Lecture 4

Biological Basis of Learning and Memory

…and a Review of Basic Synaptic Mechanisms

Review!

- Key points about action potentials and synapses

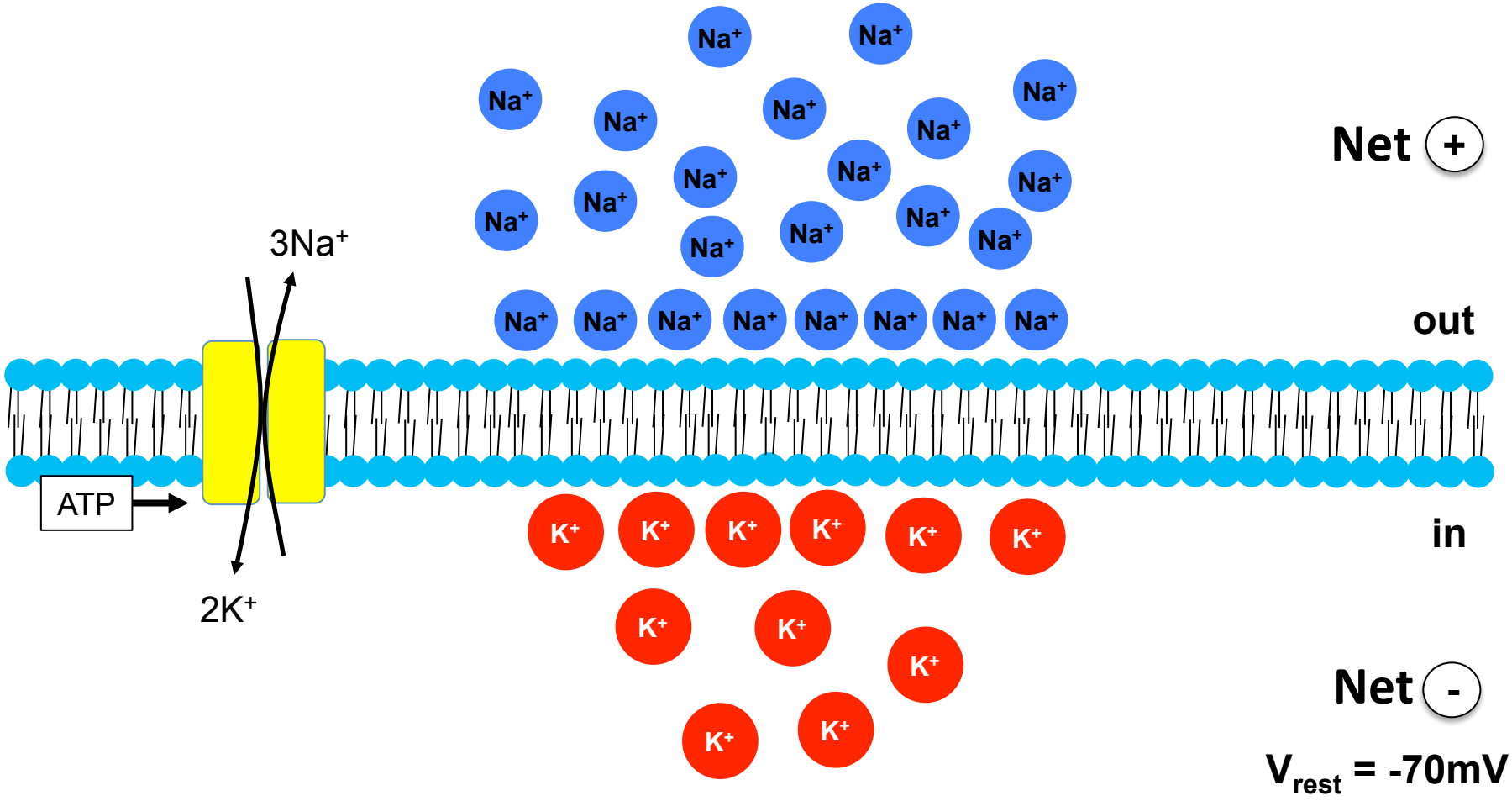
Synaptic Transmission

- Excitatory Transmission
- Inhibitory Transmission

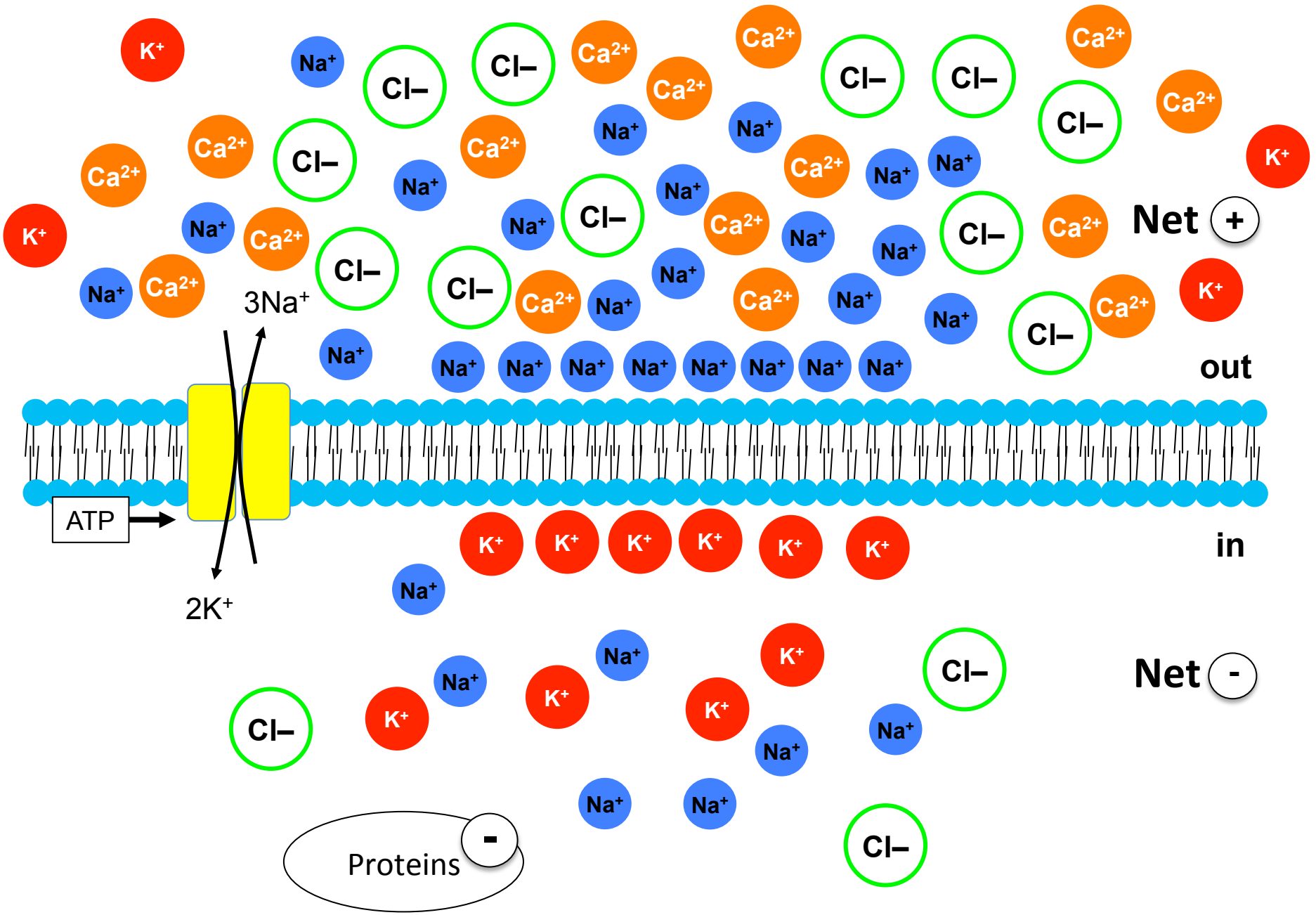
Molecular Mechanisms (Proteins!)

Synaptic Modification and the Basis of Learning

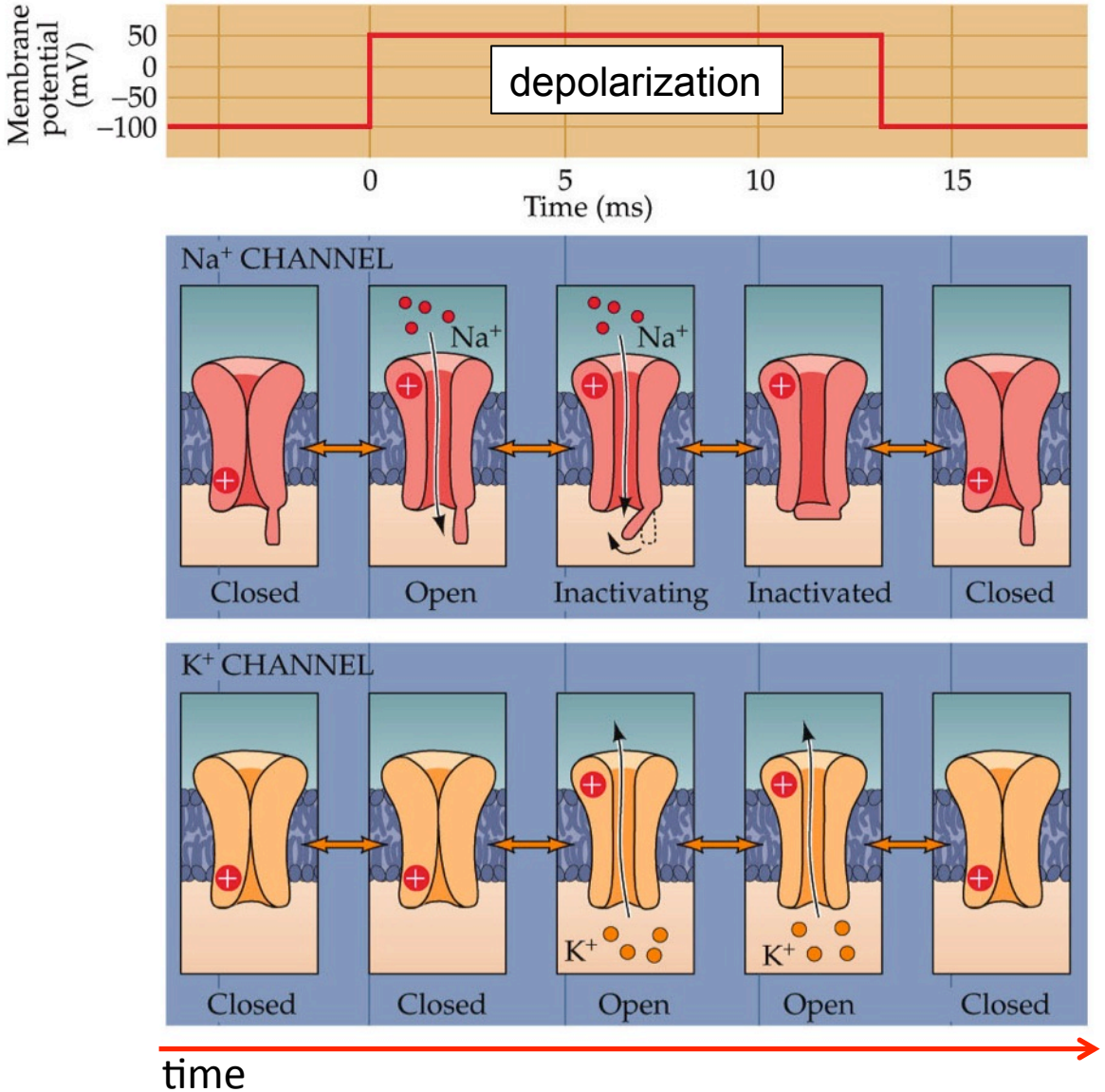
Principle #1: neurons have a separation of charge and concentration across their membranes



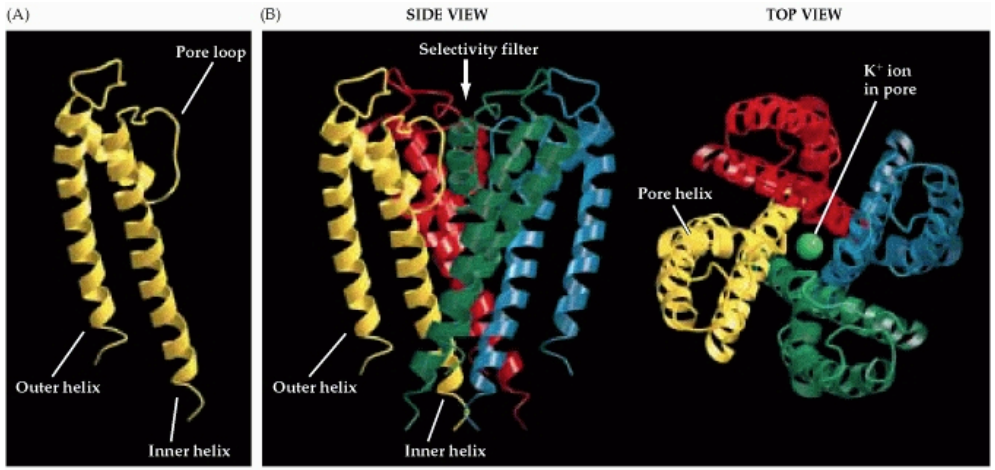
electrochemical gradient

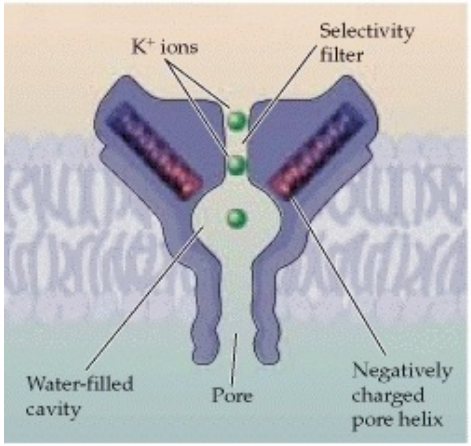

K+
Na+
Cl–
Ca2+
Net +
out
in
3Na+
2K+
ATP
Net -
Proteins
-

Principle #2: ion channels open/close in response to voltage, allow ions to flow down their electrochemical gradients



Ion Channels





① Conduction: moving hydrophilic ions through a hydrophobic membrane

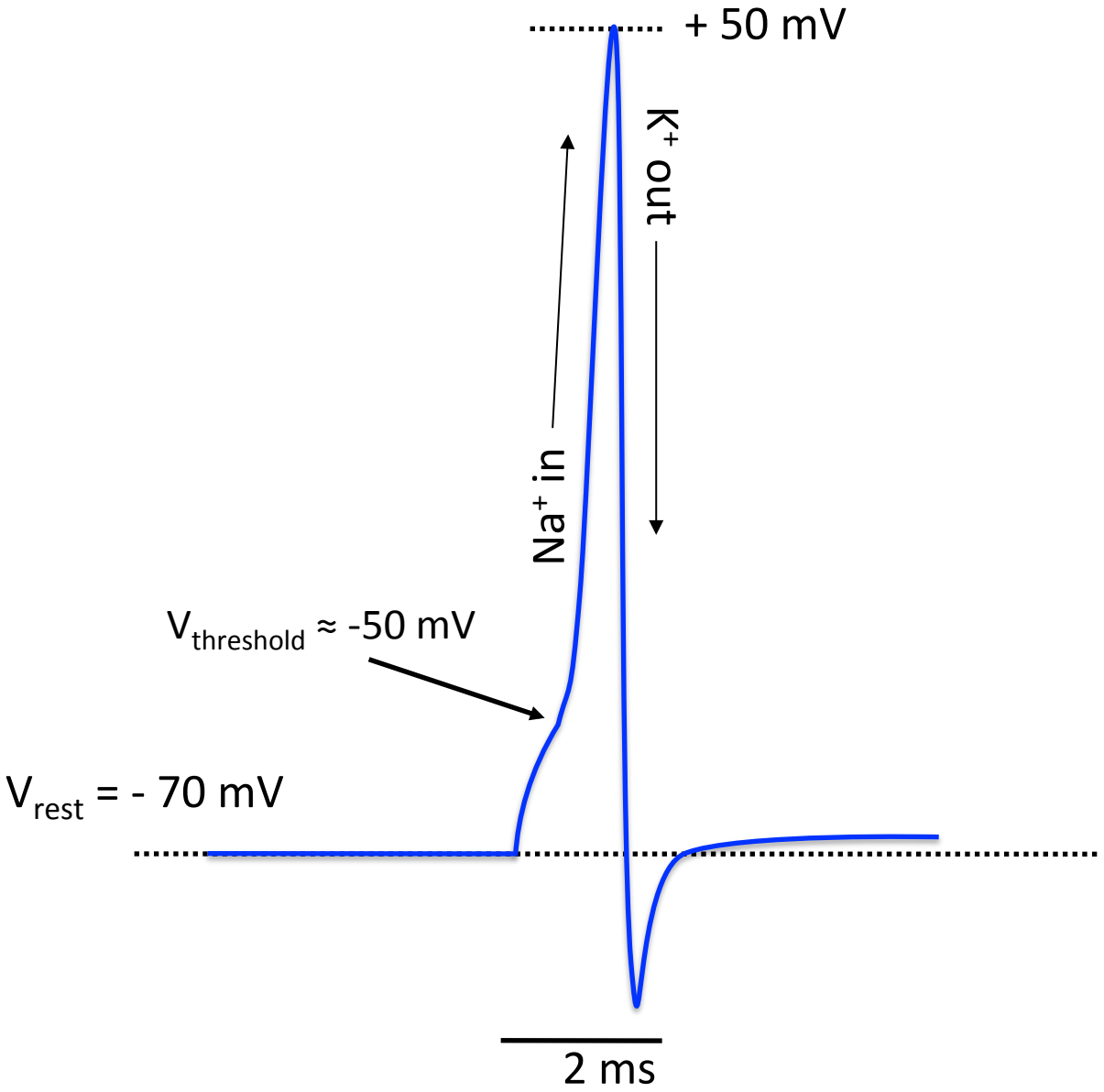
② Selection: restrict movement to a single ionic species!

