Synaptic Communication

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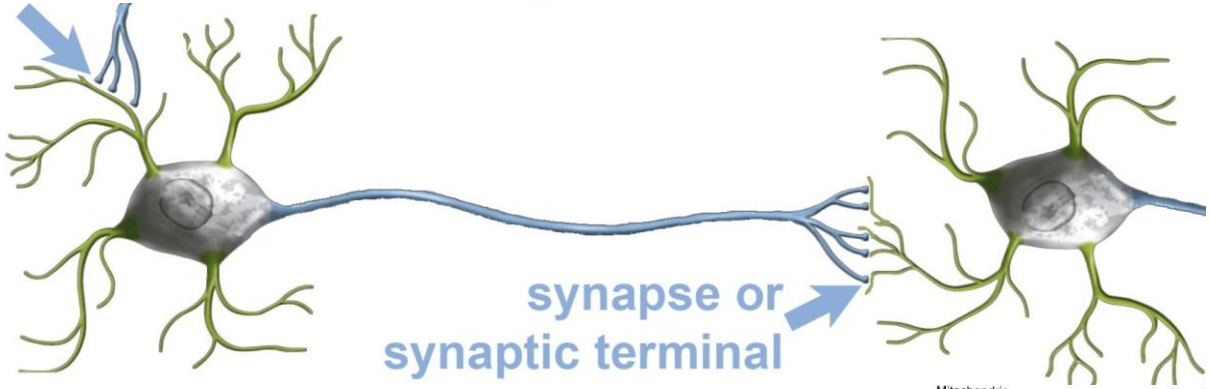
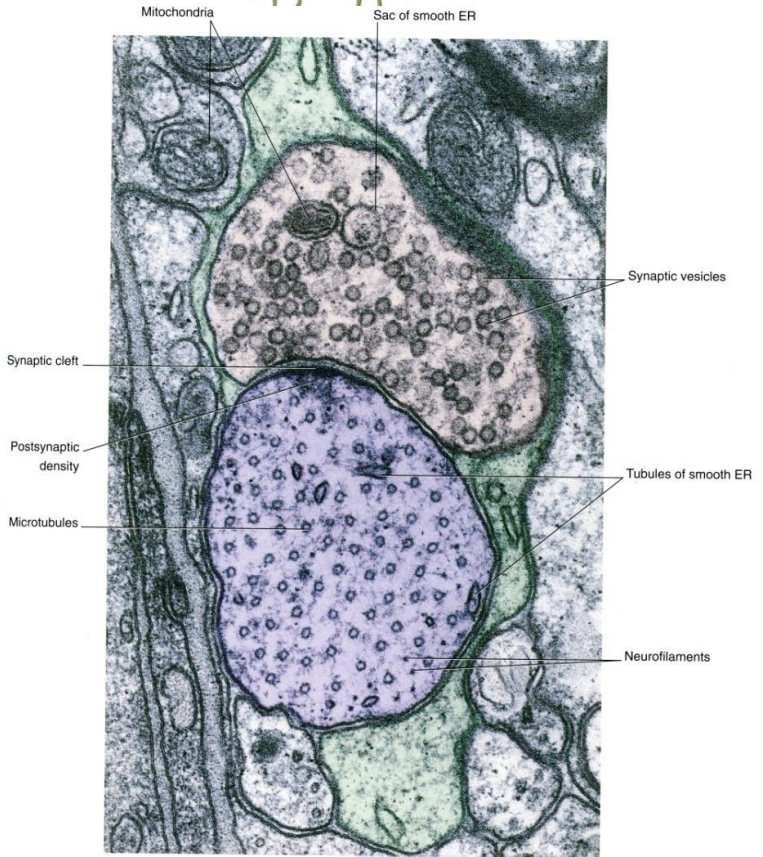
Neurotransmitter Release

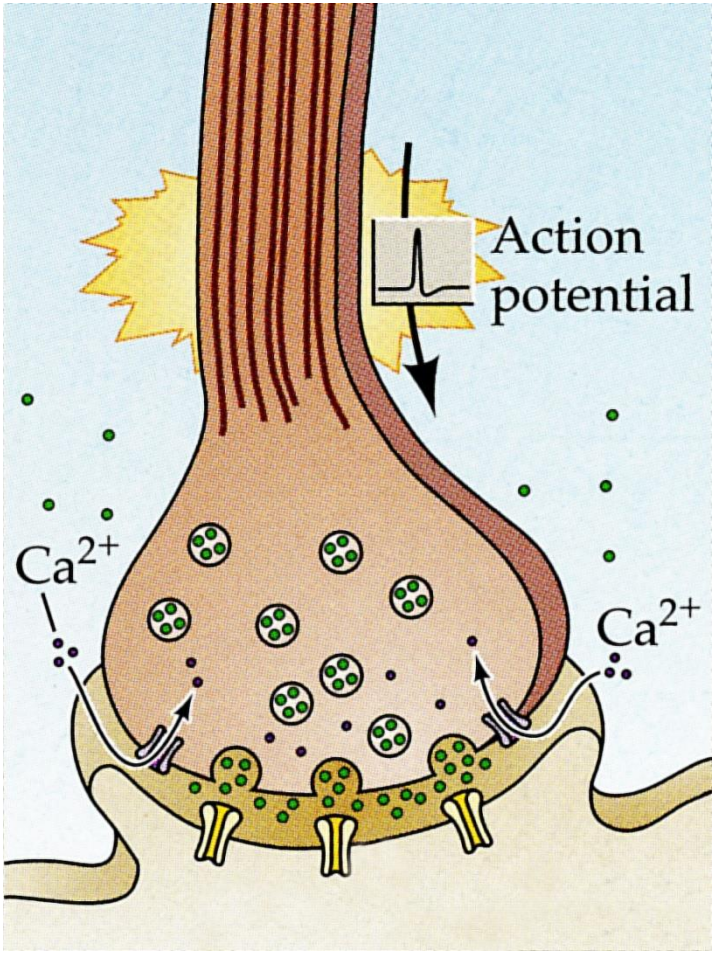


- When an action potential reaches the synapse, it initiates release of neurotransmitter into the synaptic cleft.



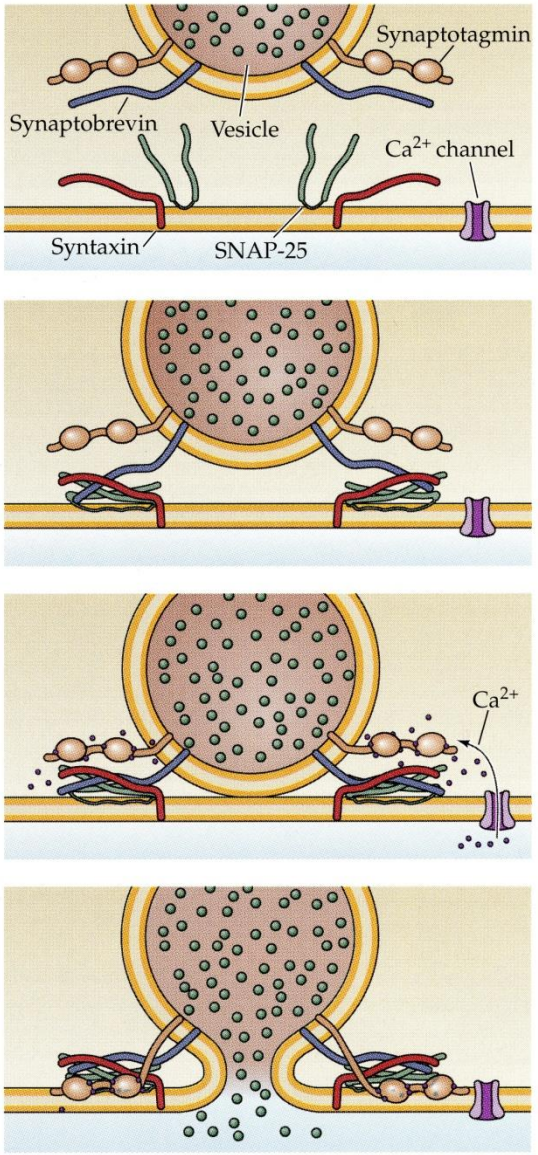
Neurotransmitter Release

- The arrival of an action potential depolarizes the axon terminal.
- Depolarization opens voltage-gated calcium (Ca^{++}) channels.



