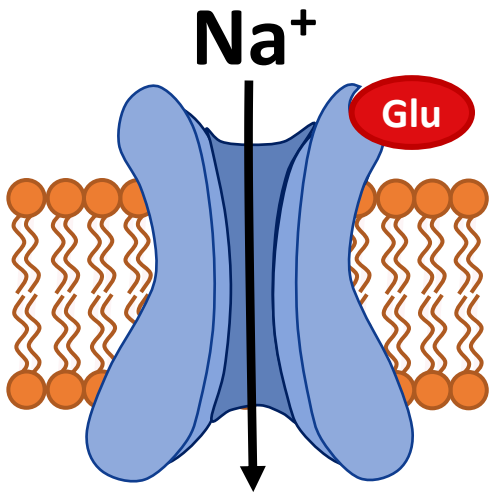
Neurotransmitters

Pharmacology of Neurotransmission

Neurotransmitter action is defined by receptor kinetics

Ion channel-linked receptors

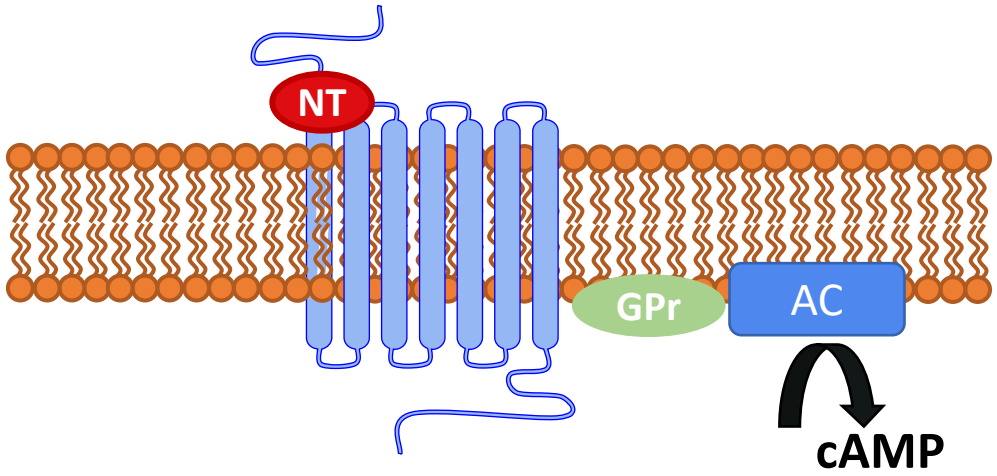
FAST response (msecs)



Mediate all fast excitatory and inhibitory transmission

G-protein-coupled receptors

SLOW response (secs/mins)

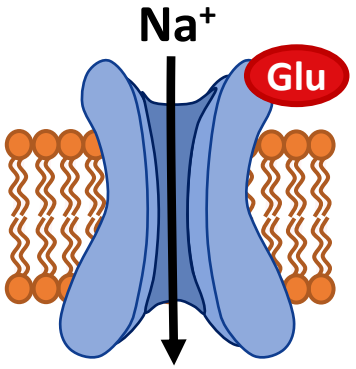


Effectors may be **enzymes** (adenyl cyclase, phospholipase C, cGMP-PDE) or **channels** (e.g. Ca^{2+} or K^{+})

Examples

Ion channel-linked receptors

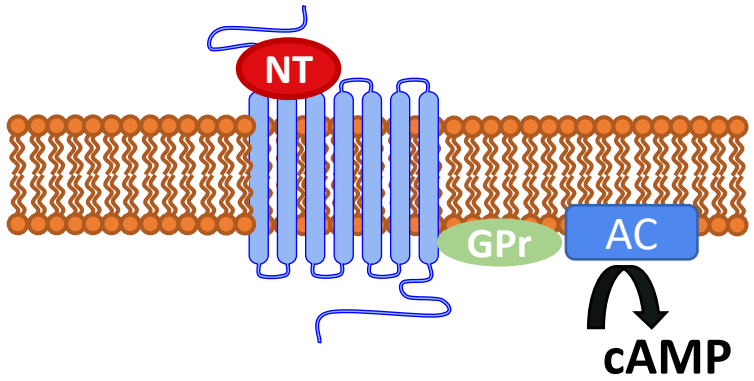
FAST response (msecs)