Na^+ 1.86 Å K^+ 2.27 Å

③ Gating: direct sensors of the environment

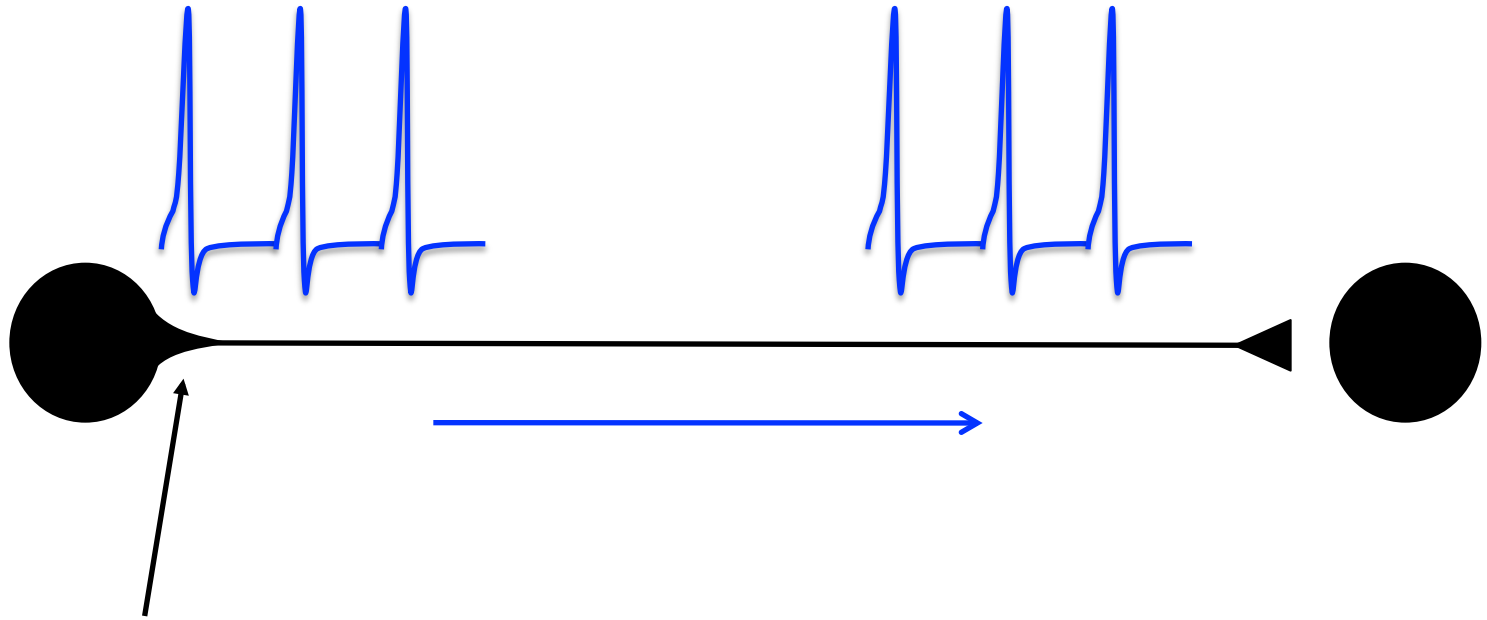
i.e. voltage

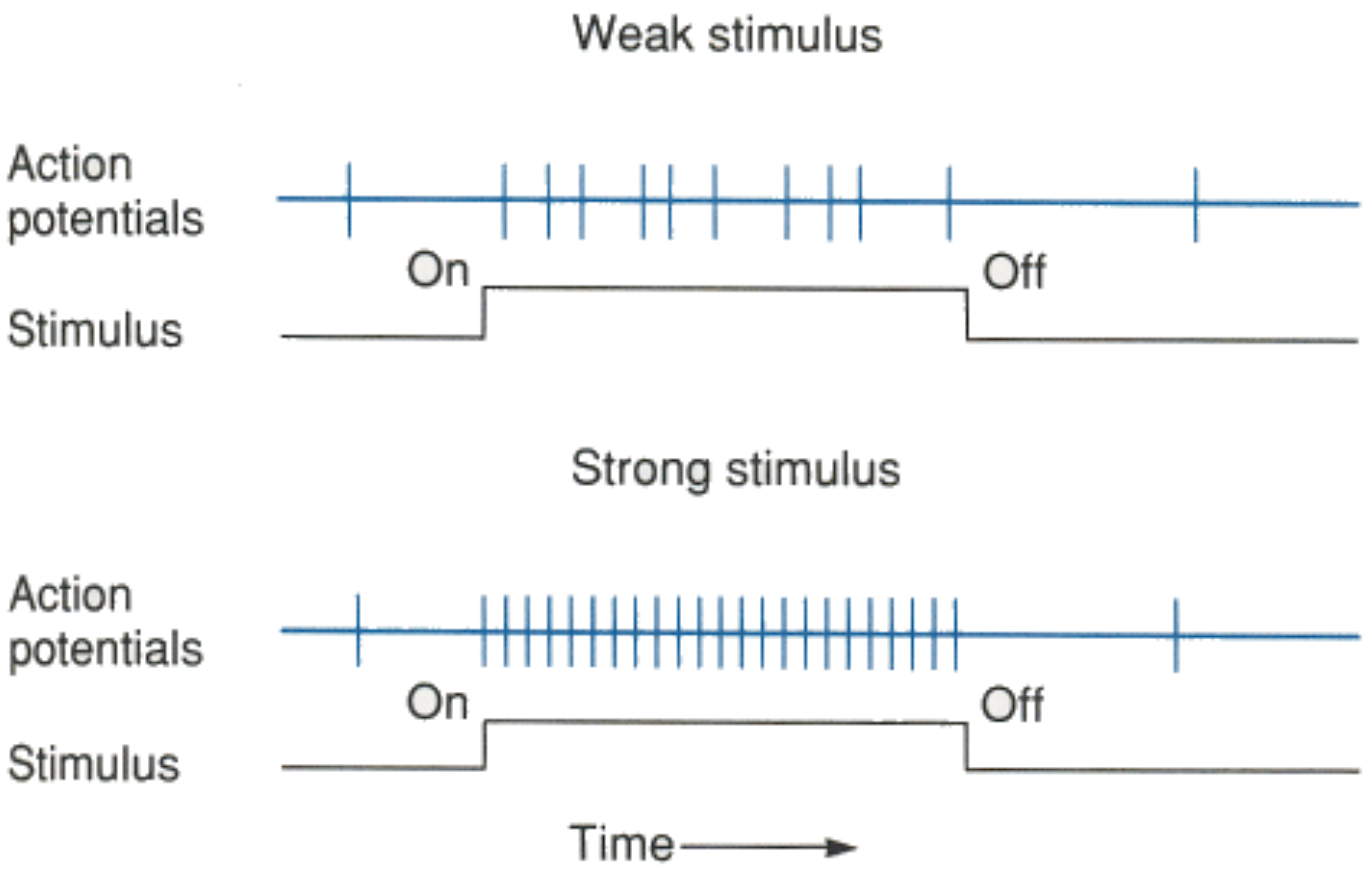
Principle #3: action potentials are generated by the alternate opening of sodium and potassium channels



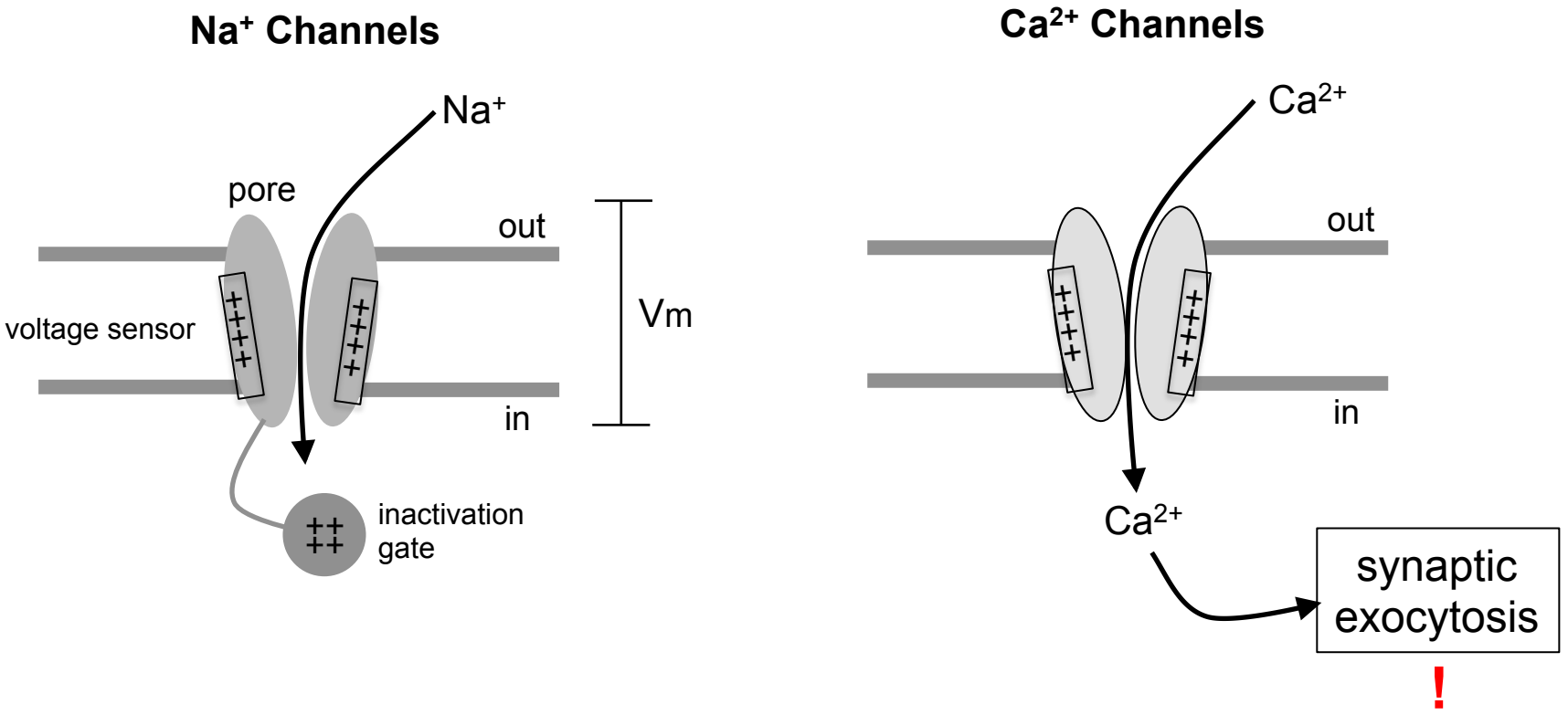
Action potentials:

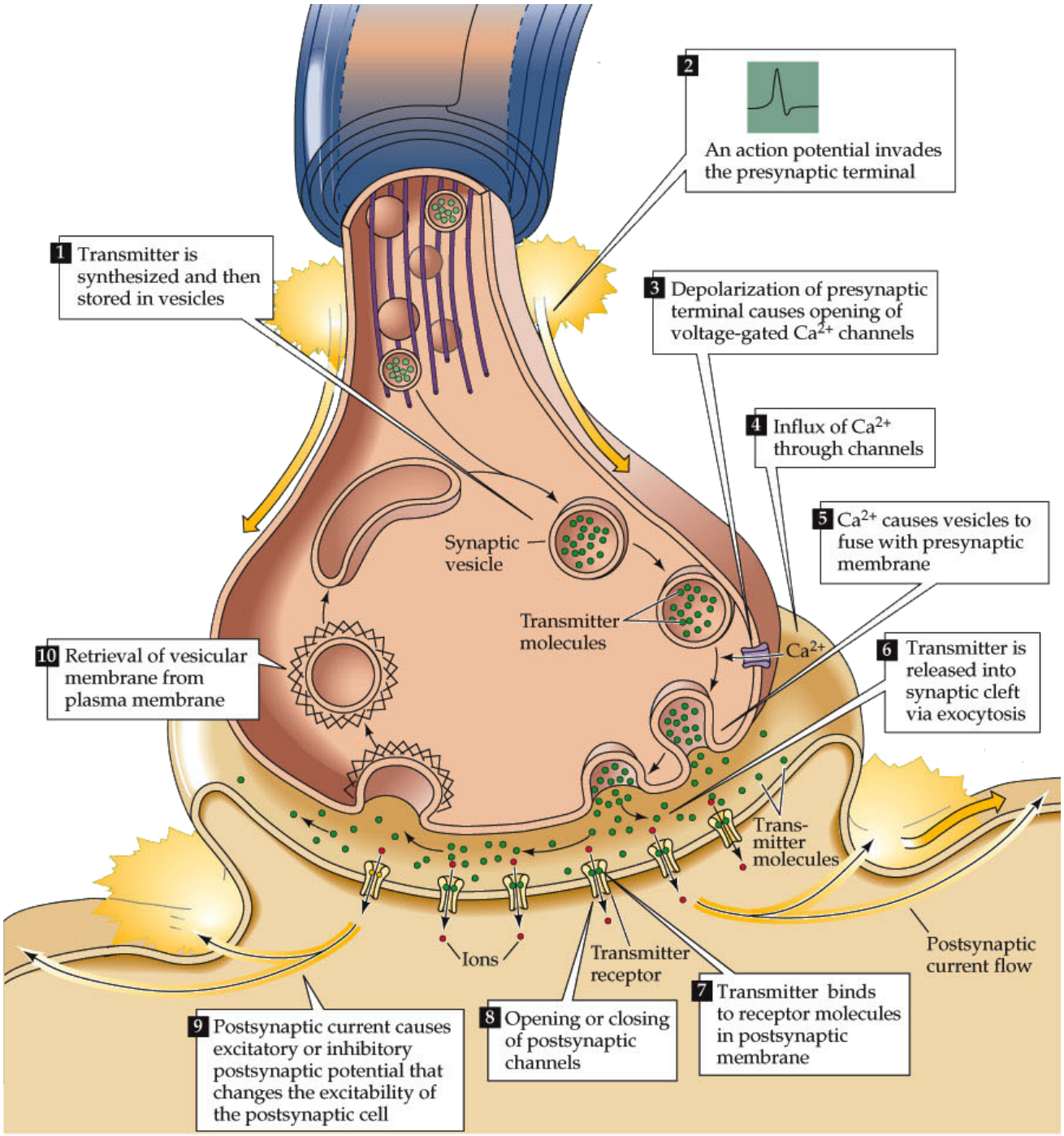
- "all-or-none" (always the same size)
- rapid (spike and return to baseline in < 2ms)
- start in initial segment
- propagate to axon terminals
- myelin speeds propagation (reduces leak of ions)