Neurotransmitter Release

- Synaptic vesicles filled with neurotransmitter are ‘docked’ at the active zone of the synapse.
- Ca^{++} initiates an interaction between SNARE proteins on the vesicle with SNARE proteins on the cell membrane.
- The vesicle membrane is pulled into contact with the cell membrane, and the two fuse.
- Neurotransmitter is released into the synaptic cleft.
- This process is called exocytosis.



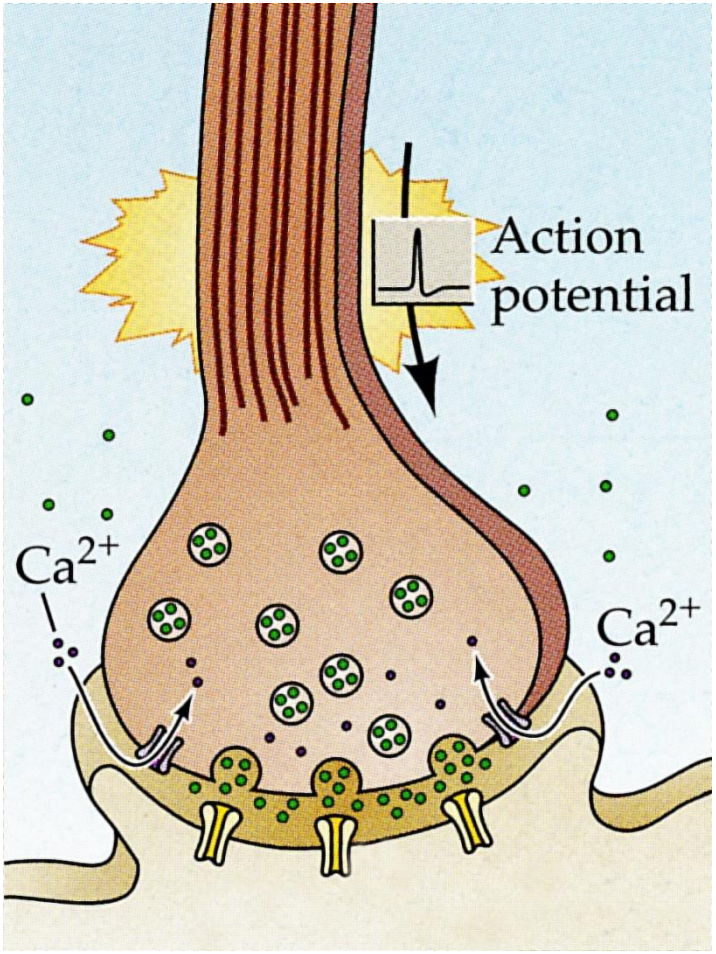
Tetanus

- Clostridium bacteria is common in soil. It is often introduced into the body by a puncture wound.
- The bacteria produces tetanus toxin, which is preferentially taken up by inhibitory spinal interneurons.
- The toxin degrades SNARE proteins needed for synaptic vesicle exocytosis.
- The loss of inhibition results in uncontrolled motor neuron activation and massive muscle contraction... tetanus.
- Tetanus resulted in 59,000 deaths in 2013.
- Tetanus can be prevented by a vaccine that protects for about 10 years.

painting by Sir Charles Bell, 1809

Neurotransmitter Release

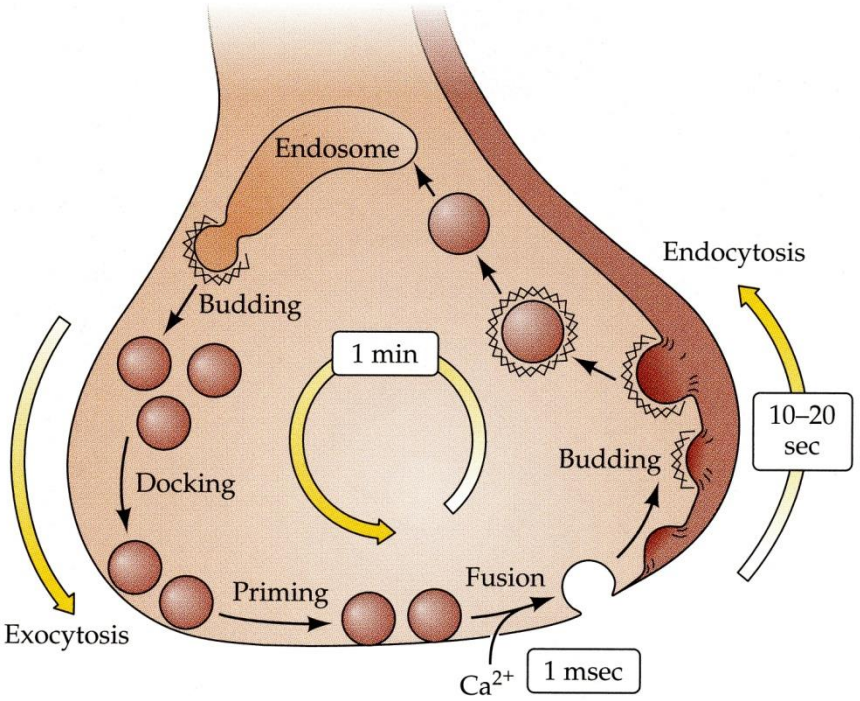
If the membrane of vesicles fuses with the cell membrane at the synapse, does that mean that the synaptic terminal gets larger and larger?



Neurotransmitter Release

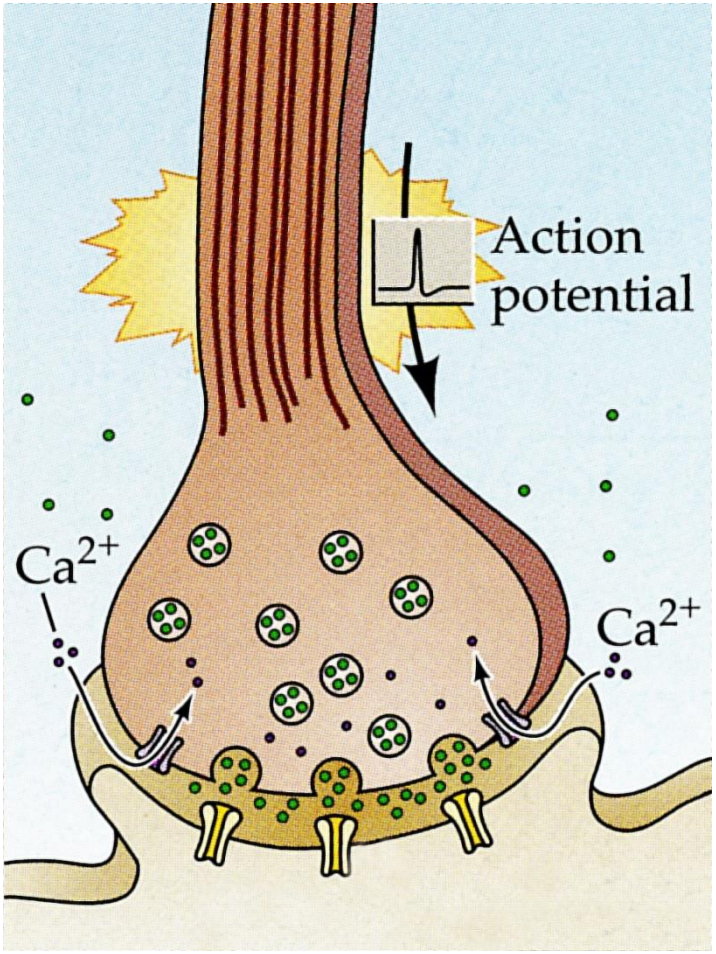
- Vesicle membrane is removed from the cell membrane and recycled through the local uptake of an endosome.

- This process is called endocytosis.