CNS: Glutamate, γ-aminobutyric acid (GABA)
NMJ: Acetylcholine (ACh) at nicotinic receptors

G-protein-coupled receptors

SLOW response (secs/mins)

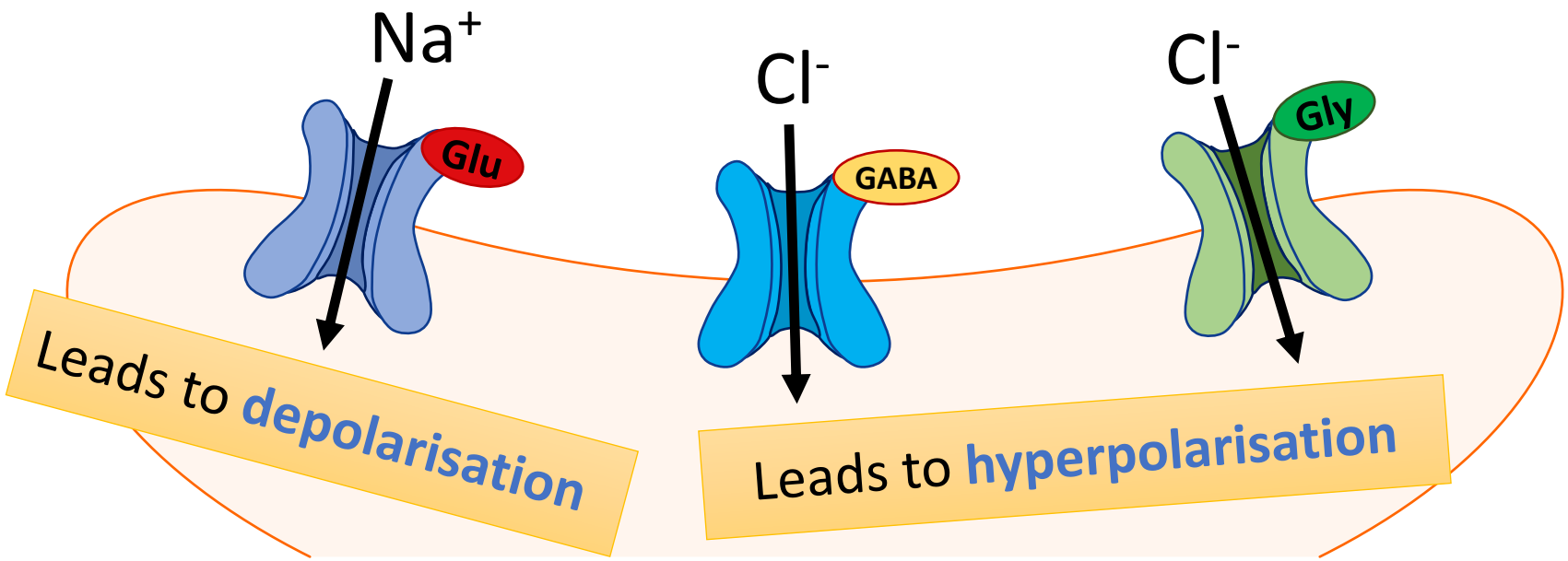


CNS and PNS: **ACh** at muscarinic receptors, dopamine (DA), noradrenaline (NA), serotonin (5HT) and neuropeptides (e.g. enkephalin)