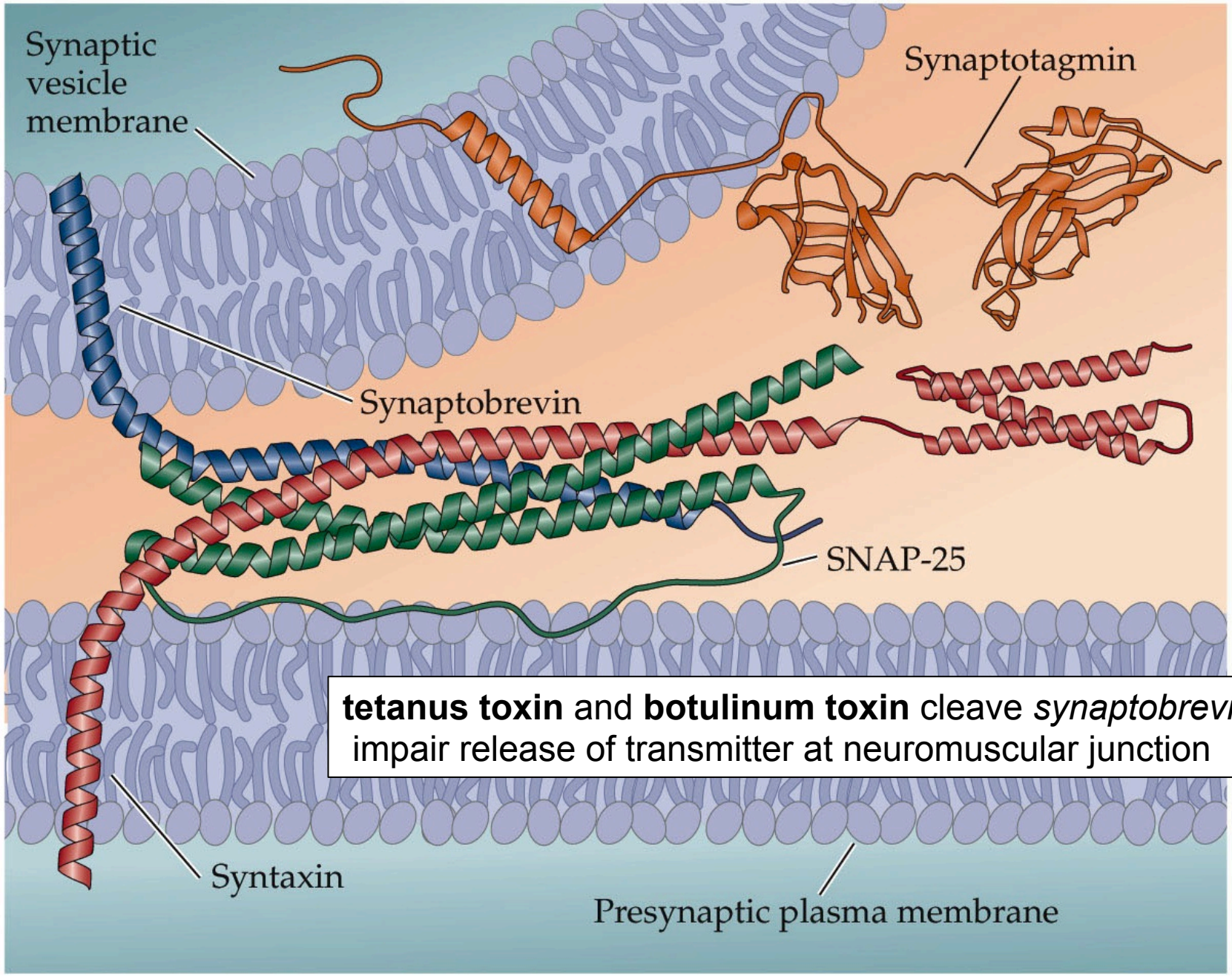



Weak stimulus
Action potentials
On
Off
Stimulus
Strong stimulus
Action potentials
On
Off
Stimulus
Time

Principle #4: action potentials lead to opening of calcium channels in axon terminal; calcium triggers exocytosis (release of transmitter)

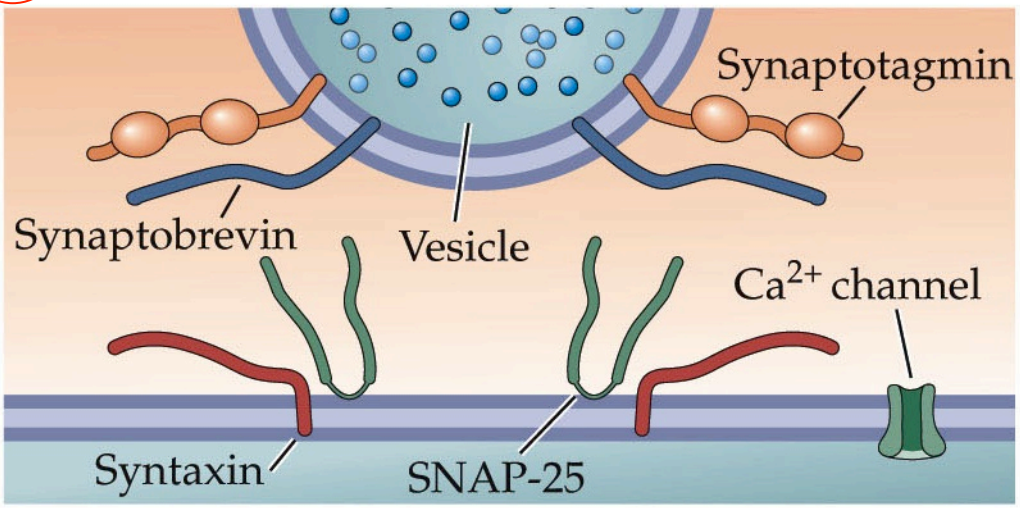



2
An action potential invades the presynaptic terminal
1 Transmitter is synthesized and then stored in vesicles
3 Depolarization of presynaptic terminal causes opening of voltage-gated Ca^{2+} channels
4 Influx of Ca^{2+} through channels
5 Ca^{2+} causes vesicles to fuse with presynaptic membrane
Synaptic vesicle
Transmitter molecules
Ca^{2+}
6 Transmitter is released into synaptic cleft via exocytosis
10 Retrieval of vesicular membrane from plasma membrane
Trans-mitter molecules
Ions
Transmitter receptor
Postsynaptic current flow
9 Postsynaptic current causes excitatory or inhibitory postsynaptic potential that changes the excitability of the postsynaptic cell
8 Opening or closing of postsynaptic channels
7 Transmitter binds to receptor molecules in postsynaptic membrane

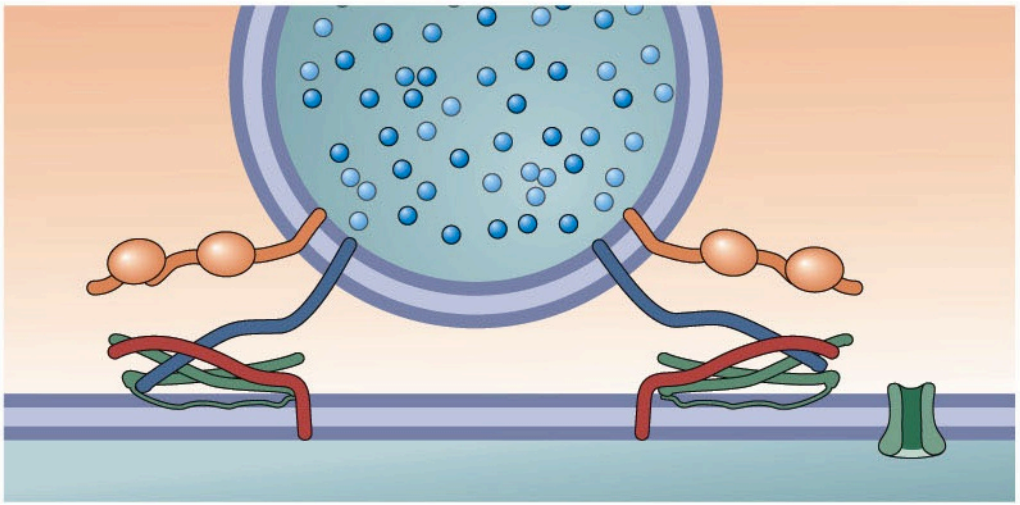


tetanus toxin and **botulinum toxin** cleave *synaptobrevin*, impair release of transmitter at neuromuscular junction

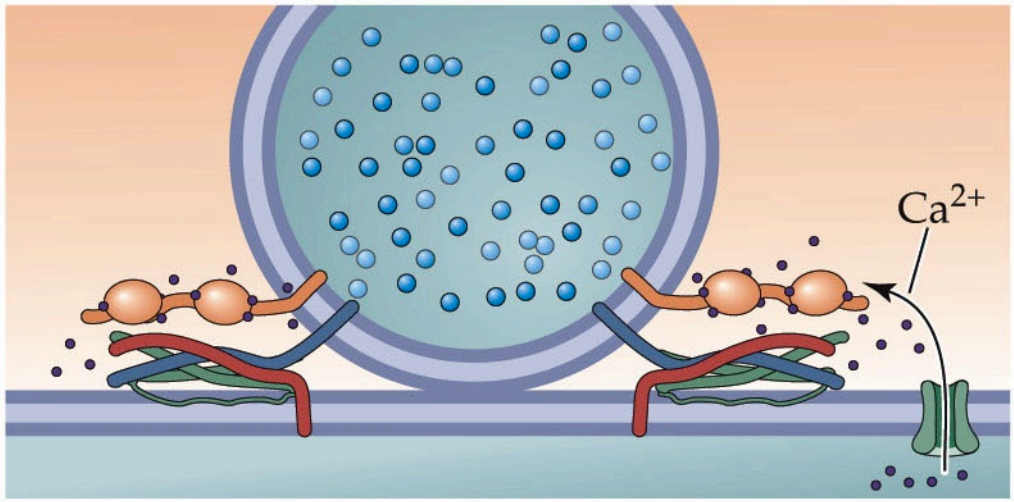
1 Vesicle docks



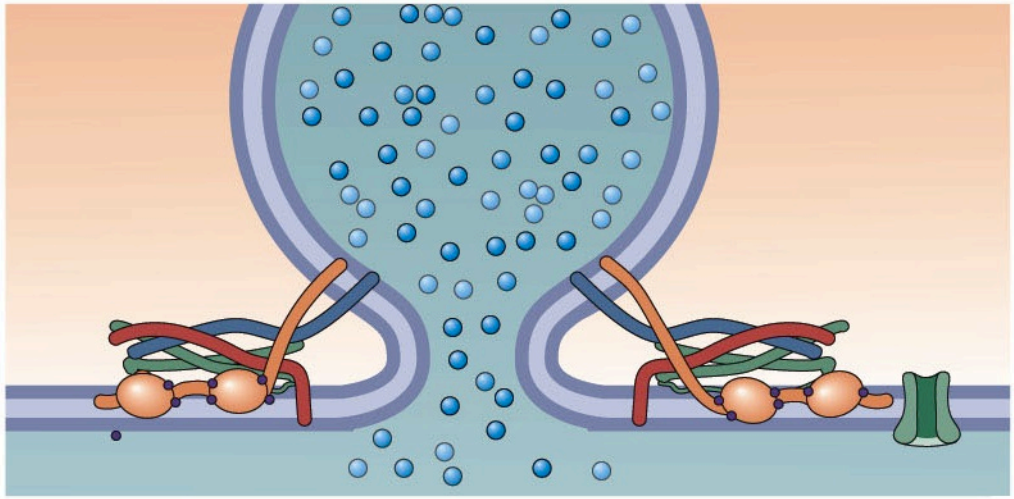
2 SNARE complexes form to pull membranes together

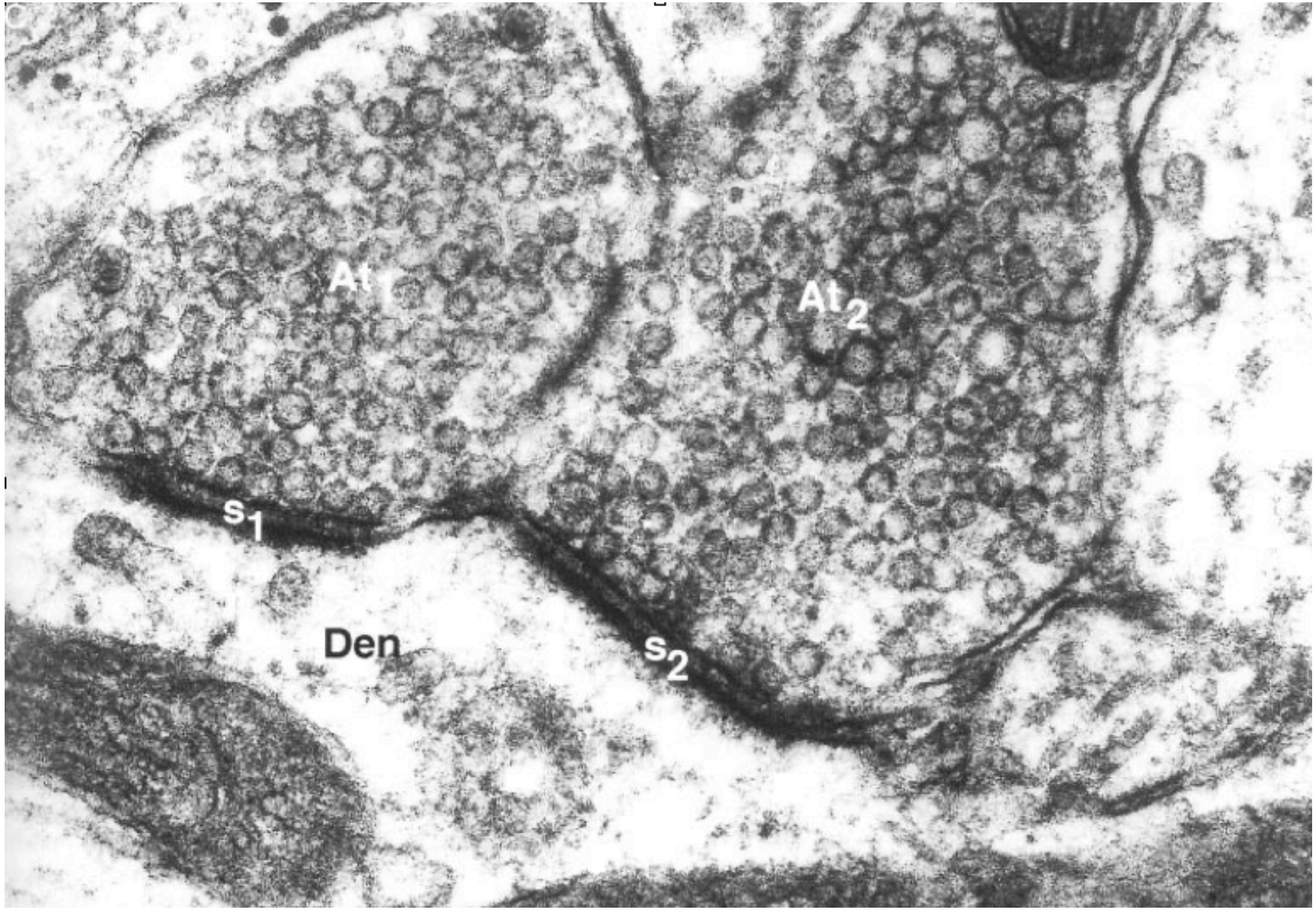


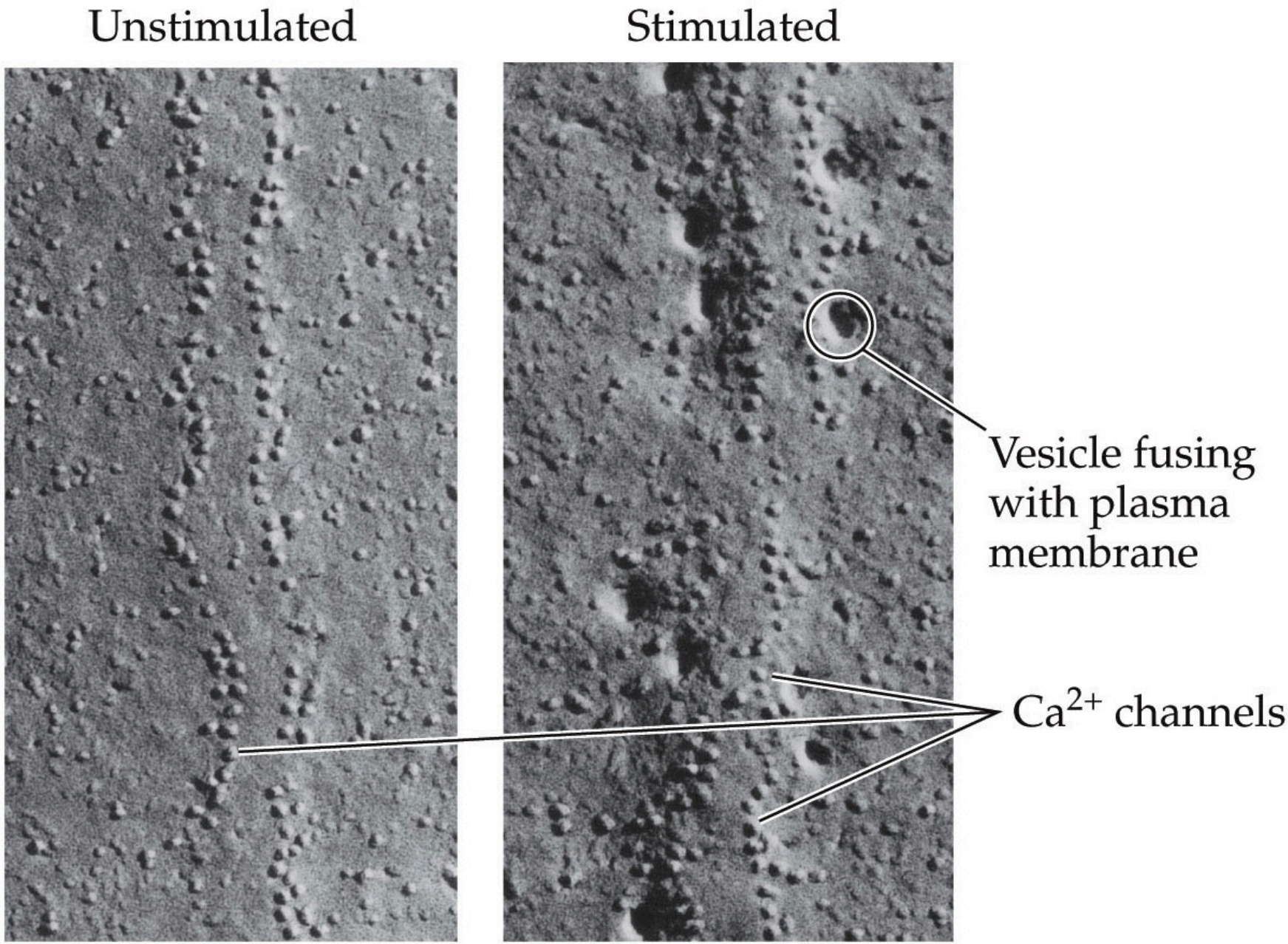
3 Entering Ca^{2+} binds to synaptotagmin