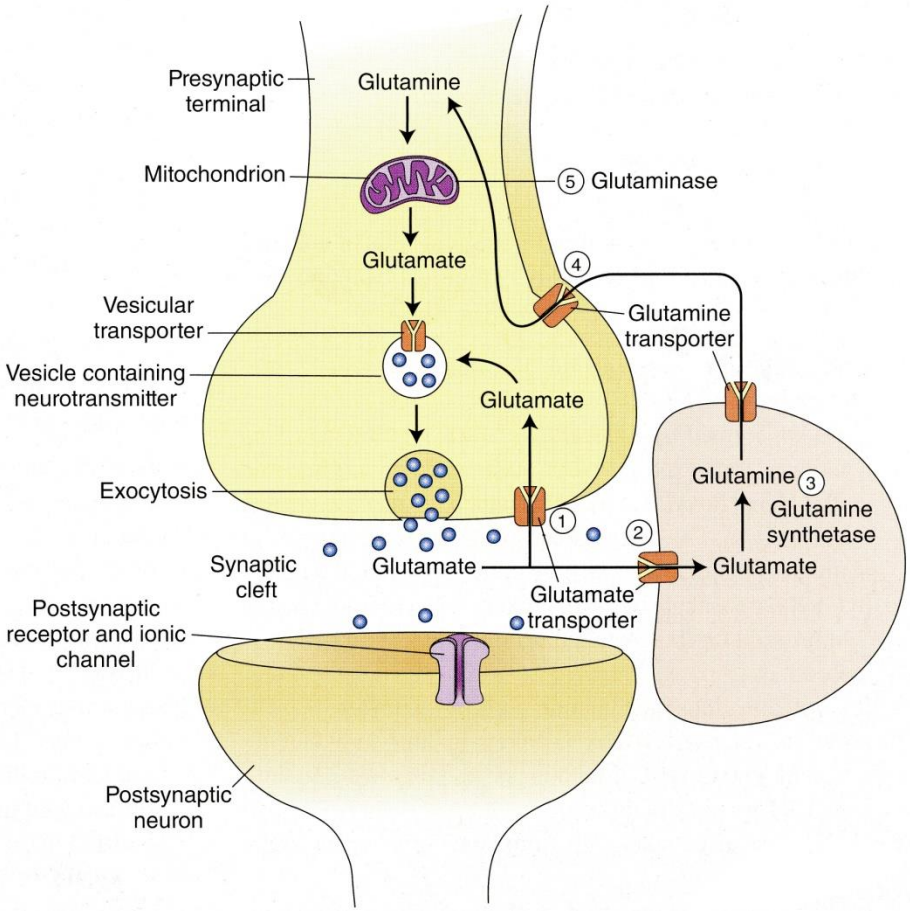
Neurotransmitter Release

- Neurotransmitter released from vesicles diffuses across the 20-50 nm synaptic cleft.
- Neurotransmitter binds its receptors in the postsynaptic cell membrane.



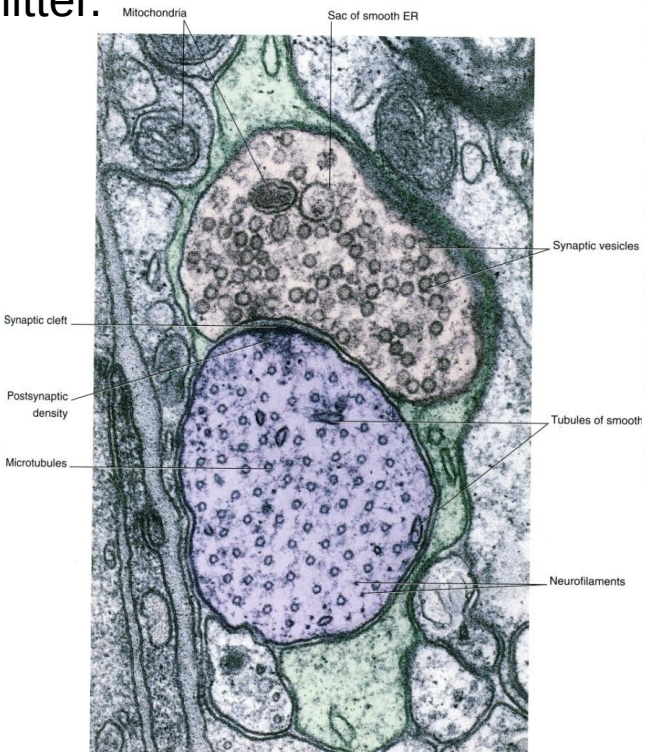
Neurotransmitter Clearance

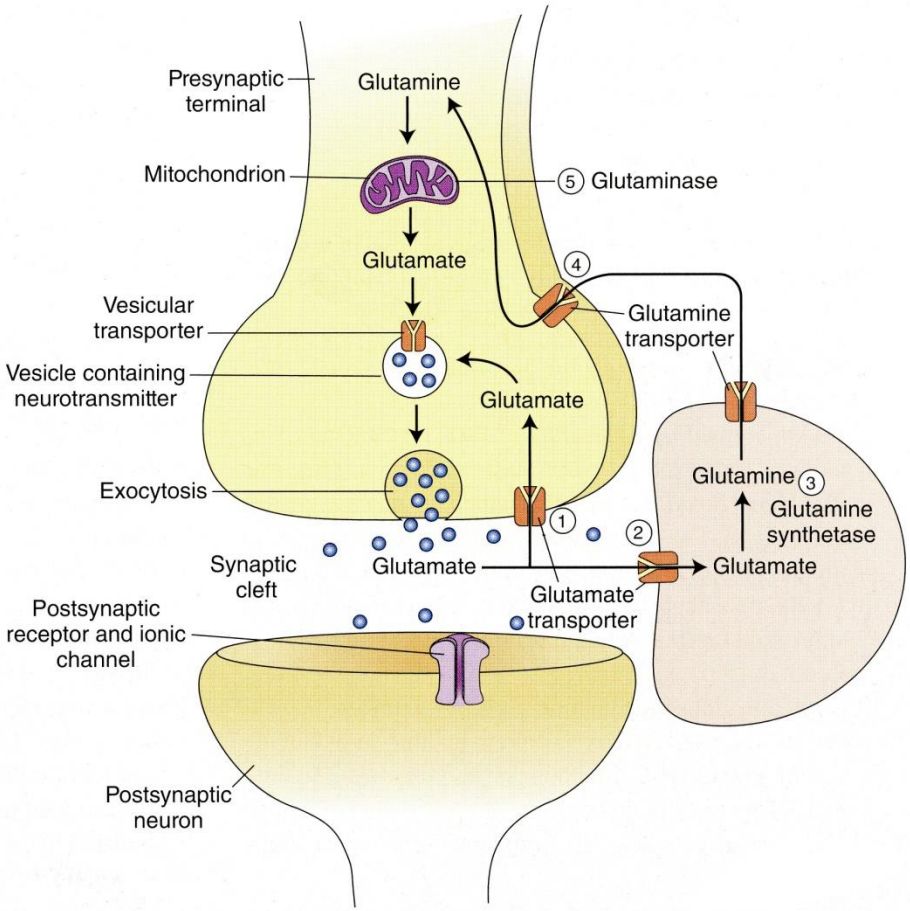
- Neurotransmitters must be rapidly cleared from the synaptic cleft so that they do not continually activate their receptors.
- Most neurons have transporters for their neurotransmitter in the membrane of their axon terminals.



Neurotransmitter Clearance

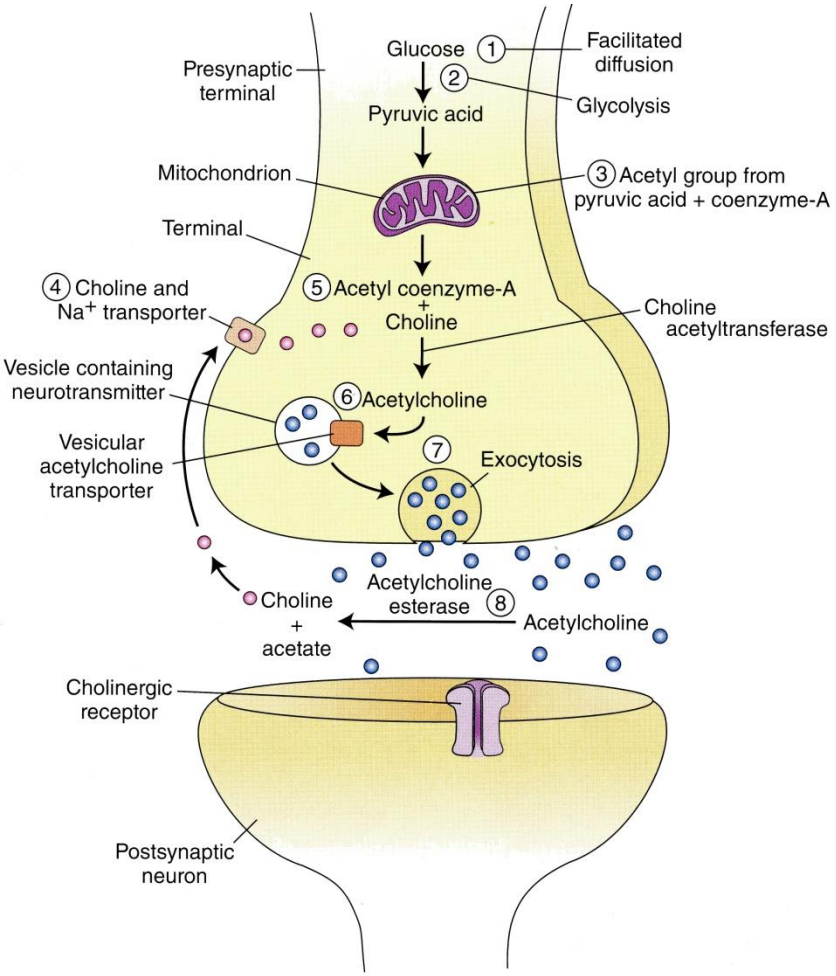
- Glutamate and GABA can be cleared and recycled through local astrocytes.
- Astrocytes convert them to glutamine.
- Glutamine is transferred to the axon terminal where it is used for synthesis of new transmitter.