Ion channel-linked receptors

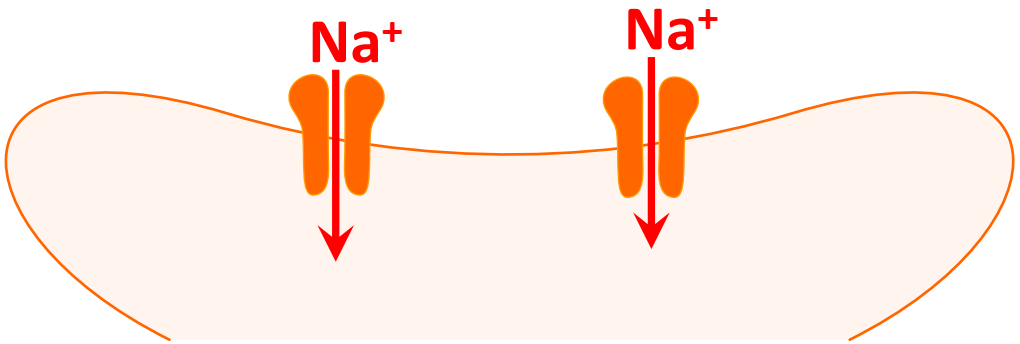
Rapid activation µ to msec
Rapid information flow
Multiple subunit combinations → distinct functional properties

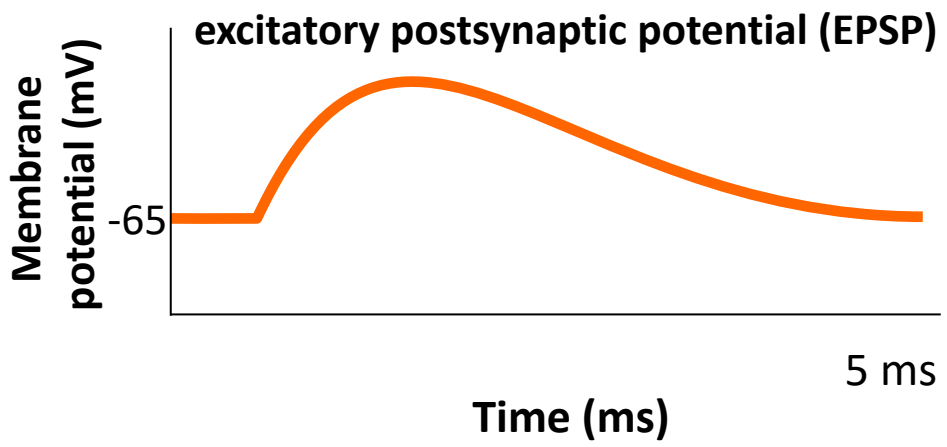
Nicotinic cholinergic receptors (**nAChR**), glutamate (**GluR**), GABA (**GABAR**), glycine (**GlyR**) receptors