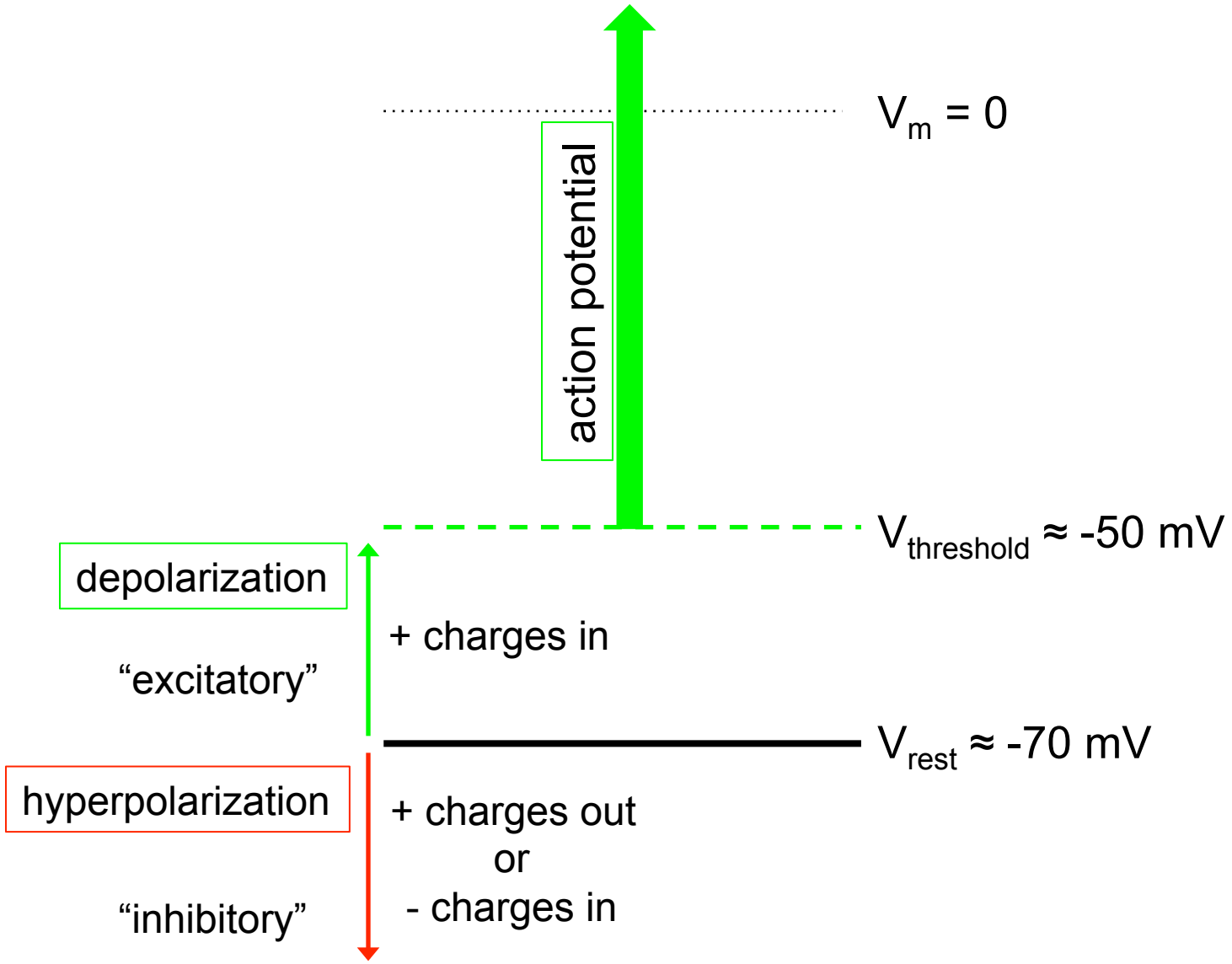


4 Ca^{2+}-bound synaptotagmin catalyzes membrane fusion




At1
At2
S1
S2
Den

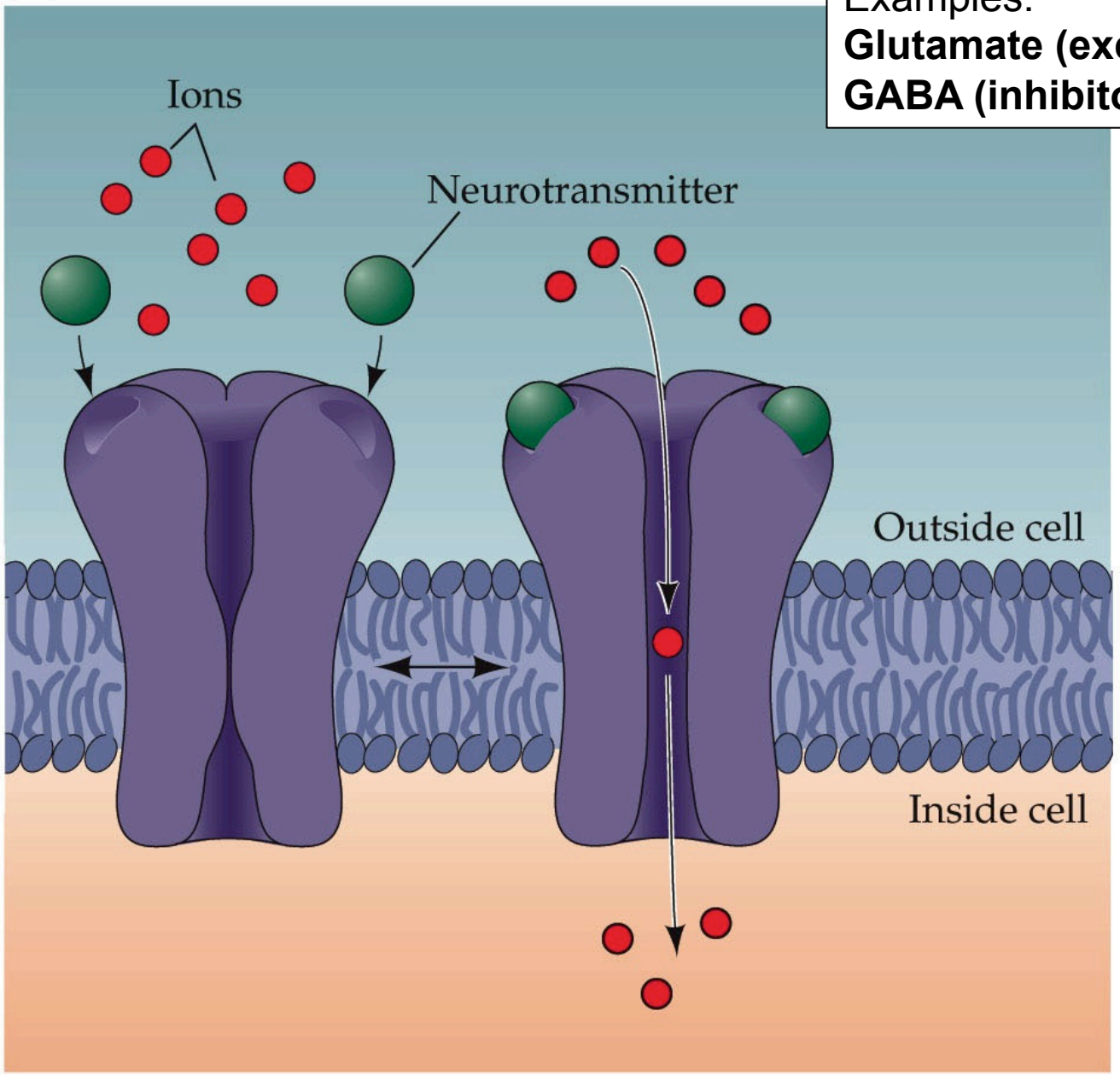

Unstimulated
Stimulated
Vesicle fusing with plasma membrane
Ca^{2+} channels



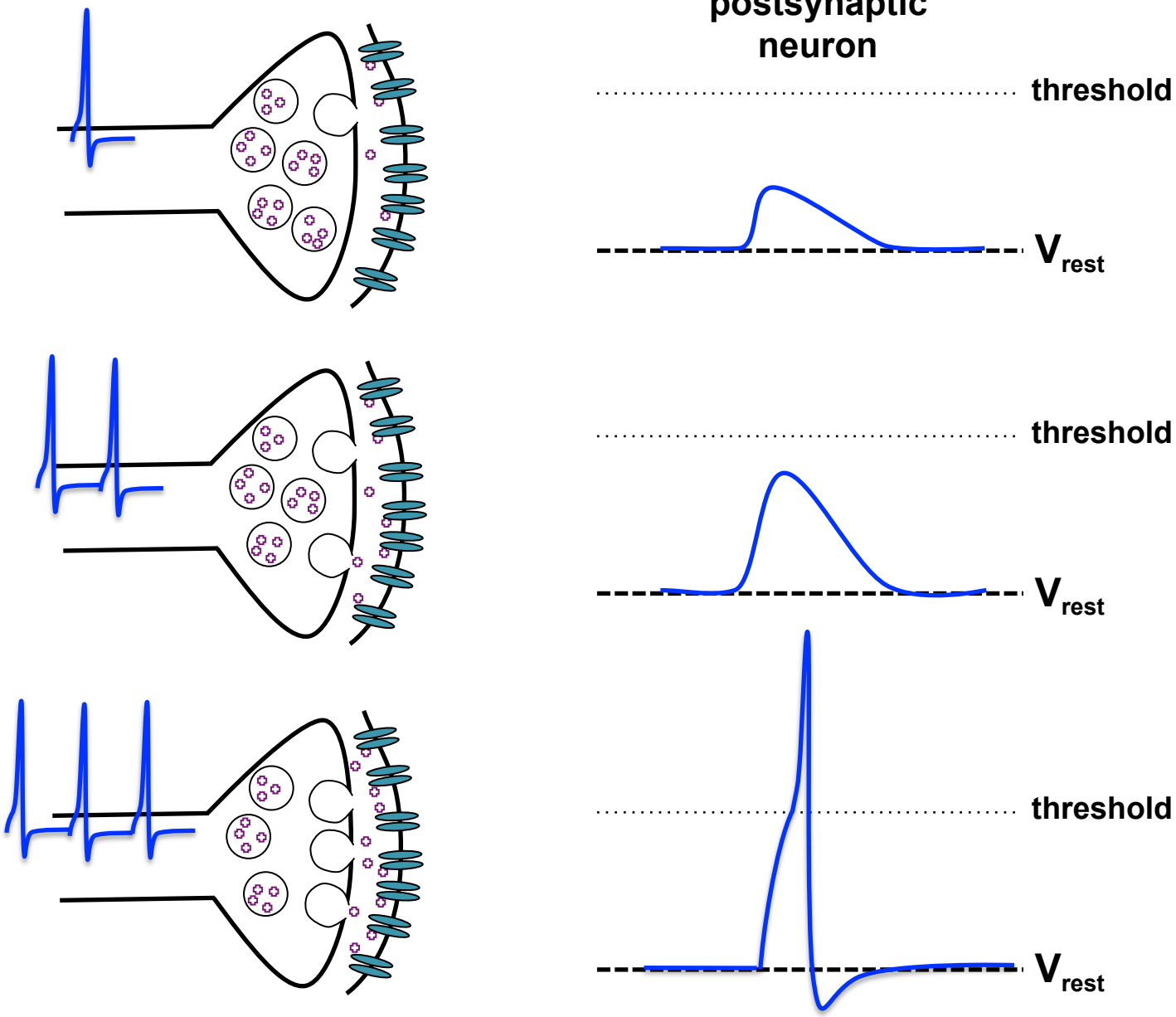
excitatory = *depolarizing* = closer to firing action potential

inhibitory = *hyperpolarizing* = further from firing action potential

(A) LIGAND-GATED ION CHANNELS



Examples:
Glutamate (excitatory)
GABA (inhibitory)


postsynaptic
neuron
threshold
V_{rest}
threshold
V_{rest}
threshold
V_{rest}

Which ions are flowing (and in which direction) in the postsynaptic cell?

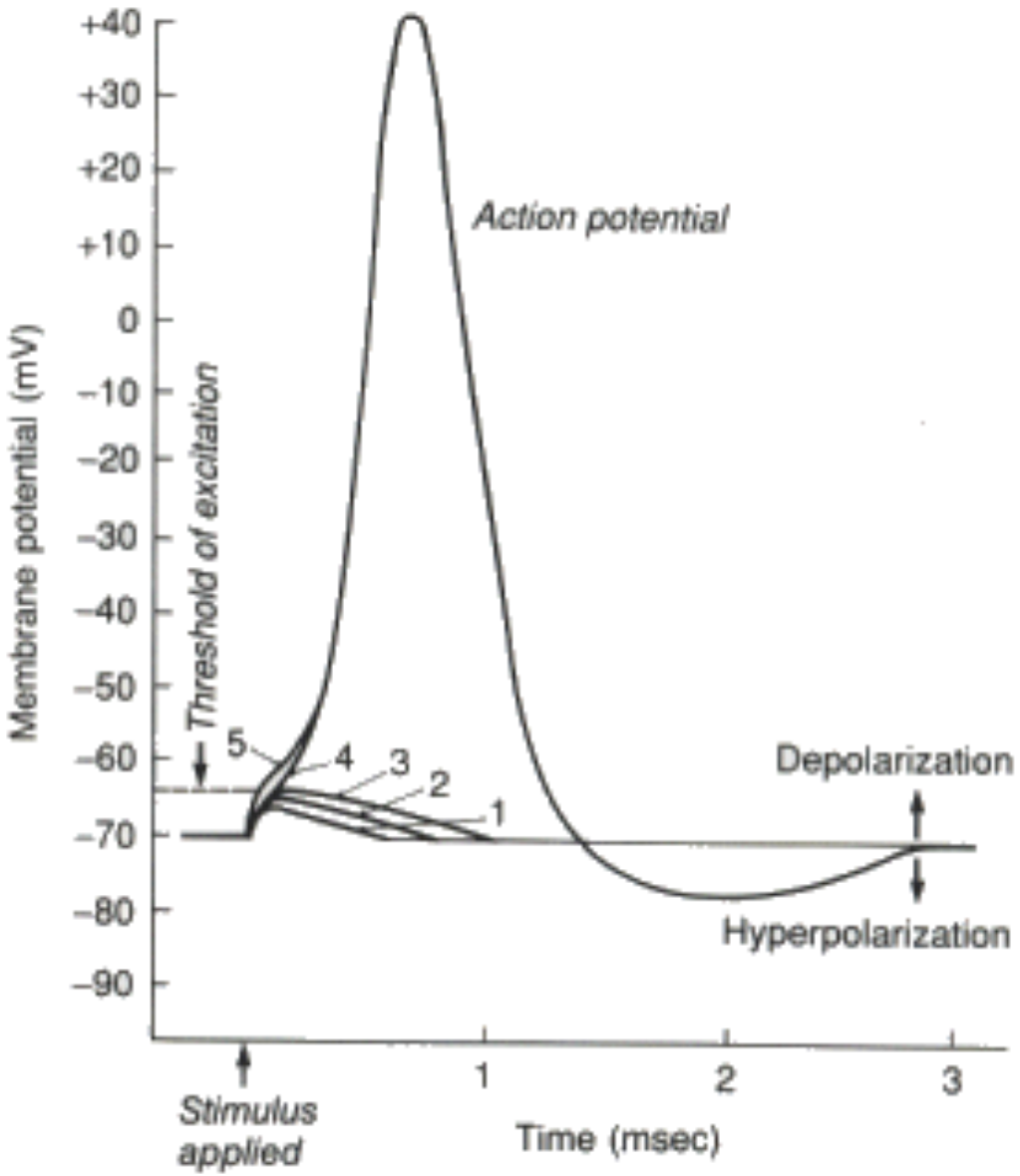
Glutamate Receptors 2 Types { AMPA receptors; NMDA receptors*