Neurotransmitter Clearance

- The enzyme, acetylcholinesterase, is present in the cleft of cholinergic synapses.
- It breaks acetylcholine (Ach) into choline (and acetate).
- Choline is taken up into the terminal by a choline transporter, where it is used for synthesis of new transmitter.



Neurotransmitter Clearance

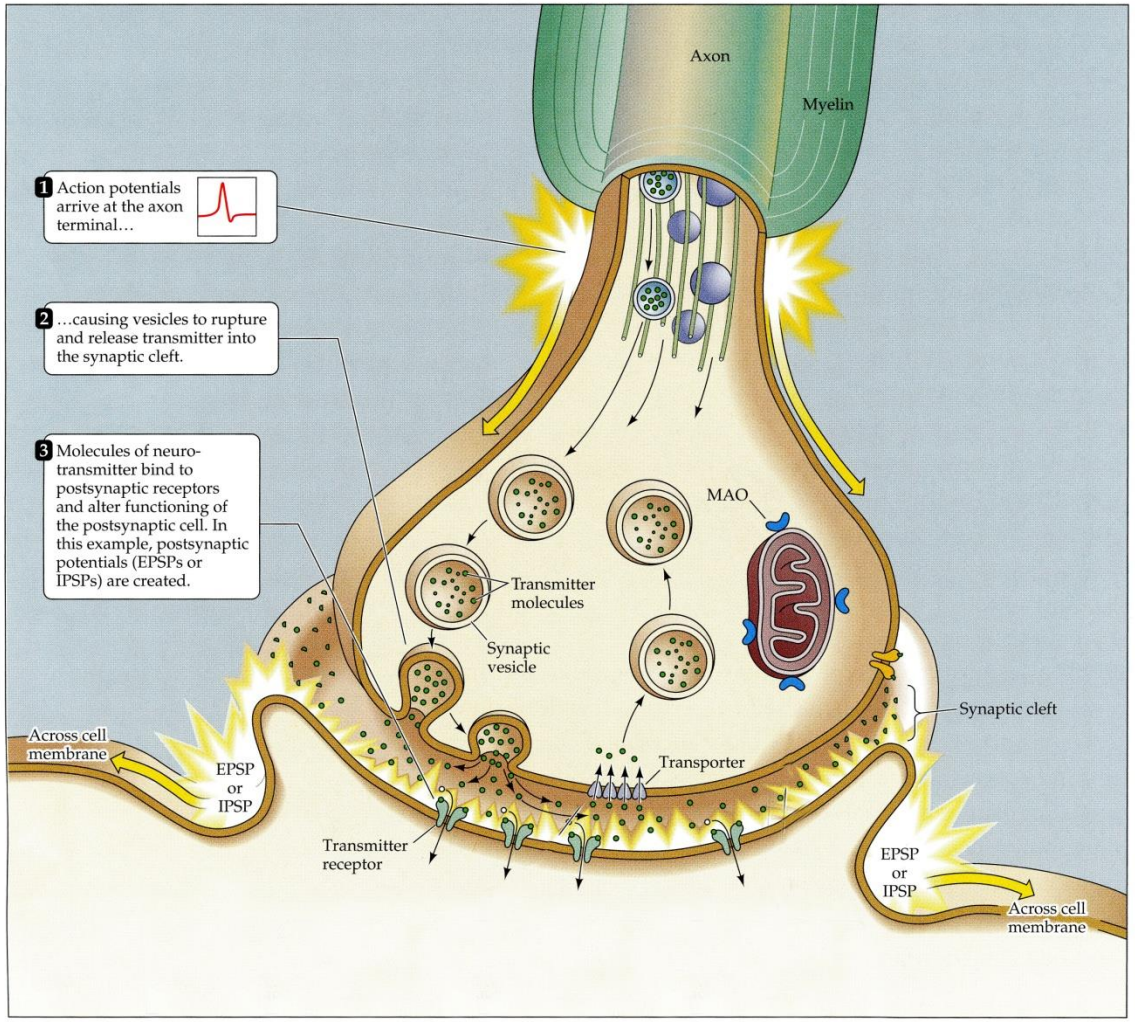
- Some psychoactive drugs work by blocking neurotransmitter reuptake.
- Cocaine blocks reuptake of dopamine, serotonin and norepinephrine by blocking their transporters.

Neurotransmitter Receptors

Neurotransmitter receptors…

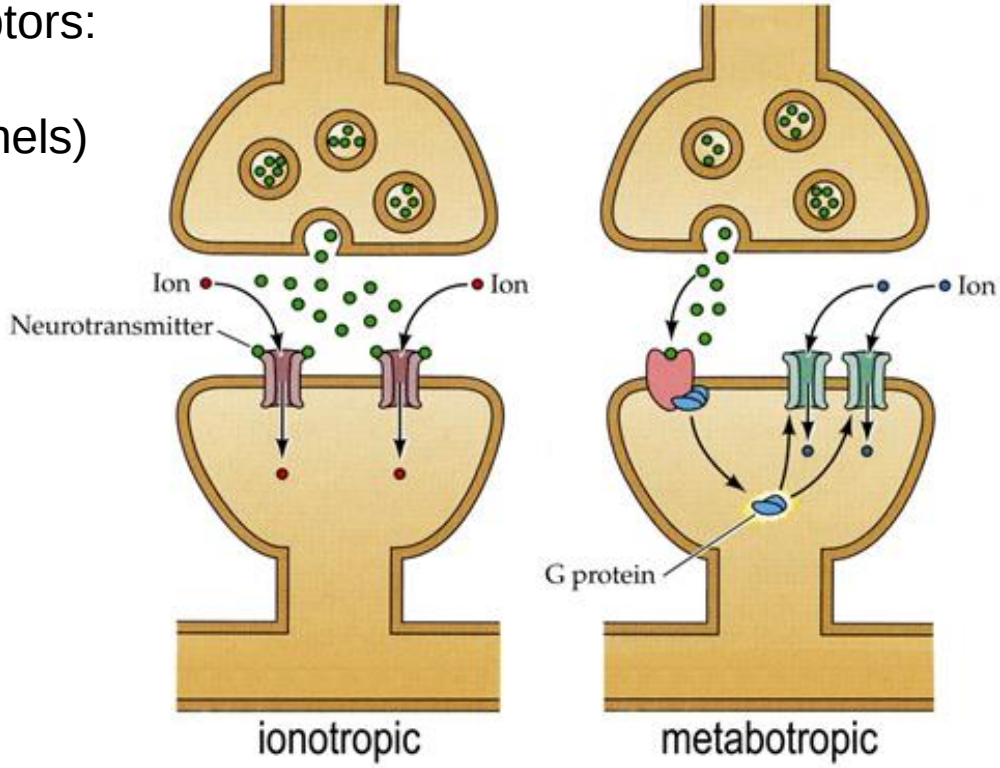
- are present in the postsynaptic membrane.
- are membrane spanning proteins.
- have an extracellular ligand binding domain.
- after binding its ligand results in opening or closing ion channels in the postsynaptic cell.

(A molecule that binds and activates a receptor is its ligand, in this case neurotransmitters.)