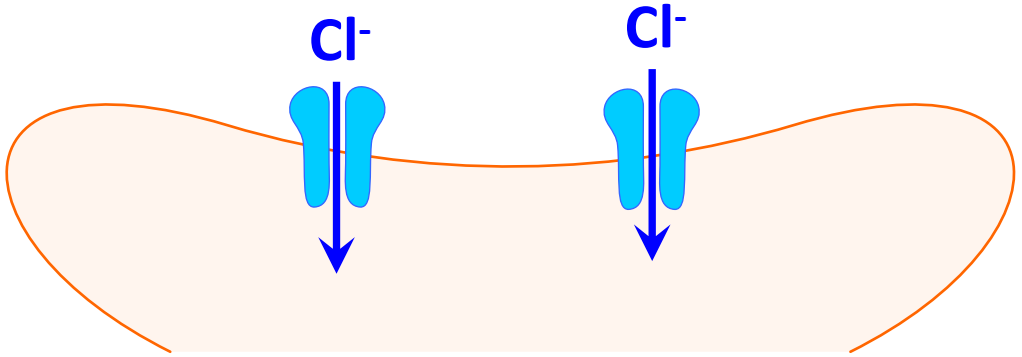
Postsynaptic potentials

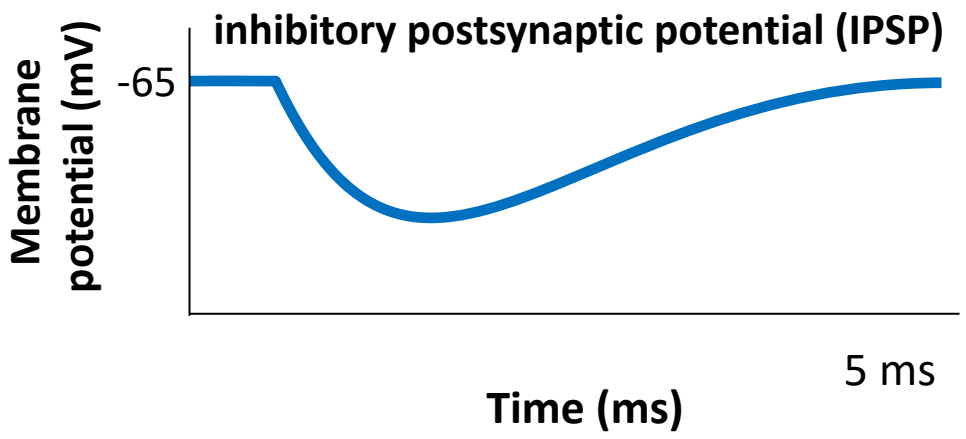
Excitatory neurotransmitter receptor





Inhibitory neurotransmitter receptor





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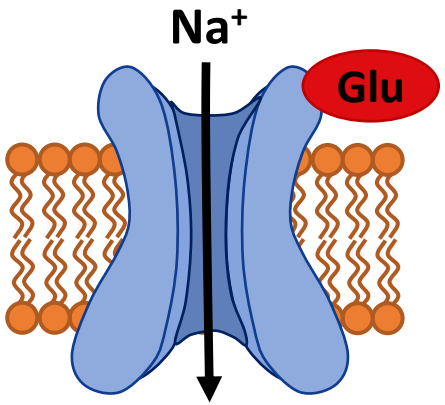
Glutamate receptors

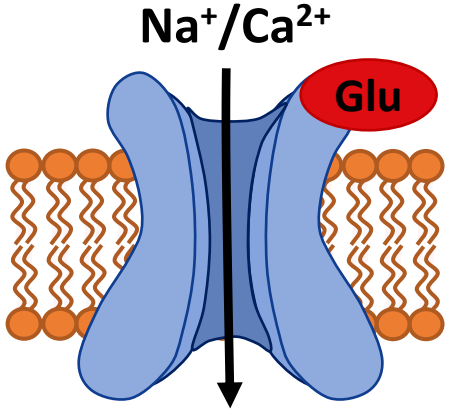
AMPA RECEPTORS
α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid

NMDA RECEPTORS
N-methyl-D aspartate



Most (not all) glutamate synapses have both AMPA and NMDA Rs.