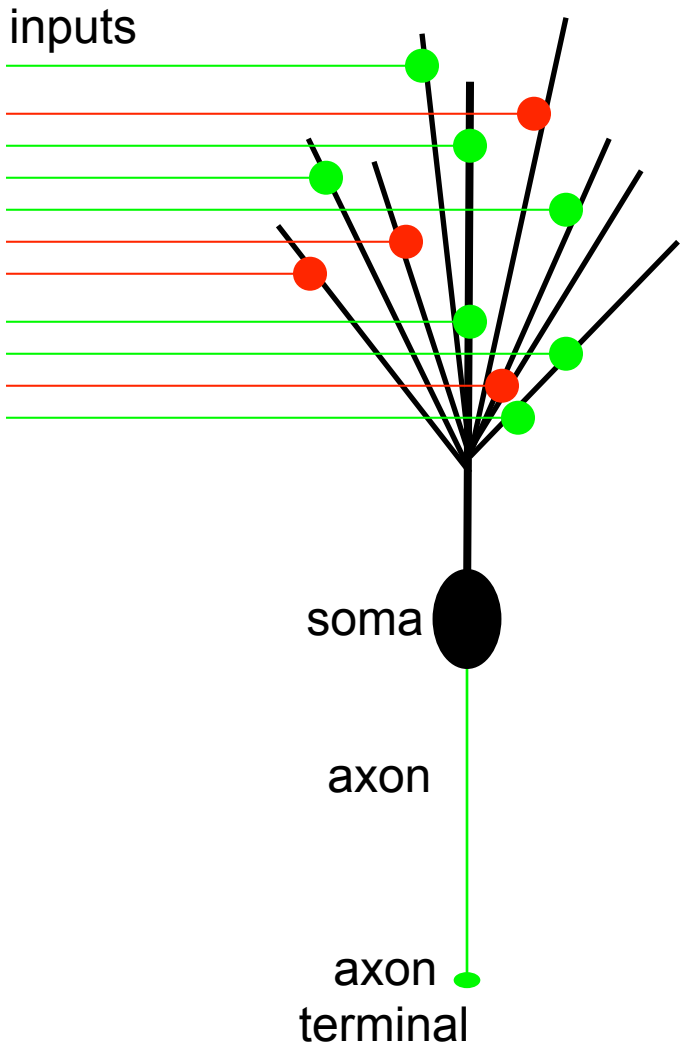
- ligand-gated ion channels
- permeable to Na^+, K^+ (and sometimes Ca^{2+})

GABA Receptors

- also ligand-gated ion channels
- permeable to Cl^- only

Many inputs may be needed to cause the cell to spike



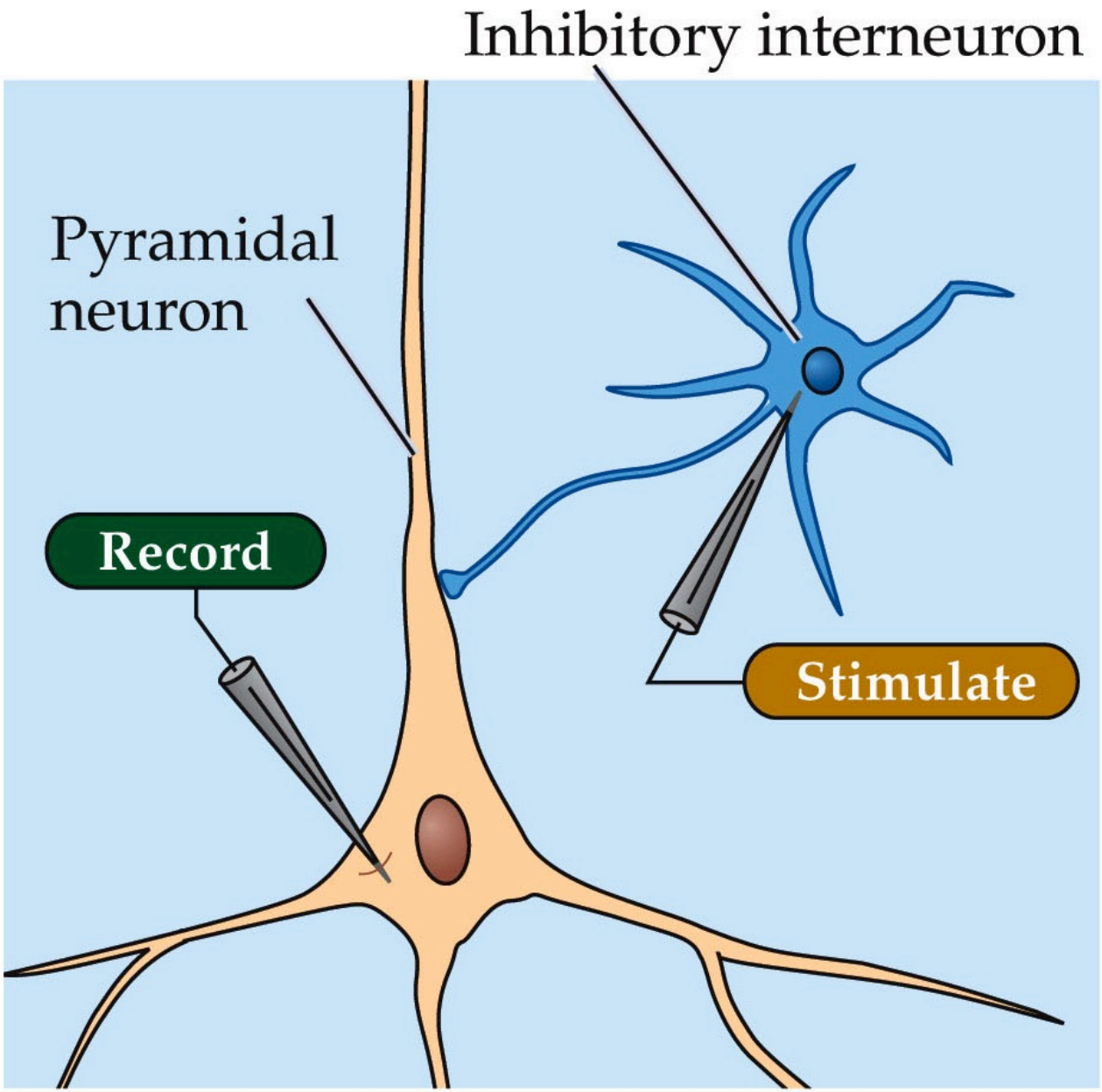


simple computation by a neuron:

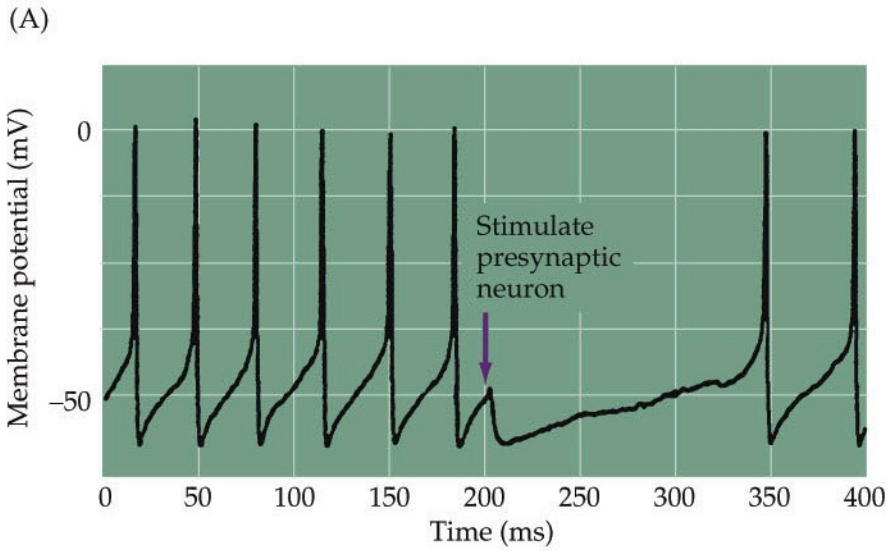
if $\sum_{\text{(sum)}}$ +/- inputs > $V_{\text{threshold}}$

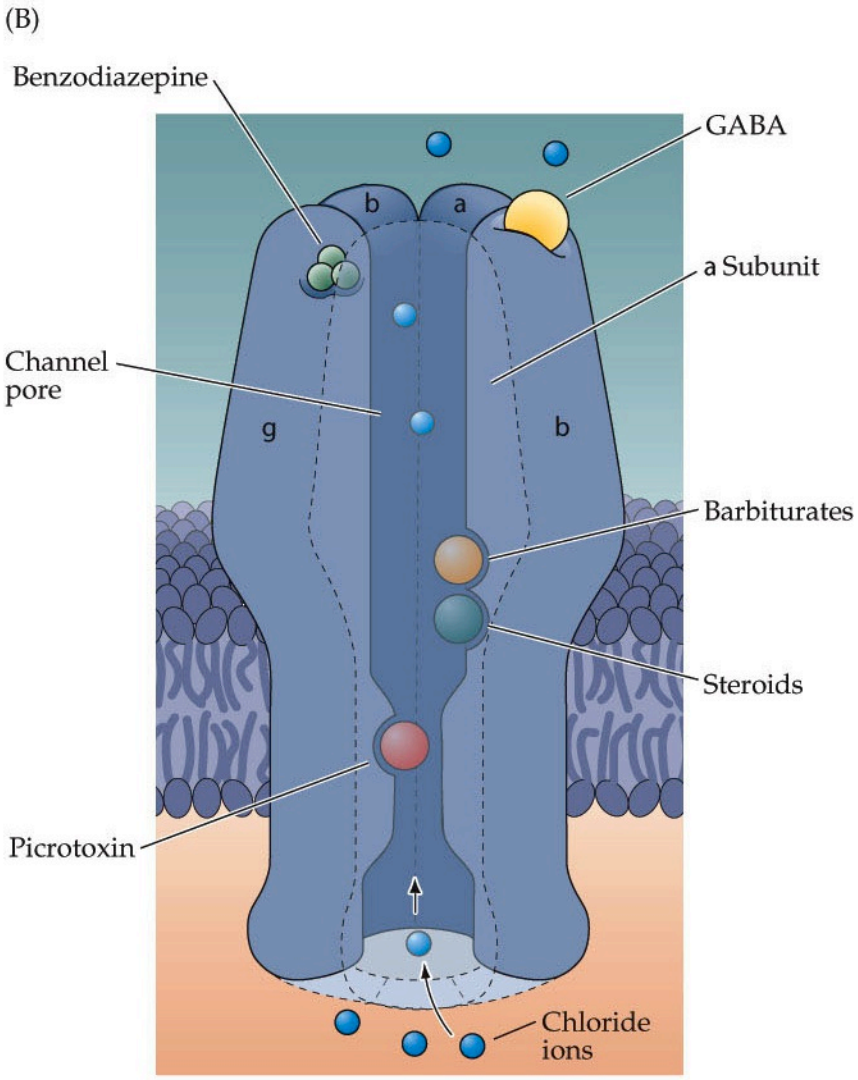
then,

fire action potential

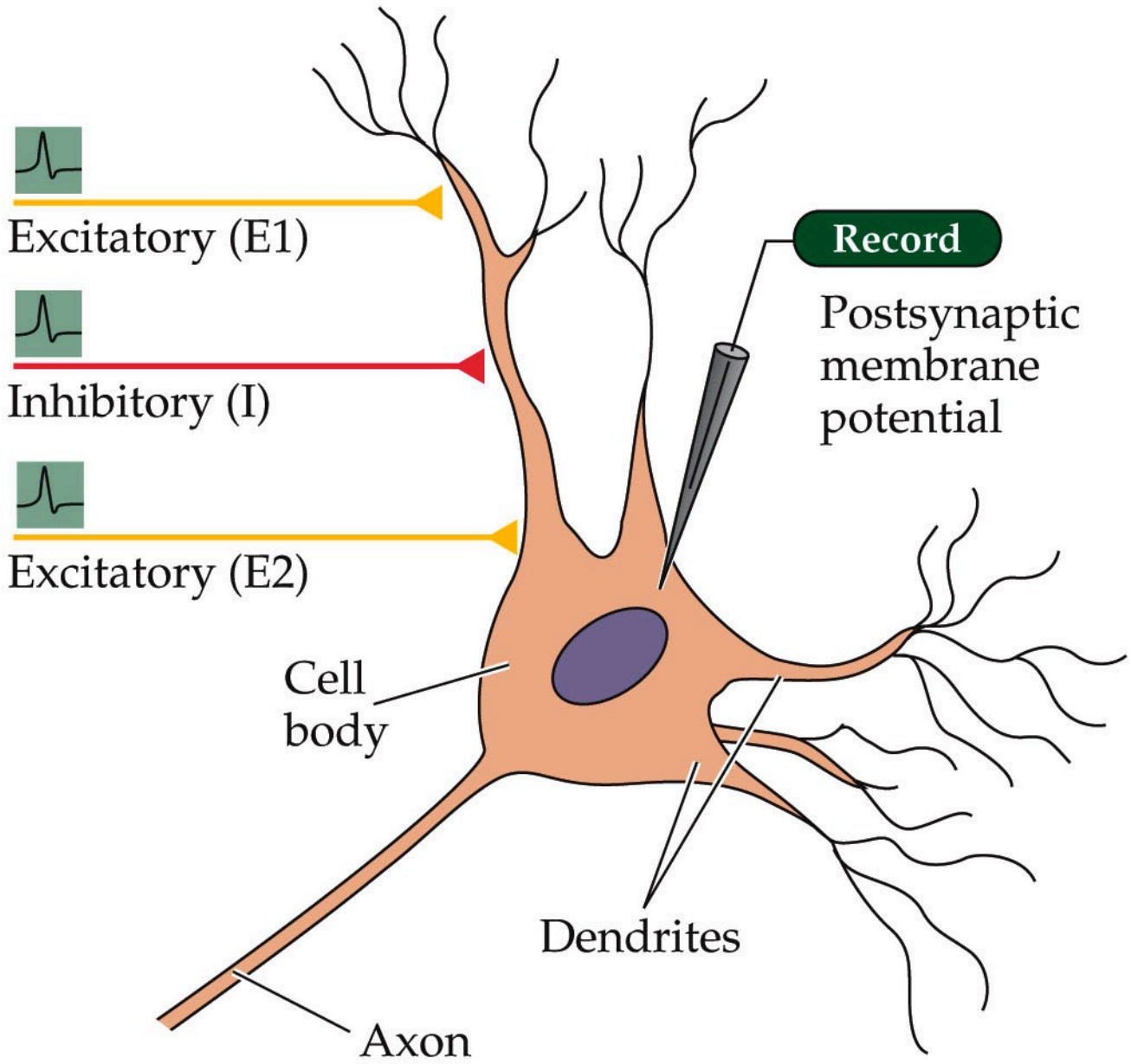

Inhibitory interneuron
Pyramidal neuron
Record
Stimulate

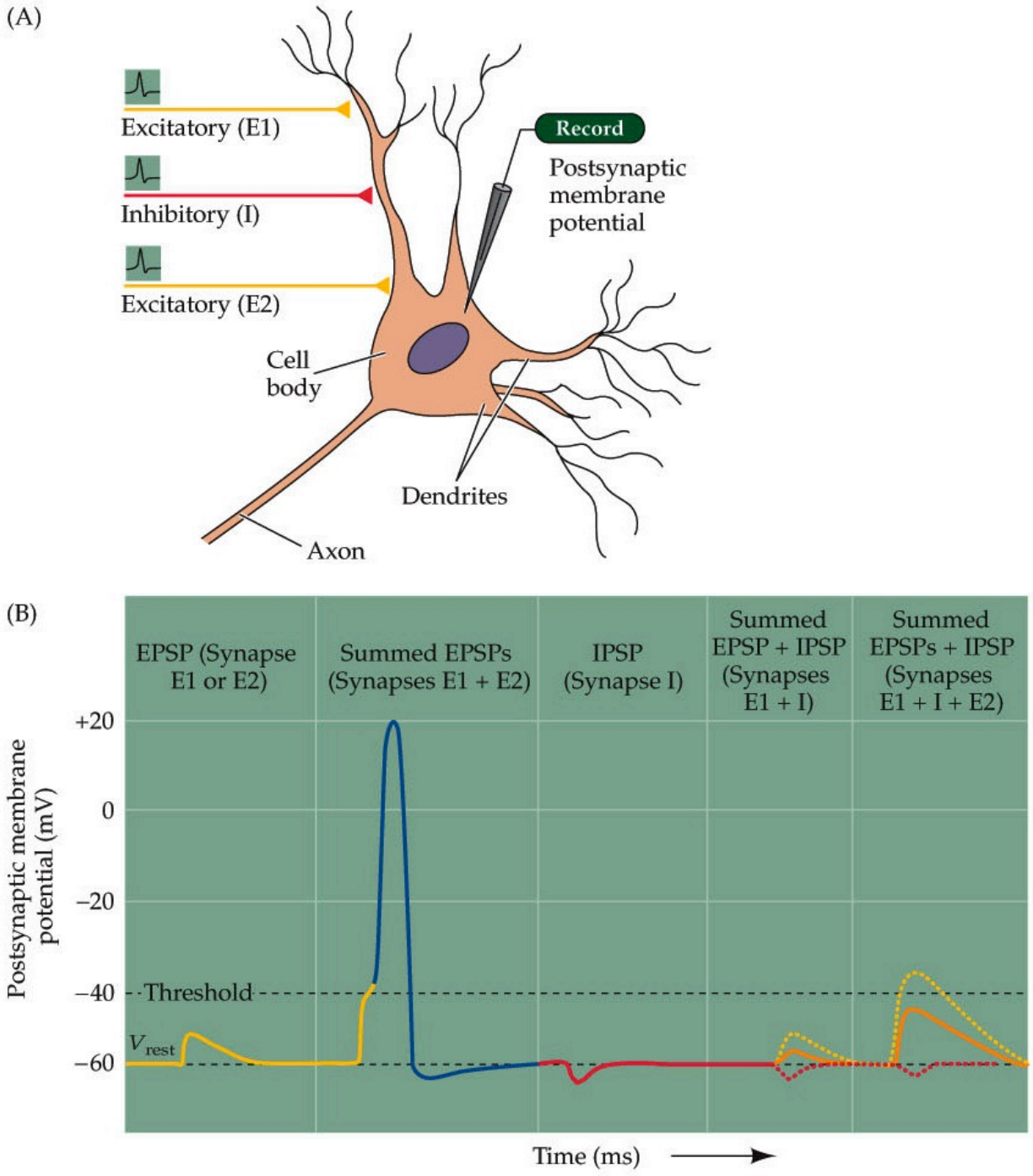
GABA receptors are chloride channels





A = inhibitory, interneuron


Excitatory (E1)
Inhibitory (I)
Excitatory (E2)
Record
Postsynaptic membrane potential
Cell body
Dendrites
Axon