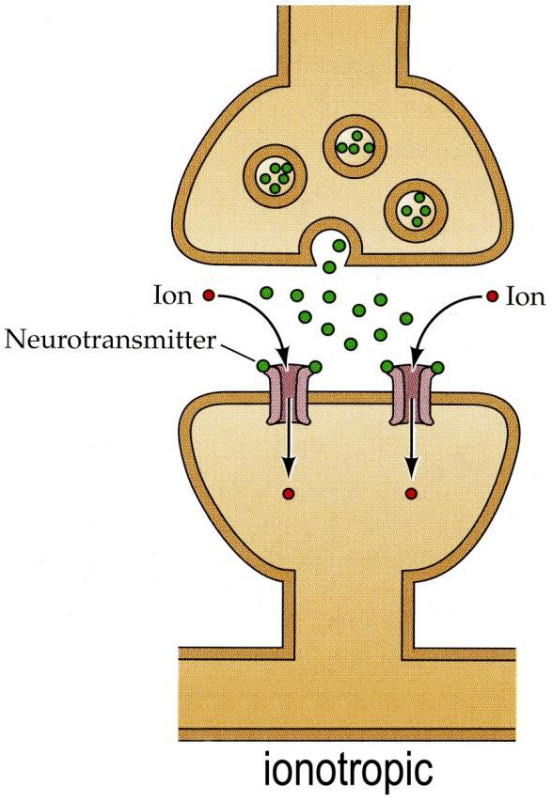
Neurotransmitter Receptors

- Two families of neurotransmitter receptors:
  - Ionotropic (ligand-gated ion channels)
  - Metabotropic (G-protein coupled)

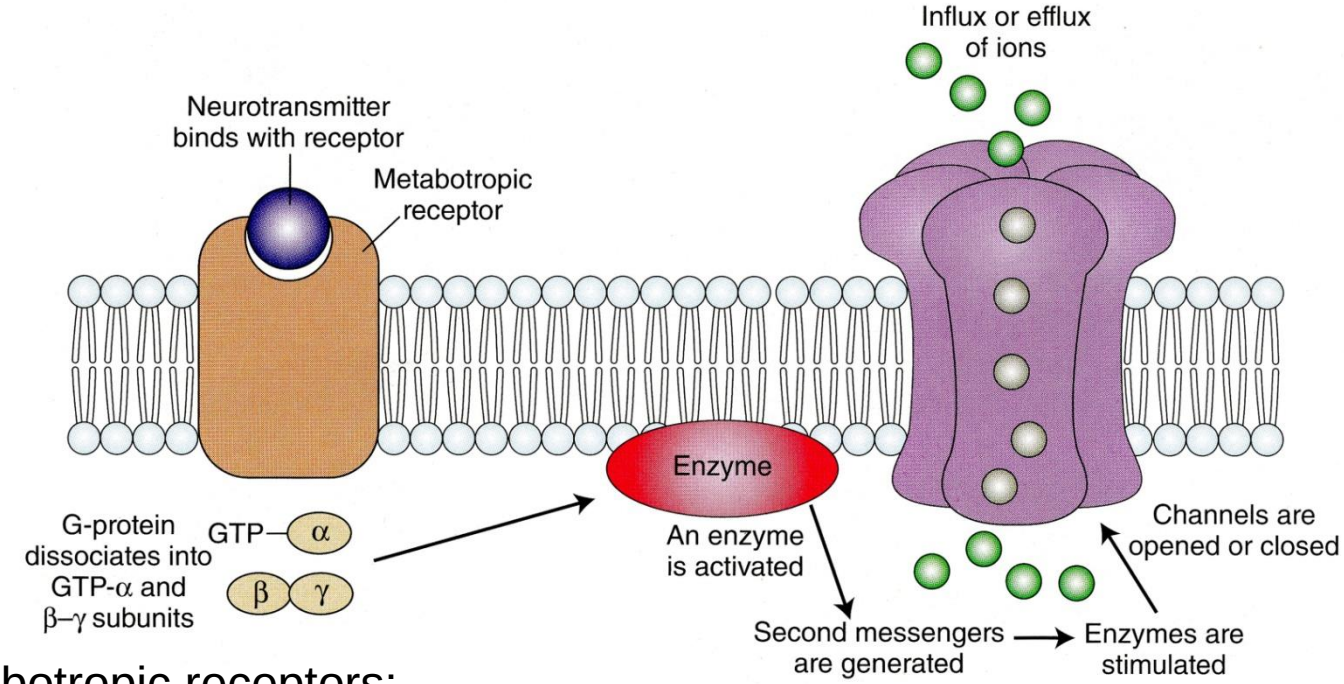


Neurotransmitter Receptors

- Ionotropic receptors:
  - Receptor includes a gated-channel through the membrane.
  - Transmitter binding results in the channel opening and specific ions passing into or out of the cell.
  - Action of these receptors typically is rapid and of short duration.



Neurotransmitter Receptors



- Metabotropic receptors:
  - Transmitter binding activates a coupled G-protein.
  - The G-protein activates an enzymatic cascade that results in opening nearby ion channels.
  - Action of these receptors typically is slow and of long duration.

Neurotransmitter Receptors

TABLE 7.3 Ionotropic and Metabotropic Receptors for Different Neurotransmitters

Neurotransmitter	Ionotropic Receptor	Metabotropic Receptor
Acetylcholine (Ach)	Cholinergic nicotinic	Cholinergic muscarinic
Glutamate	NMDA, AMPA, kainate	$mGlu_1$–$mGlu_8$
GABA	$GABA_A$	$GABA_B$
Glycine	Strychnine-sensitive glycine receptor	—
Dopamine	—	D_1–D_5
Norepinephrine	—	α- and β-adrenergic receptors
Epinephrine	—	α- and β-adrenergic receptors
Serotonin	$5\text{-}HT_3$	$5HT_1$, $5HT_2$, $5HT_4$
Histamine	—	H_1, H_2, H_3
Adenosine	—	$A_1 - A_3$
Opioid peptides	—	Mu, delta, kappa, ORL_1

AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate; GABA, gamma aminobutyric acid; NMDA, N-methyl-D-aspartic acid.

[Siegel & Sapru, 2015]

Neurotransmitter Receptors

- Each receptor is activated by very specific neurotransmitters, usually by only one.
- A neurotransmitter can use multiple receptors.
- Postsynaptic cells can have more than one receptor for a given transmitter.

Neurotransmitter Receptors

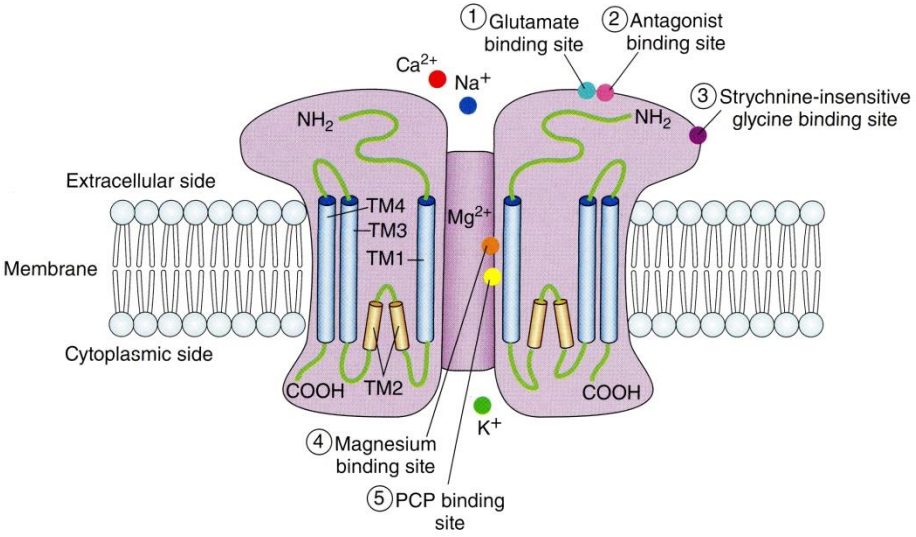
- The function of a neurotransmitter at a synapse is determined by the specific receptors expressed by the postsynaptic cell:
    - Acetylcholine activates nicotinic cholinergic receptors on skeletal muscle, which initiates muscle contraction.
    - Acetylcholine activates muscarinic cholinergic receptors on cardiac muscle (heart), which slows the muscle contraction.

Neurotransmitter Receptors

- Receptors can be very complex.

The NMDA receptor is one of the main glutamate receptors. As well as a glutamate binding site, it has many other binding sites.