Require co-agonist glycine



Majority of **FAST** excitatory synapses

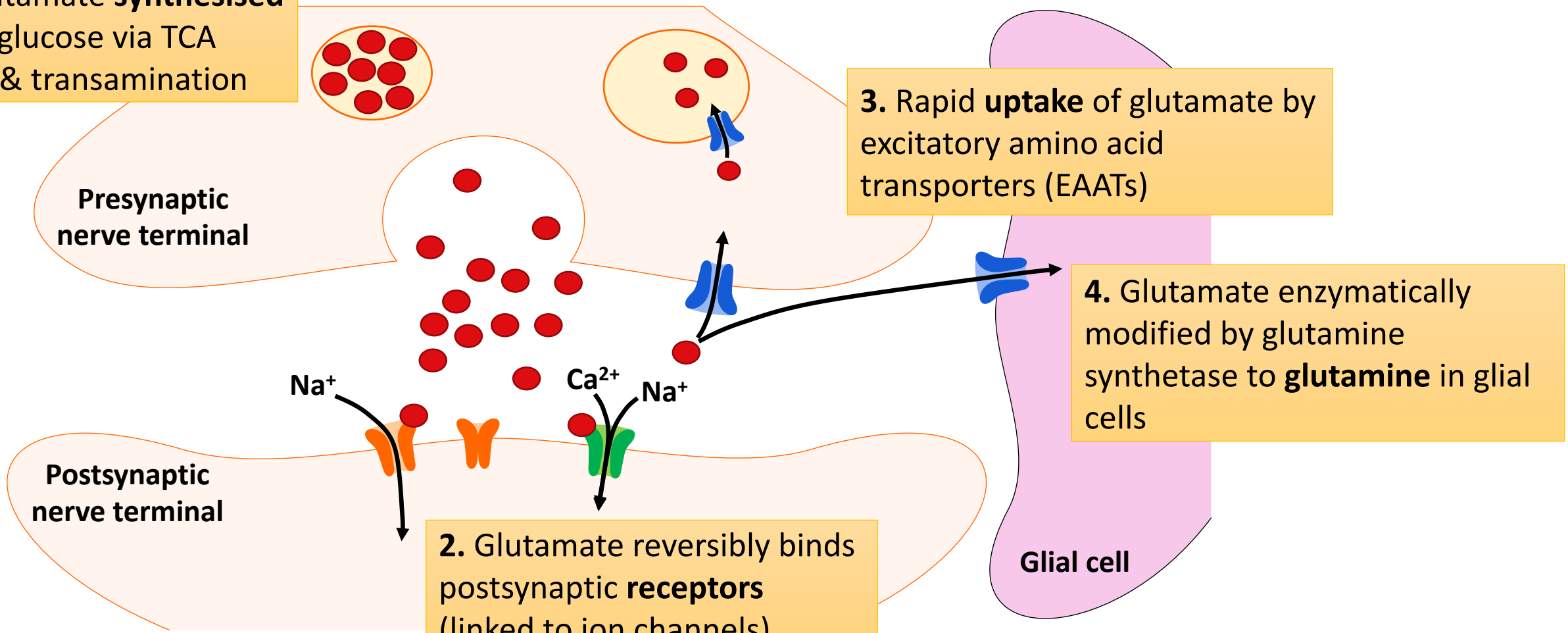
Rapid onset, offset and desensitisation

Slow component of excitatory transmission

Ca^{2+} acting as 2nd messenger

An excitatory Glu synapse

1. Glutamate **synthesised** from glucose via TCA cycle & transamination



3. Rapid **uptake** of glutamate by excitatory amino acid transporters (EAATs)

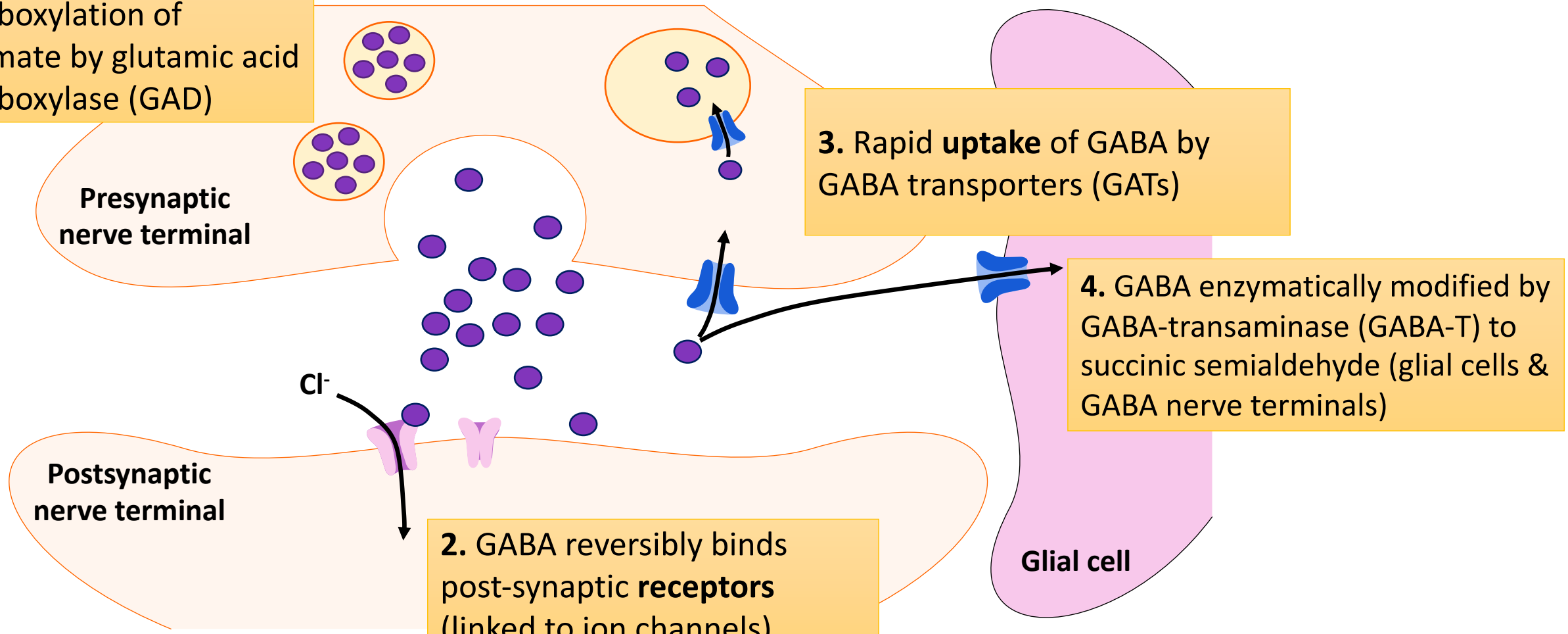
4. Glutamate enzymatically modified by glutamine synthetase to **glutamine** in glial cells