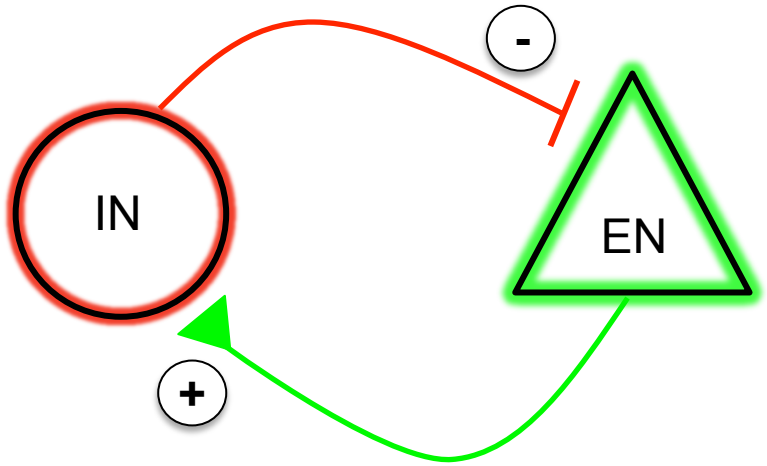

(A)
Excitatory (E1)
Inhibitory (I)
Excitatory (E2)
Record
Postsynaptic membrane potential
Cell body
Dendrites
Axon
(B)
EPSP (Synapse E1 or E2)
Summed EPSPs (Synapses E1 + E2)
IPSP (Synapse I)
Summed EPSP + IPSP (Synapses E1 + I)
Summed EPSPs + IPSP (Synapses E1 + I + E2)
Postsynaptic membrane potential (mV)
+20
0
−20
−40
−60
Threshold
V_{rest}
Time (ms)

Networks of Neurons in the Brain are Mainly Excitatory and Inhibitory Neurons

(glutamatergic) (GABAergic)

Human (Mammalian) Brain

- **~ 80% excitatory neurons** (e.g. pyramidal cells in cortex)
- **~ 20% inhibitory neurons** (interneurons)



What happens when excitation and inhibition are out of balance?

Glutamatergic cells
(excitatory)

GABAergic cells
(inhibitory)

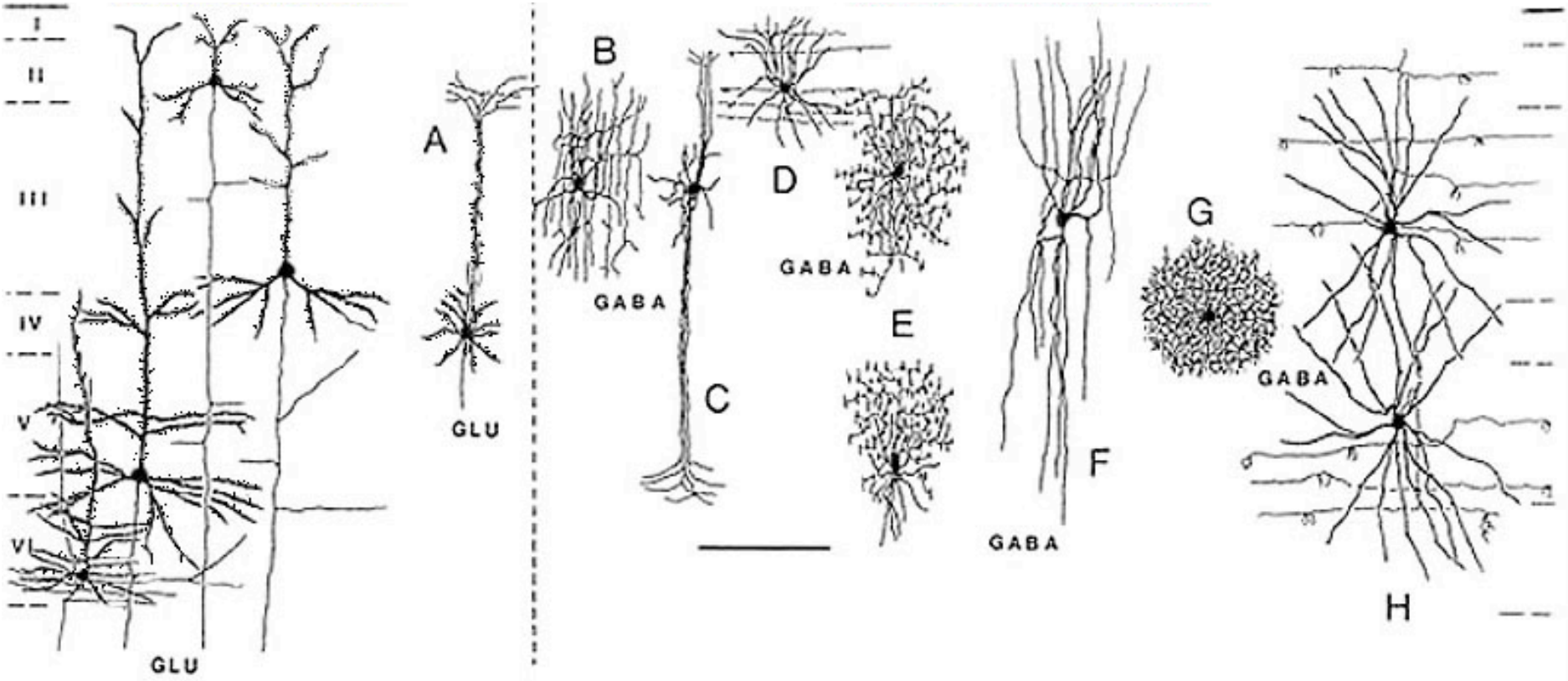
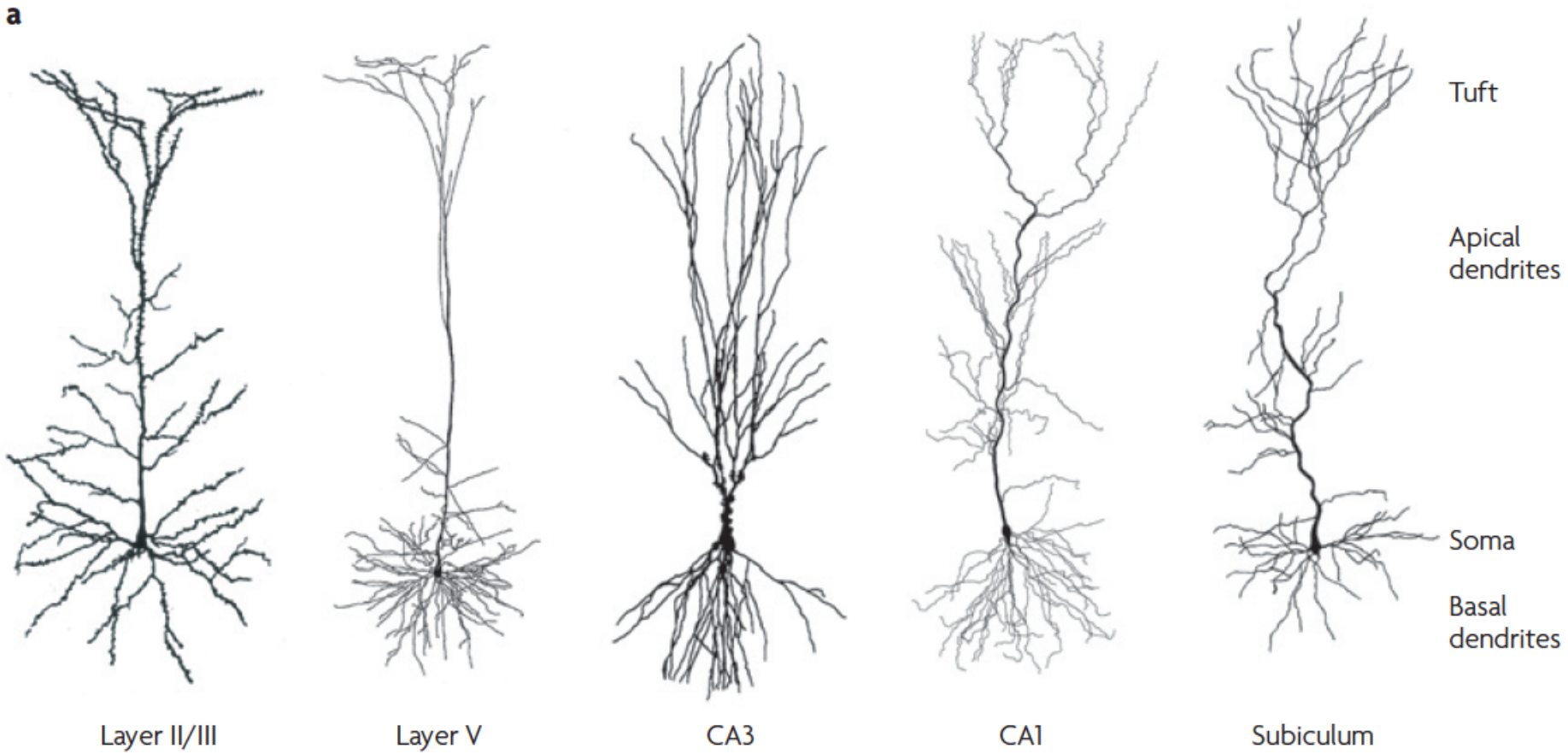


Figure 12. Basic cell types in the monkey cerebral cortex. Left: spiny neurons that include pyramidal cells and stellate cells (A). Spiny neurons utilize the neurotransmitter glutamate (Glu). Right: smooth cells that use the neurotransmitter GABA. B, cell with local axon arcades; C, double bouquet cell; D, H, basket cells; E, chandelier cells; F, bitufted, usually peptide-containing cell; G, neurogliaform cell.

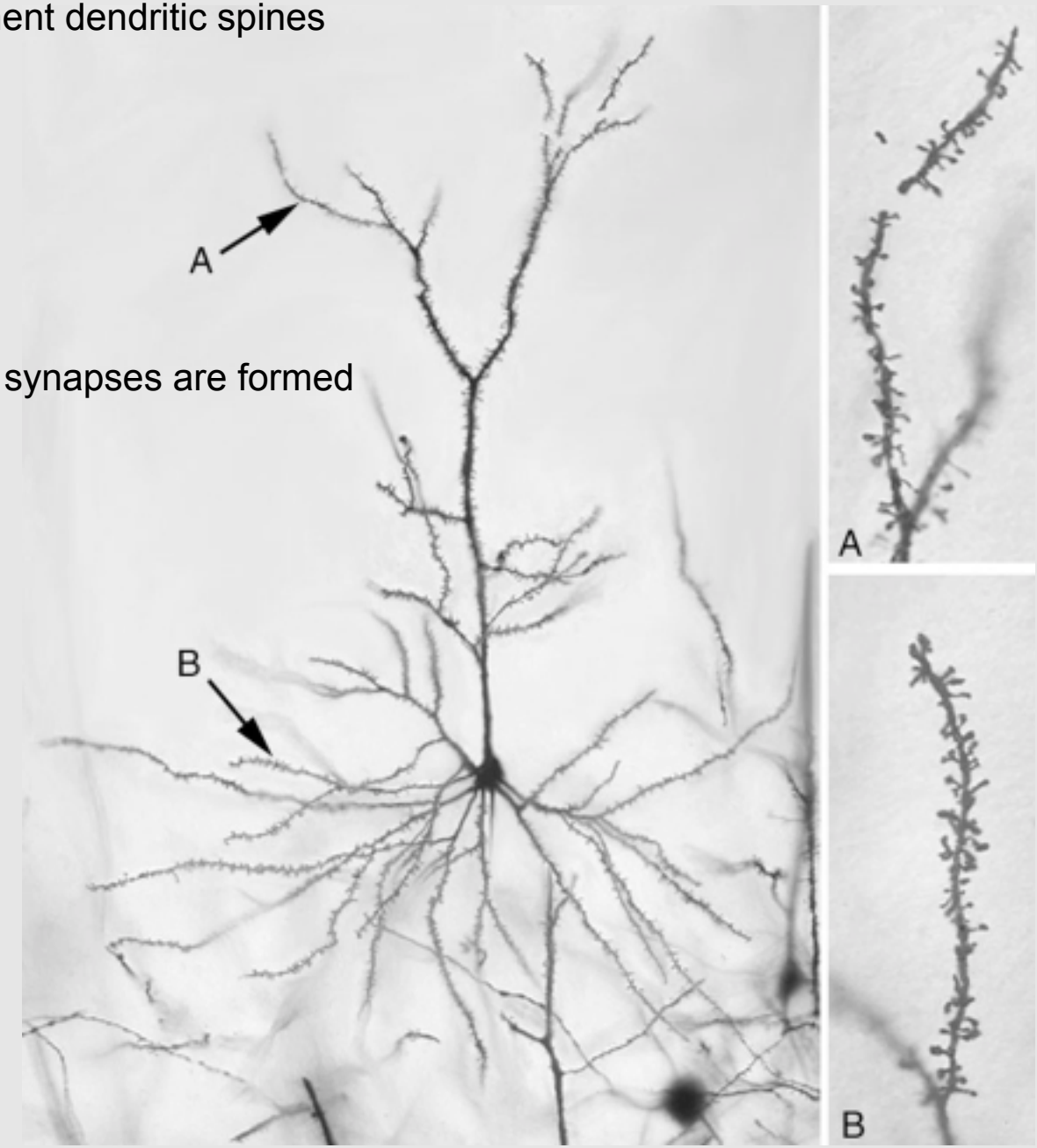
pyramidal neurons (**excitatory**)