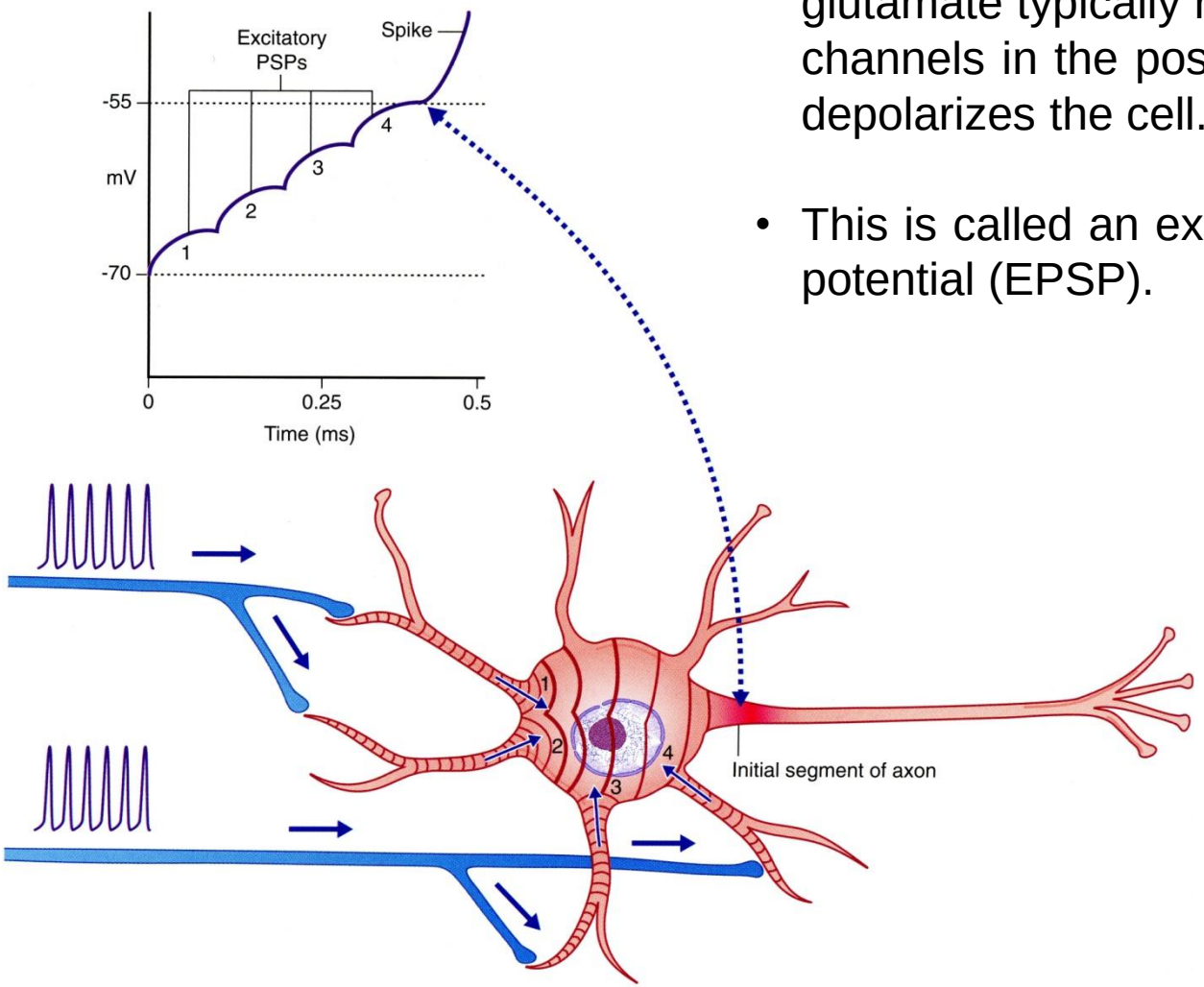
At the resting membrane potential, its pore is blocked by Mg^{++}. The neuron must be partially depolarized to remove the Mg^{++} block before glutamate can initiate opening the channel to allow passage of Na^{+}, Ca^{++} and K^{+}.



Neurotransmitter Receptors

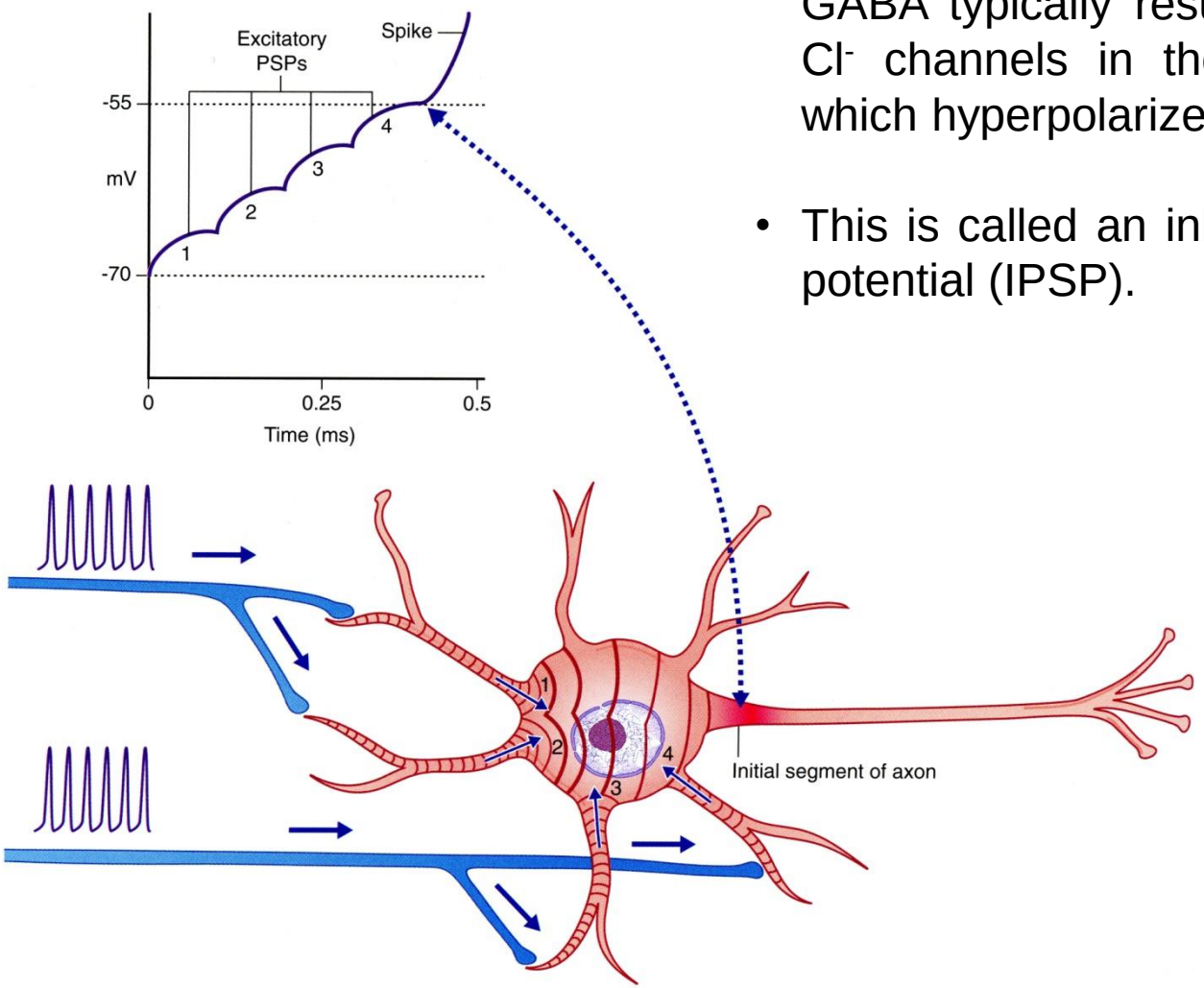
- Psychoactive drugs can be agonists (activators) or antagonists (inhibitors) of neurotransmitter receptors.
    - Ketamine is used as a sedative or anesthesia; it is an antagonist of NMDA (glutamate) receptors.
    - Nicotine, usually taken via cigarette smoke, is an agonist of nicotinic acetylcholine receptors in the brain.