2. Glutamate reversibly binds postsynaptic **receptors** (linked to ion channels)

Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

An inhibitory GABA synapse

1. GABA **synthesised** by decarboxylation of glutamate by glutamic acid decarboxylase (GAD)



3. Rapid **uptake** of GABA by GABA transporters (GATs)

4. GABA enzymatically modified by GABA-transaminase (GABA-T) to succinic semialdehyde (glial cells & GABA nerve terminals)

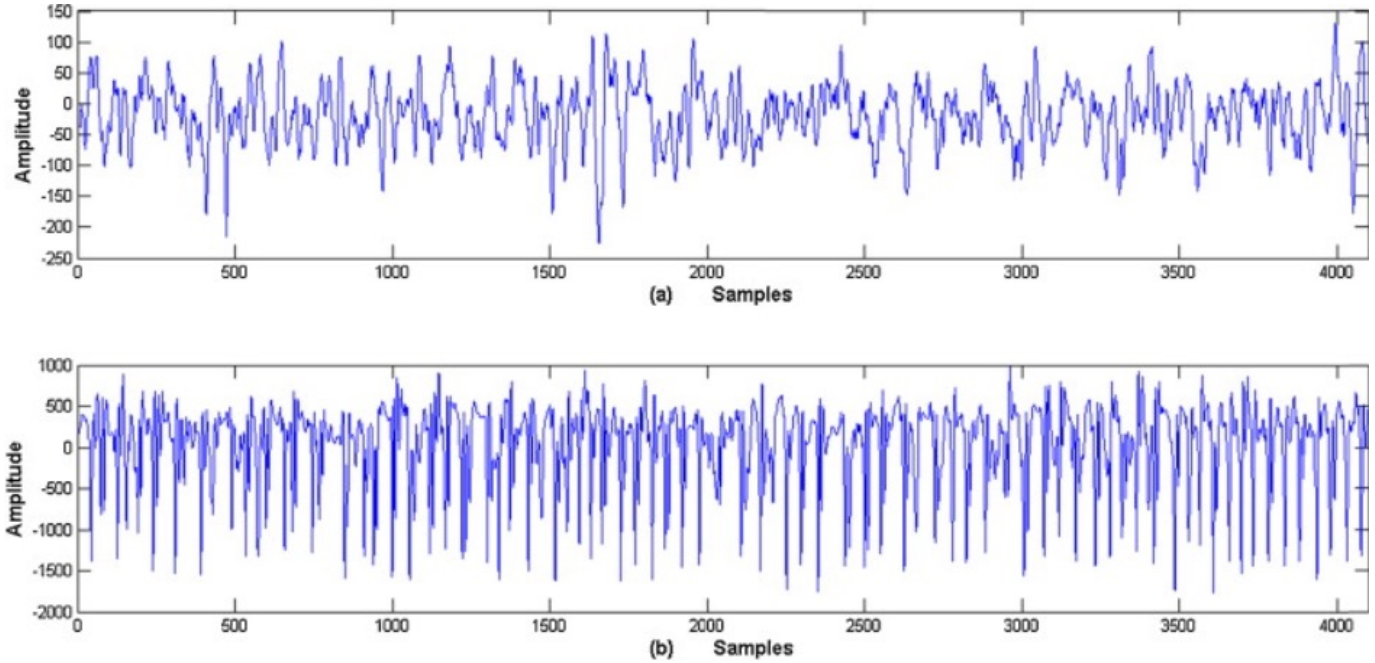
2. GABA reversibly binds post-synaptic **receptors** (linked to ion channels)