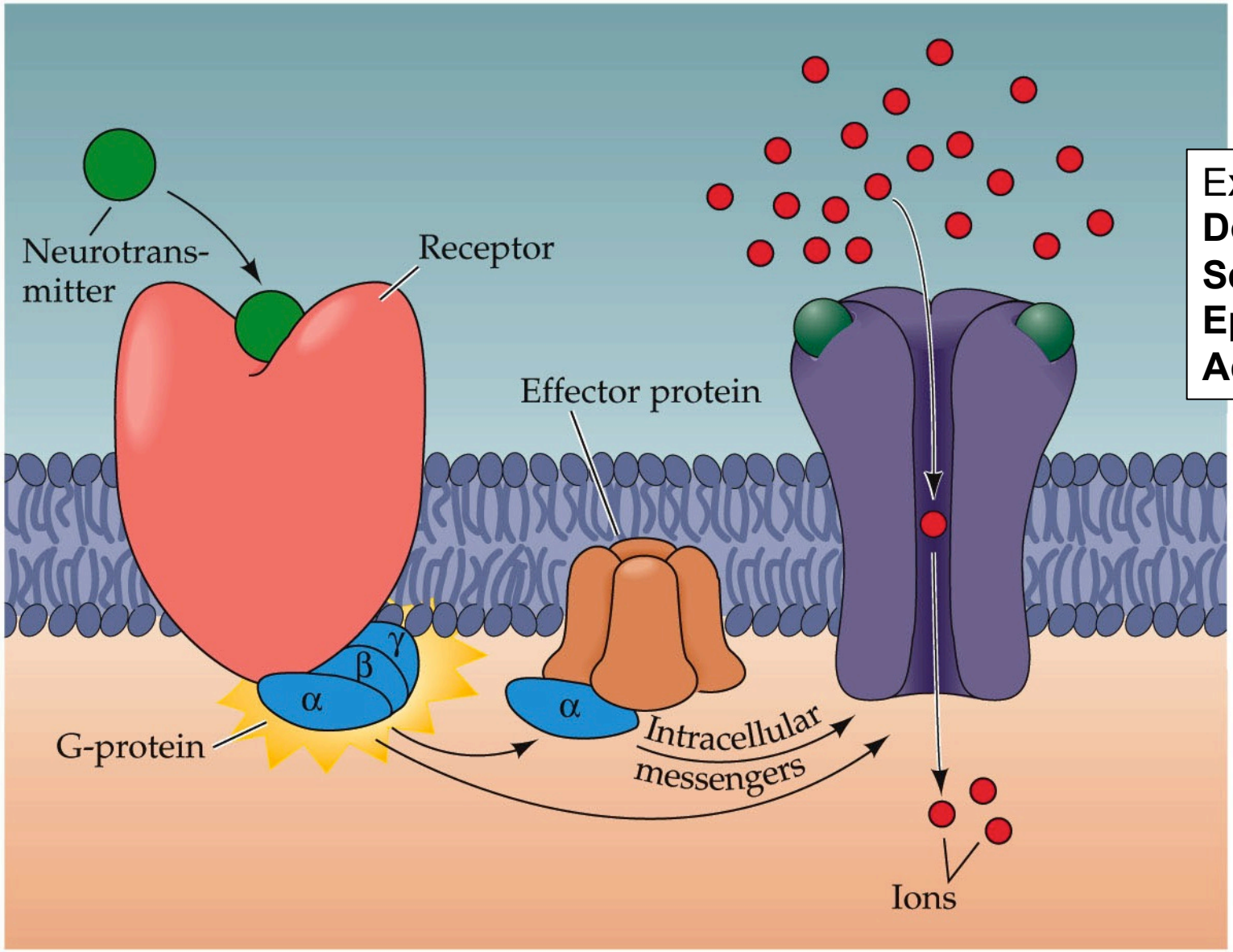
Spruston, 2008

Excitatory neurons have prominent dendritic spines

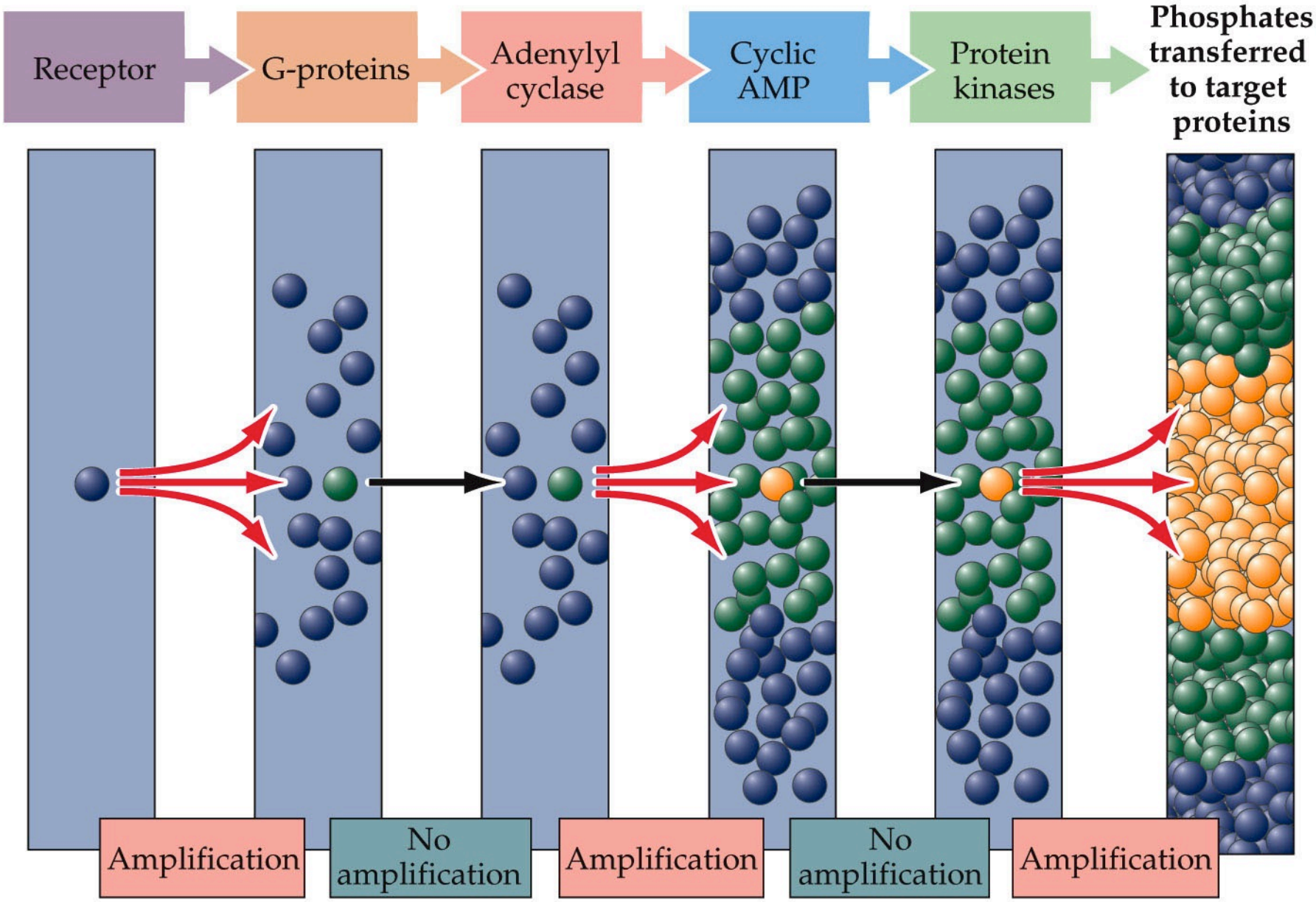
dendritic spines:
protuberances where excitatory synapses are formed

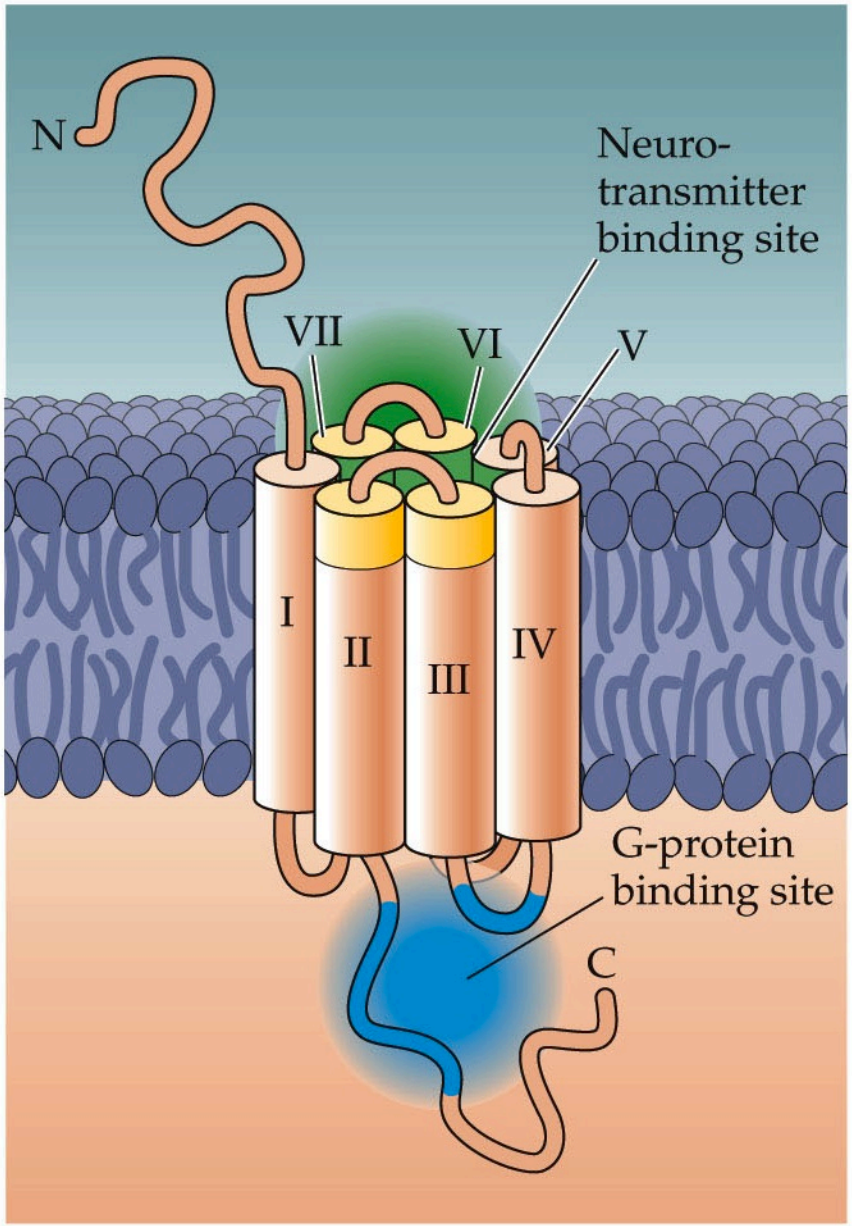


(B) G-PROTEIN–COUPLED RECEPTORS



Examples:
Dopamine
Serotonin
Epinephrine
Acetylcholine


Receptor
G-proteins
Adenylyl cyclase
Cyclic AMP
Protein kinases
Phosphates transferred to target proteins
Amplification
No amplification
Amplification
No amplification
Amplification



Examples:
Dopamine
Serotonin
Epinephrine
Acetylcholine

Neurotransmitters

Excitatory

Glutamate

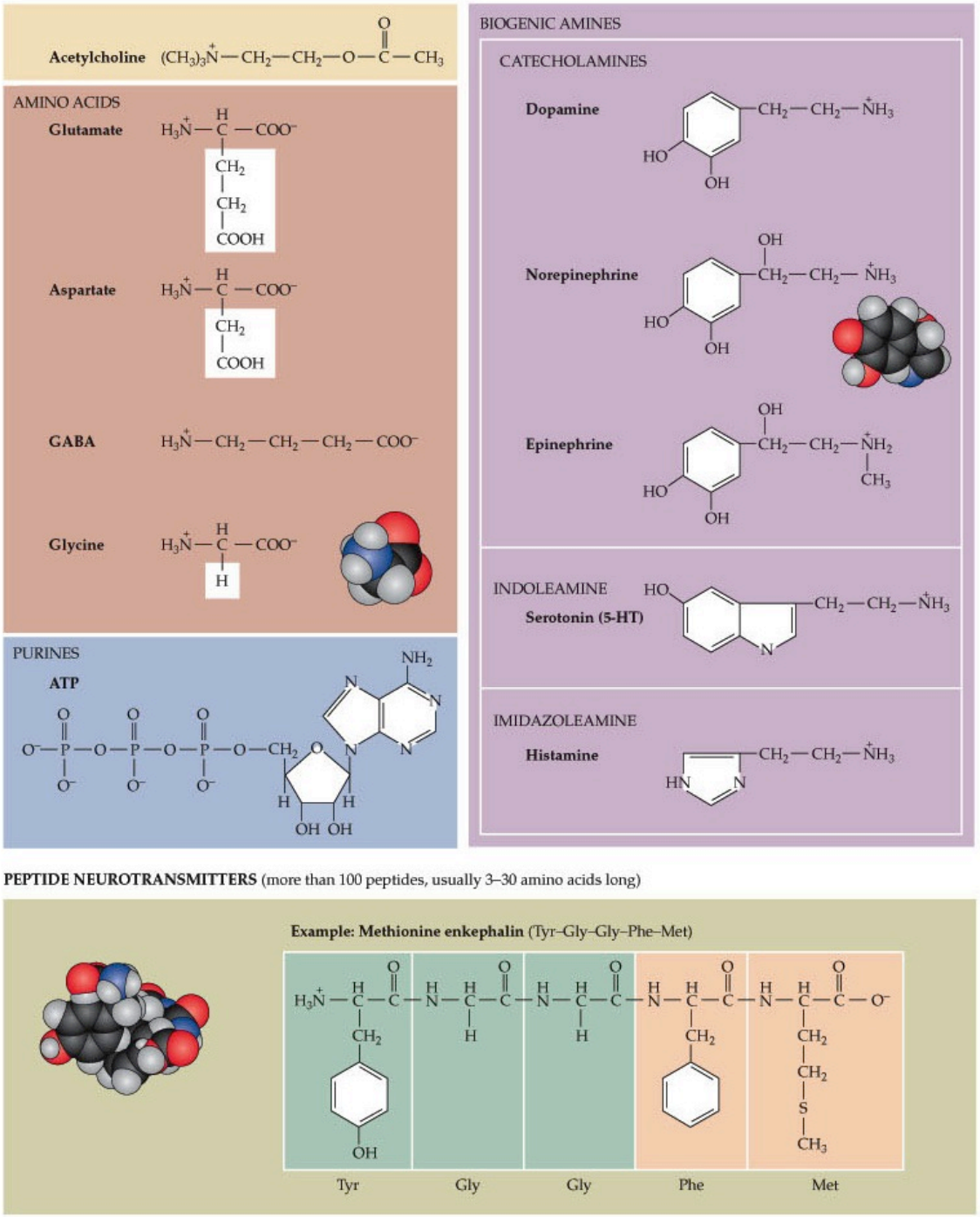
Inhibitory

GABA

Modulatory

Dopamine
Norepinephrine
Serotonin
Acetylcholine

Neuropeptides



Toxins that Affect Neurotransmission

α-bungarotoxin
blocks ACh receptors
neuromuscular junction
(also cobra α-neurotoxin)

conotoxin cocktail
block Ca^{2+} and Na^{+} channels,
glutamate receptors,
and ACh receptors

tetrodotoxin
blocks Na^{+} channels

curare
blocks ACh receptors
(neuromuscular junction)

α-latrotoxin
causes transmitter release

strychnine
blocks inhibitory glycine receptors

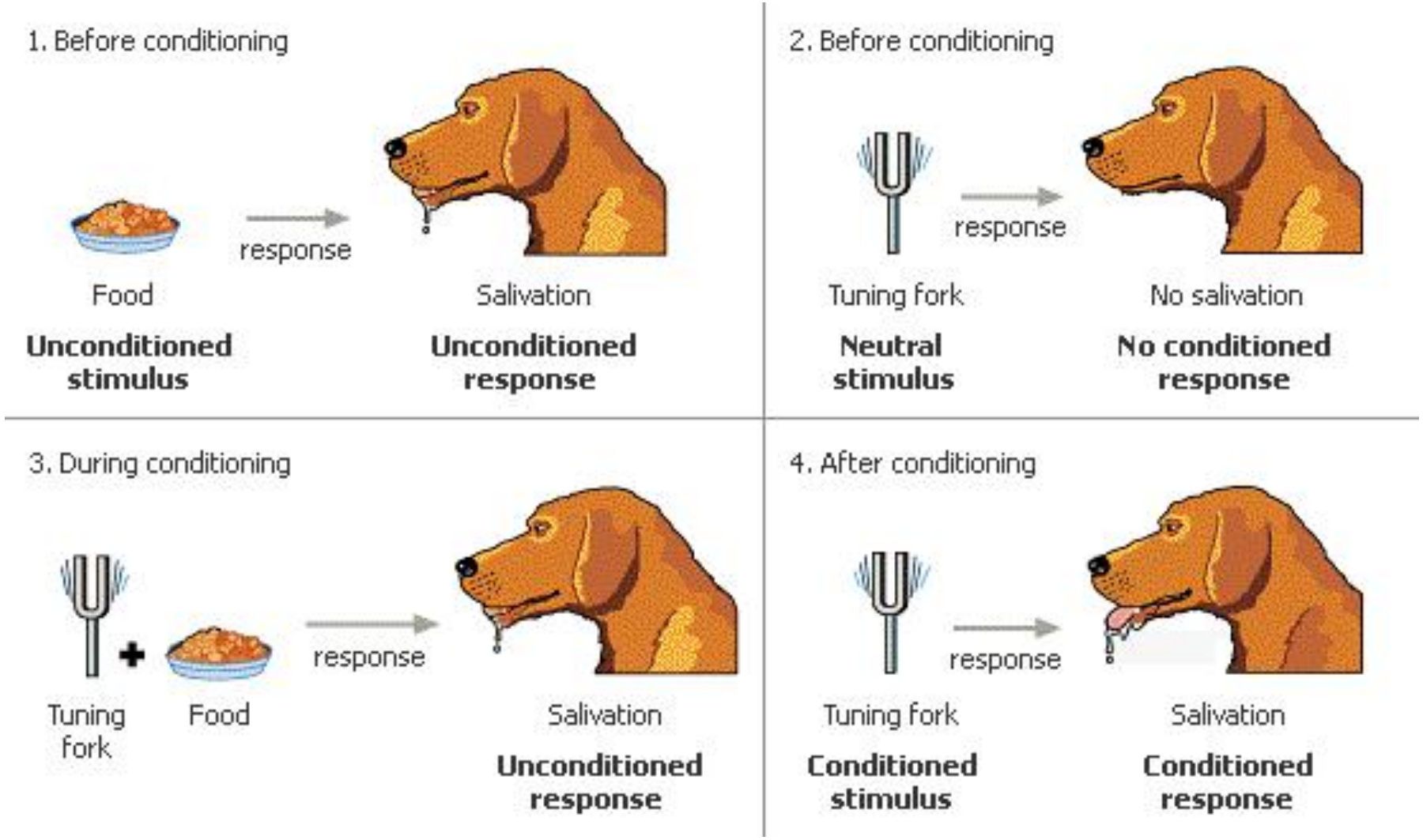
Biological Basis of Learning and Memory

Biological Basis of Memory

- NMDA Receptors
- Intracellular Signaling
- Pre-synaptic & Post-synaptic Changes
- Protein Synthesis
- Long-term Potentiation (LTP)