Graded Potentials in Dendrites & Soma



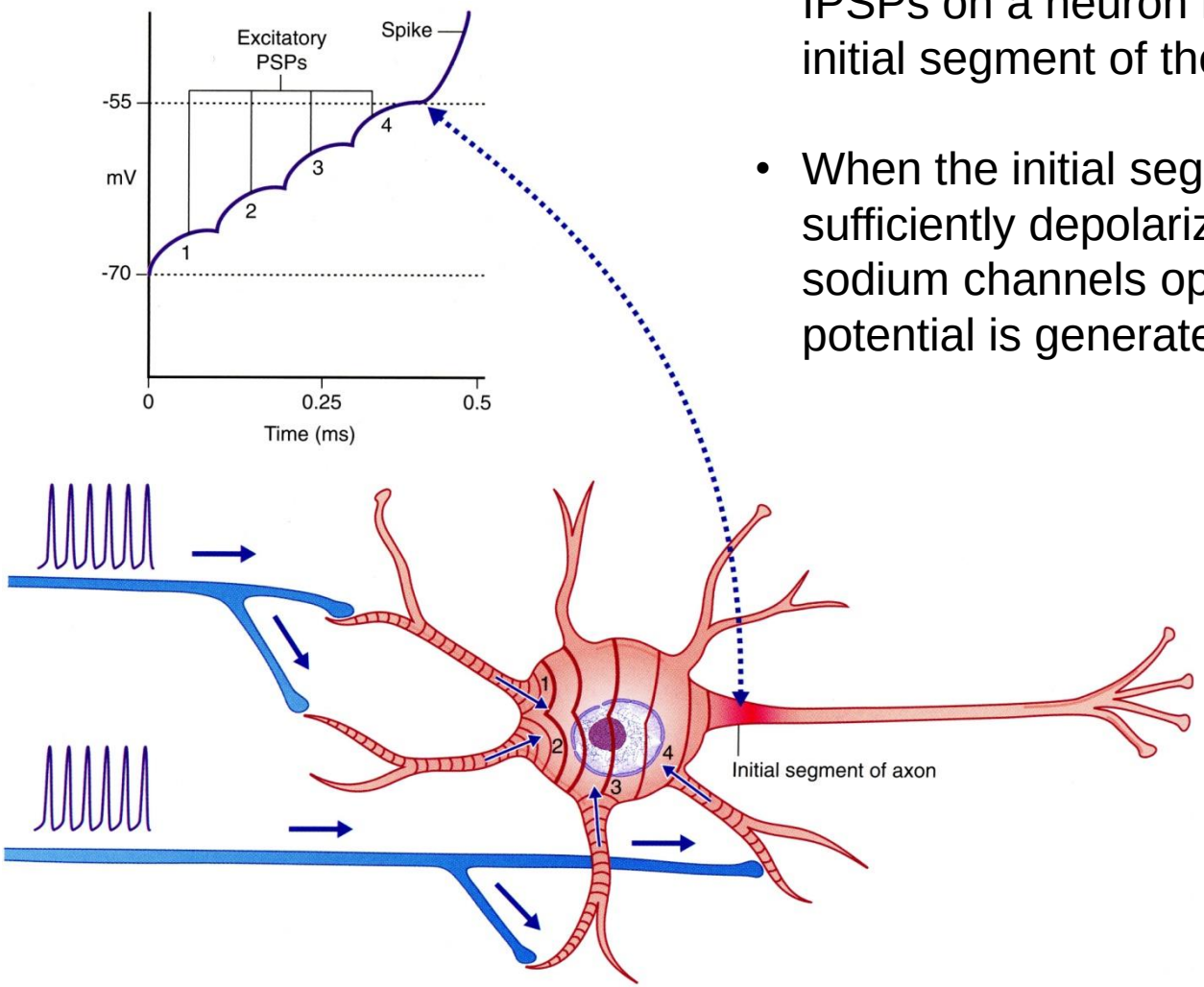
- Excitatory neurotransmitters such as glutamate typically result in opening Na^+ channels in the postsynaptic cell, which depolarizes the cell.
- This is called an excitatory postsynpatic potential (EPSP).

Graded Potentials in Dendrites & Soma



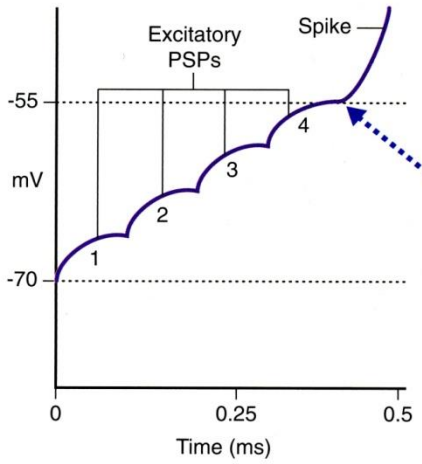
- Inhibitory neurotransmitters such as GABA typically result in opening K^+ or Cl^- channels in the postsynaptic cell, which hyperpolarizes the cell.
- This is called an inhibitory postsynpatic potential (IPSP).

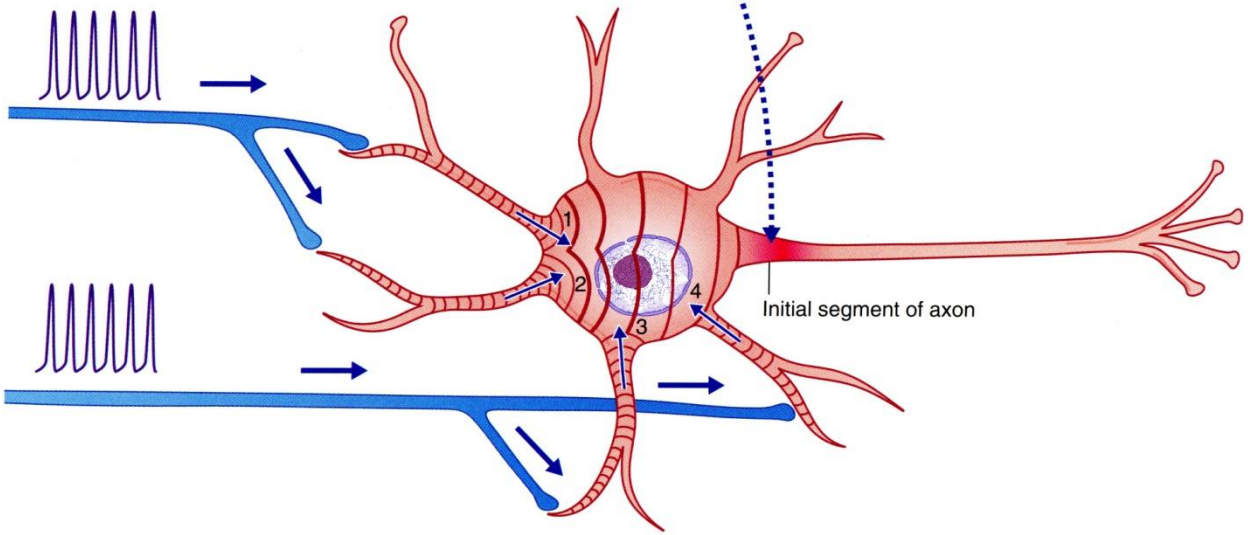
Graded Potentials in Dendrites & Soma



- The graded effect of all the EPSPs and IPSPs on a neuron is summed at the initial segment of the axon.
- When the initial segment becomes sufficiently depolarized, voltage-gated sodium channels open and an action potential is generated.

Graded Potentials in Dendrites & Soma





- Most neurons require multiple excitatory events at nearly the same time from a number of synapses before an action potential is generated (spatial summation)
  -or-
  multiple excitatory events in rapid succession from one or a few synapses (temporal summation).