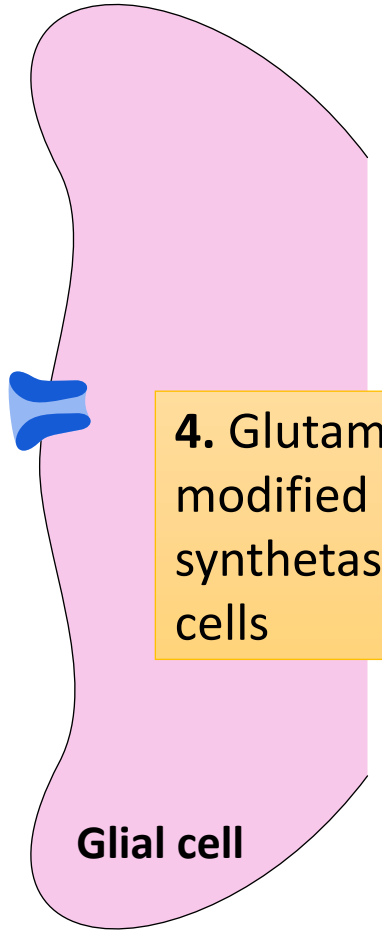
Intercellular communication: Outline communication between nerve cells, nerve and glial cells, and nerve and effector cells, including mechanisms of neurotransmission.

Seizures

Abnormal cell firing leads to seizures associated with **excess GLUTAMATE** in the synapse
Aetiology uncertain – **Glutamine synthetase?**

Electroencephalography (EEG) measures electrical activity in the brain





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Epilepsy

Available drugs target both the **Glutamate and GABA synapse**

BRS Neuro: Epilepsy tutorial

One of the commonest neurological conditions affecting **50 million** people worldwide

Characterised by recurrent seizures due to **abnormal neuronal excitability**

Despite advances in modulating seizure generation and propagation the disease can be disabling

25-30% refractory to treatment

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Neurotransmitters

- Enormous diversity in variety of transmitters and their receptors
- Amino acids (e.g. glutamate, GABA, glycine), amines (e.g. NA, DA) and neuropeptides (e.g. opioid peptides) all act as neurotransmitters
- May mediate rapid (µs - ms) or slower responses (secs or longer)
- Neurons receive multiple transmitter influences which are integrated to produce diverse functional responses

Pharmacology of Neurotransmission

- Many neurotoxins interfere with neurotransmitter release to evoke their responses
- Vesicular proteins are targets for neurotoxins
- The synaptic properties of GABA may be modulated pharmacologically as an approach to treating epilepsy