Graded Potentials vrs. Action Potentials

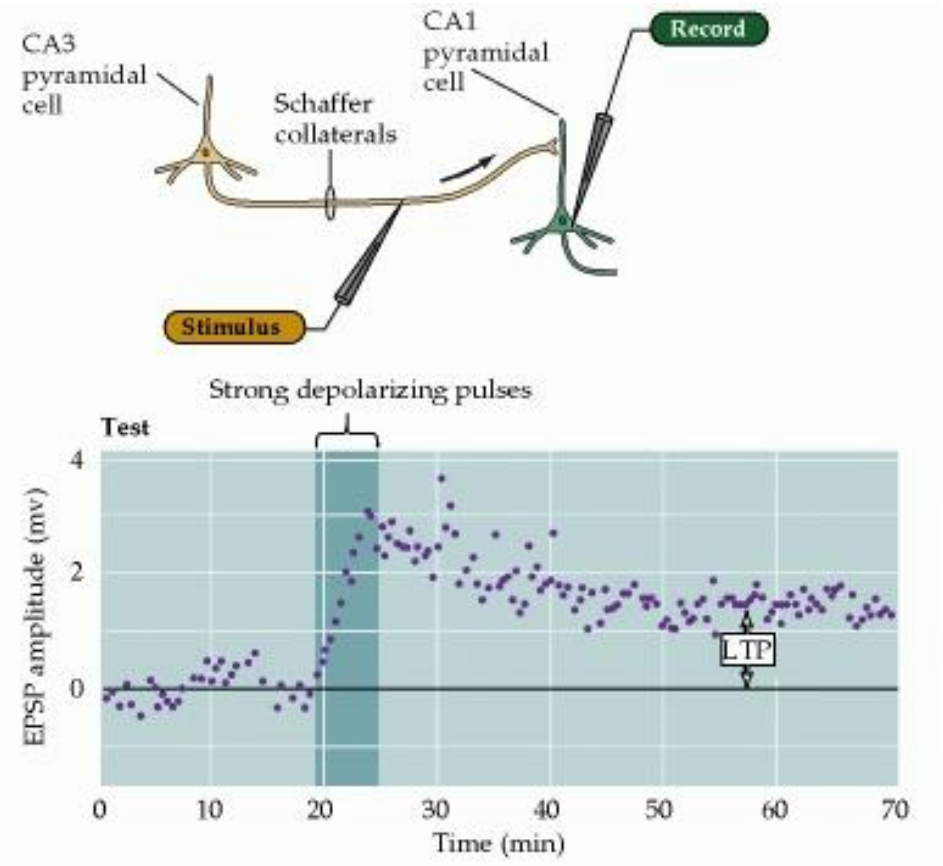
Comparison of graded membrane potentials in dendrites and the soma with action potentials in the axon:

Graded Potentials	Action Potentials
Amplitude varies with the intensity of stimulus, i.e., the response is graded.	Once the threshold is reached, the amplitude of an action potential is not dependent on the initial stimulus, i.e., it is an all-or-none phenomenon.
There is no threshold.	There is a threshold.
There is no refractory period.	There is a refractory period.
Duration is dependent on the initial stimulus.	Duration is constant.
Conduction decreases with distance (decremental conduction).	Conduction is not decremental.
Can be depolarizing or hyperpolarizing.	Are always initiated by depolarization.
Summation can occur.	No summation occurs.
Are mediated by a receptor.	Are mediated by voltage-gated ion channels.

from Sigel and Sapru

Long-Term Potentiation (LTP)

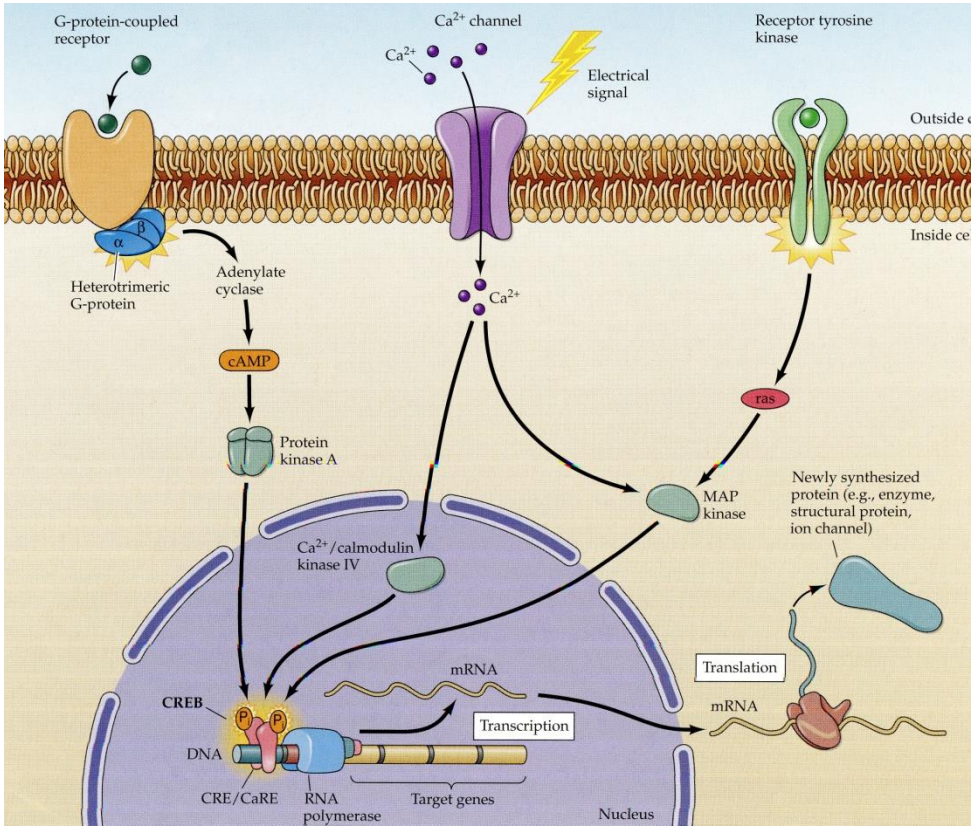
- A burst of excitatory activity on a postsynaptic neuron causes a change in that cell so that a subsequent excitatory event results in more depolarization than before the burst.
- This change is long lasting (days to weeks).
- This effect is called <u>long-term potentiation or LTP</u>.
- LTP is believed to underlie learning.



Changes in Gene Expression

- Activation of neurotransmitter receptors can lead to changes in gene expression via second messenger signaling cascades.

- This can change how a cell responds to stimuli in the future.



Balance of Excitatory & Inhibitory Activity

- A balance in excitatory and inhibitory activity is essential for normal function of the nervous system.

- The effect of tetanus toxin is lose of neuronal inhibition, which results in uncontrolled activation of muscle… tetanus.

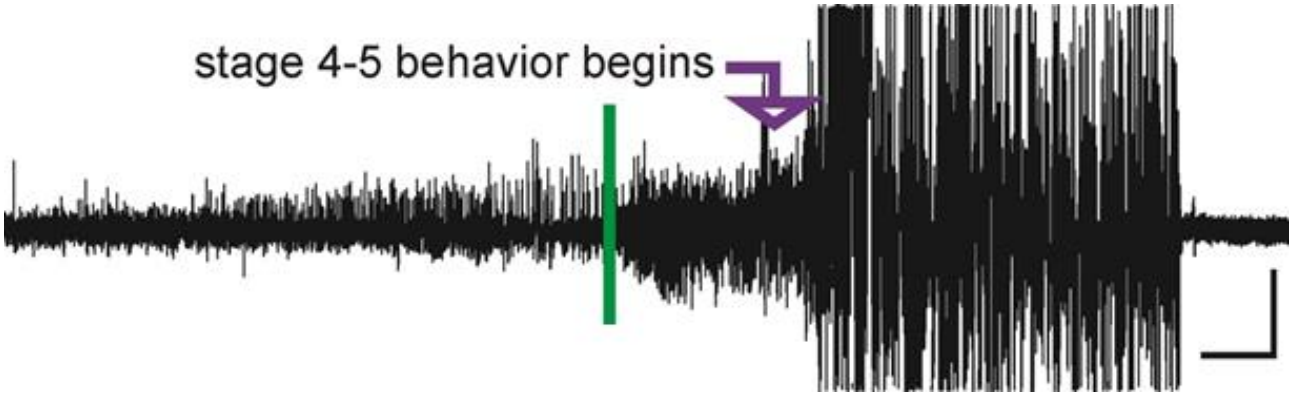
painting by Sir Charles Bell, 1809

Balance of Excitatory & Inhibitory Activity

- Too much excitatory activity in one area of cortex can result in a wave of neuronal activation that spreads across the cortex, a condition called epilepsy.

- Mild epileptic seizures may result in brief losses of attention. More severe seizures are often accompanied by uncontrollable muscle contractions.

- Currently 1 in 26 people will develop epilepsy.



Krook-Magnuson, Armstrong, Oijala, & Soltesz (2013)

Balance of Excitatory & Inhibitory Activity

- A commonly held view is that other behavioral problems including Autism and Schizophrenia are due to an imbalance in excitatory and inhibitory activity.