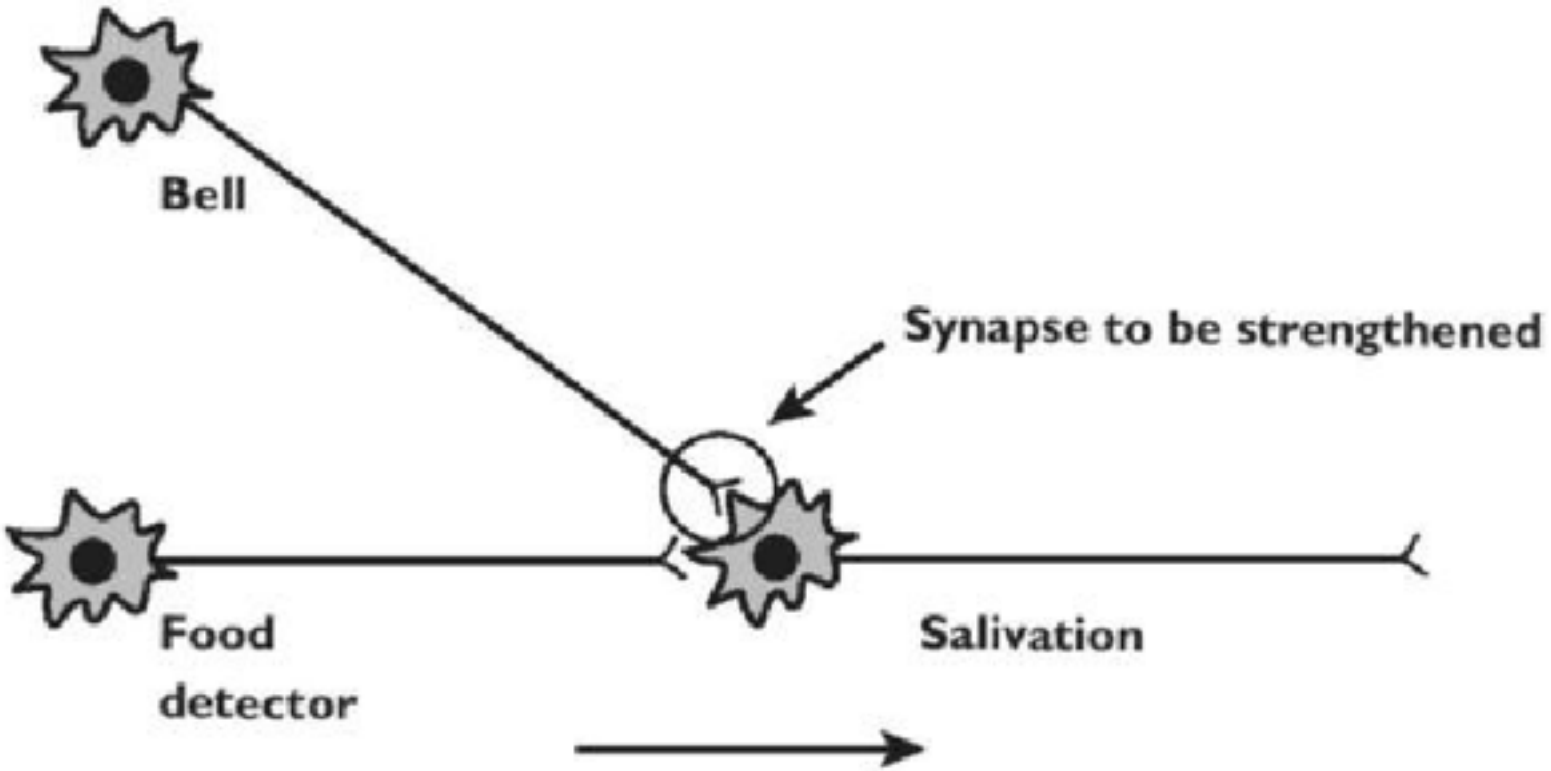
Stabilization of Synaptic Connections for Years

Classical conditioning – Pavlov's Dogs



[Conditioning video]

How could this work in the brain?



Form a connection between the neuron that represents ‘food’ and the neuron that represents the ‘bell’ sound

How does the brain form associations ?

Synaptic plasticity

or

How do the connections between neurons get stronger and weaker?

"When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."

- Donald Hebb, 1949

Simultaneous synaptic inputs and depolarization (action potentials)

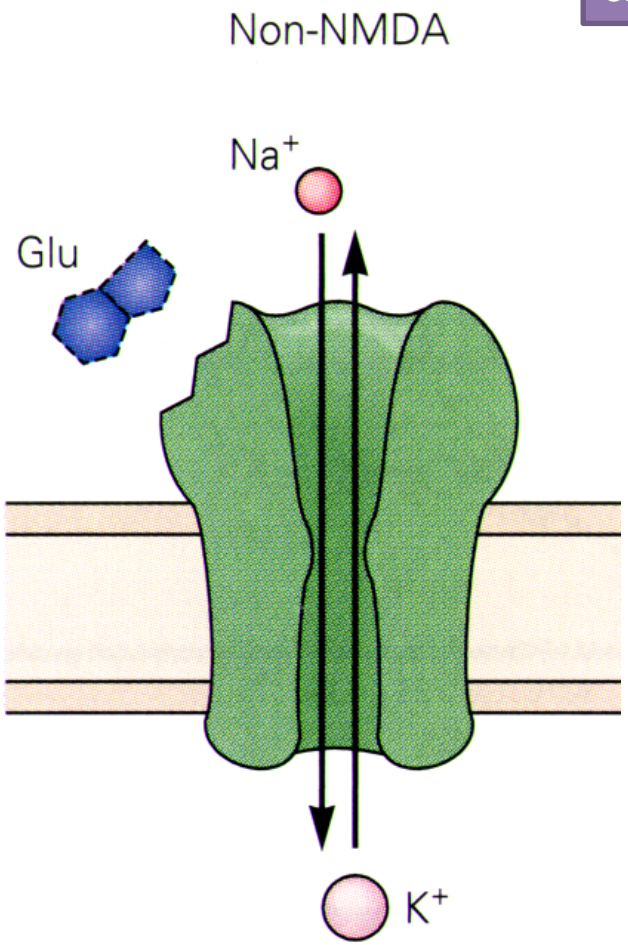
Neurons that fire together, wire together

There are two main types of glutamate receptors

Remember that glutamate is the main **excitatory** neurotransmitter

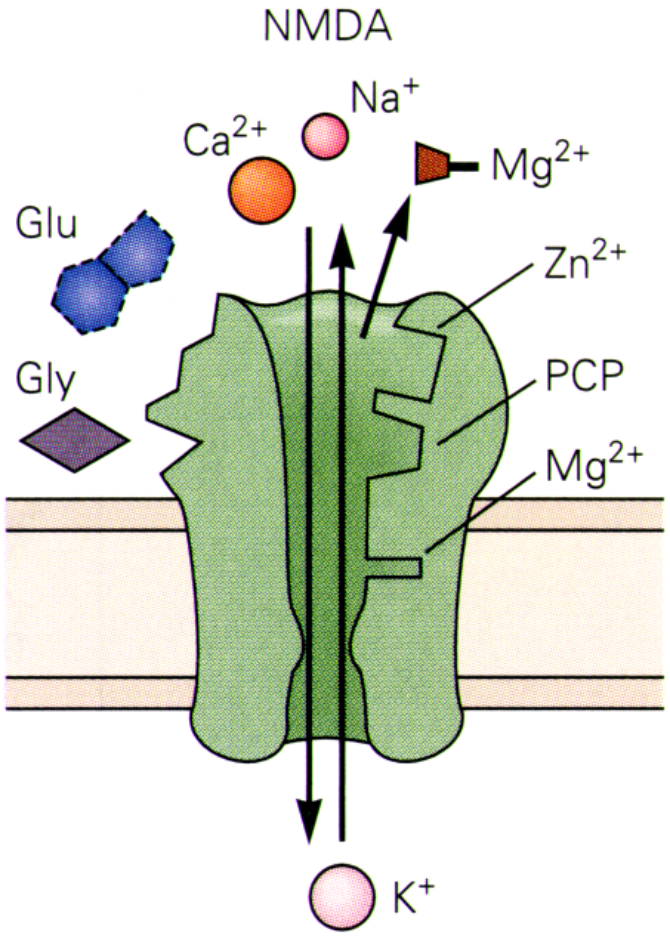
AMPA receptors

Ligand-gated (glutamate) cation channels



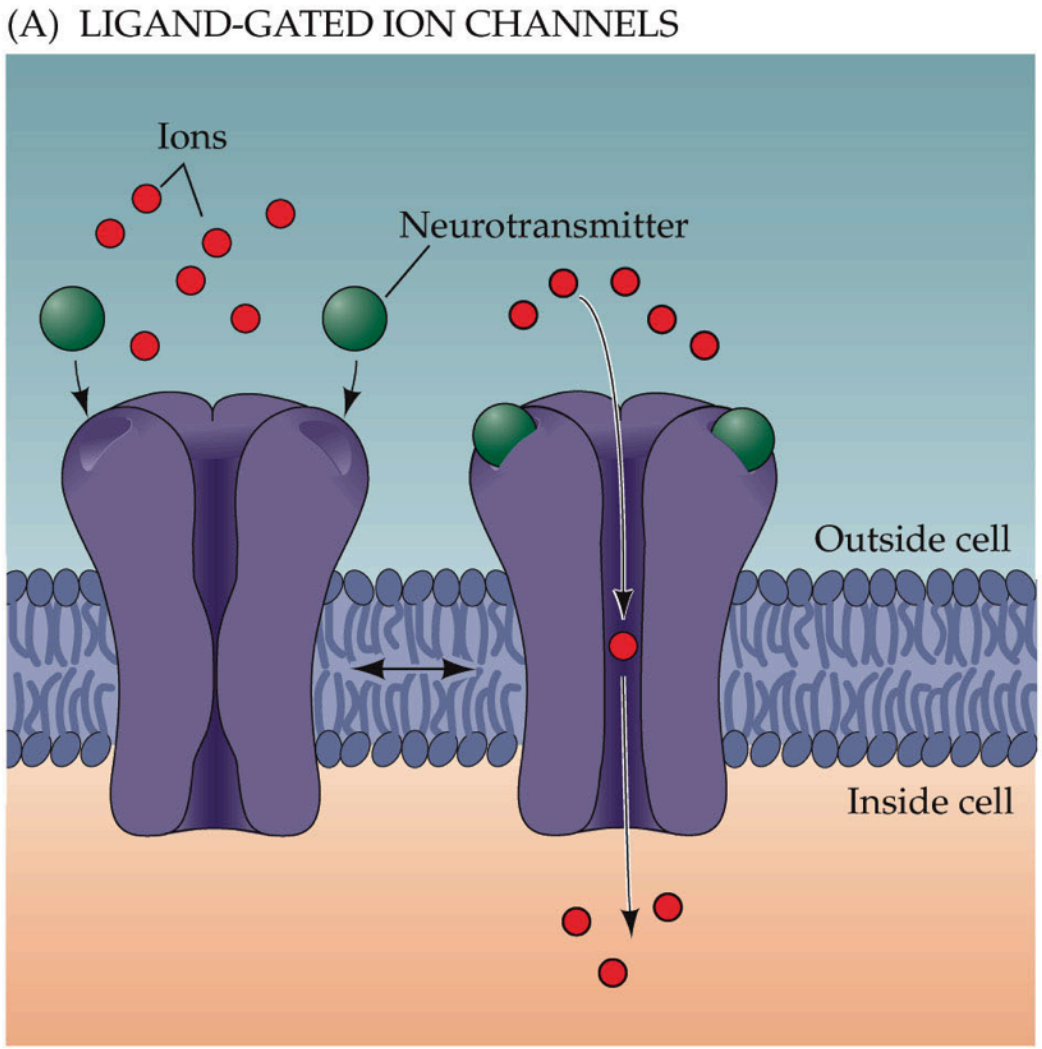
Glutamate (the ligand) binds and opens the channel, cations move according to their electrochemical gradients

NMDA receptor



Glutamate (the ligand) binds and opens the channel, cations move according to their electrochemical gradients, **but only if the Mg+ is not blocking the channel**

Both **AMPA** and **NMDA** receptors are ligand-gated channels

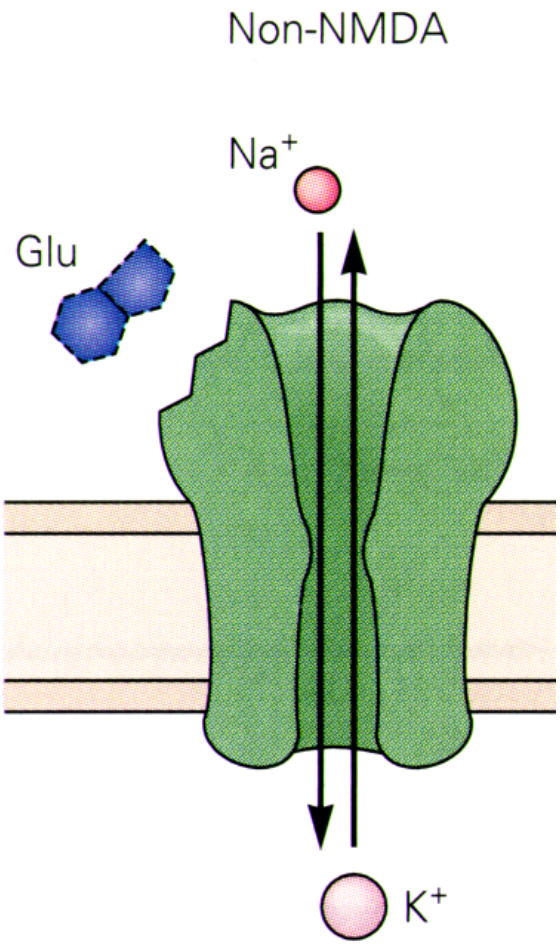


***NEUROSCIENCE, Fourth Edition,* Figure 5.23 (Part 1)**

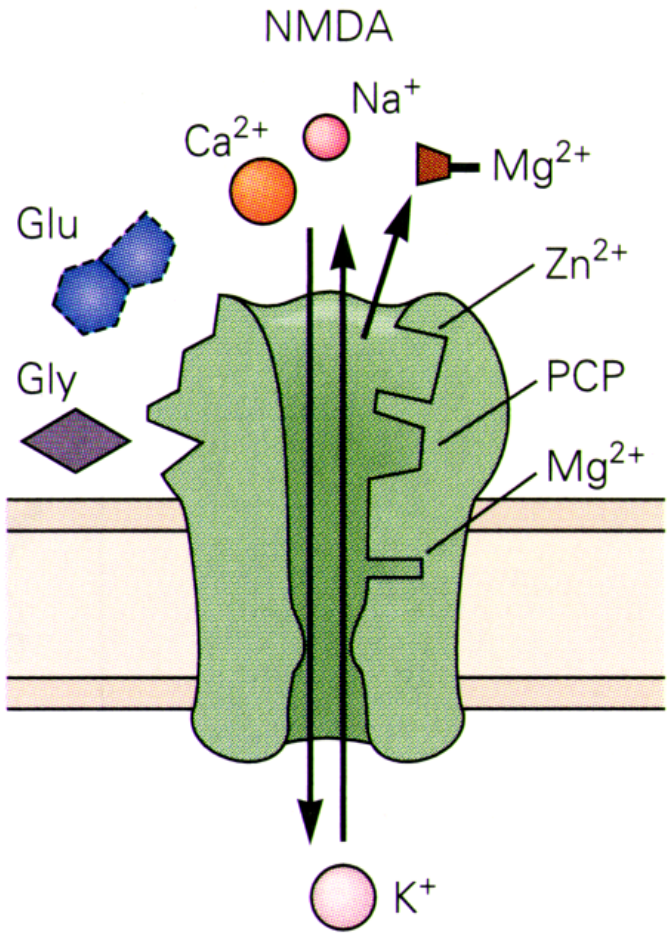
What's different about NMDA receptors?

non-NMDA

AMPA Receptor



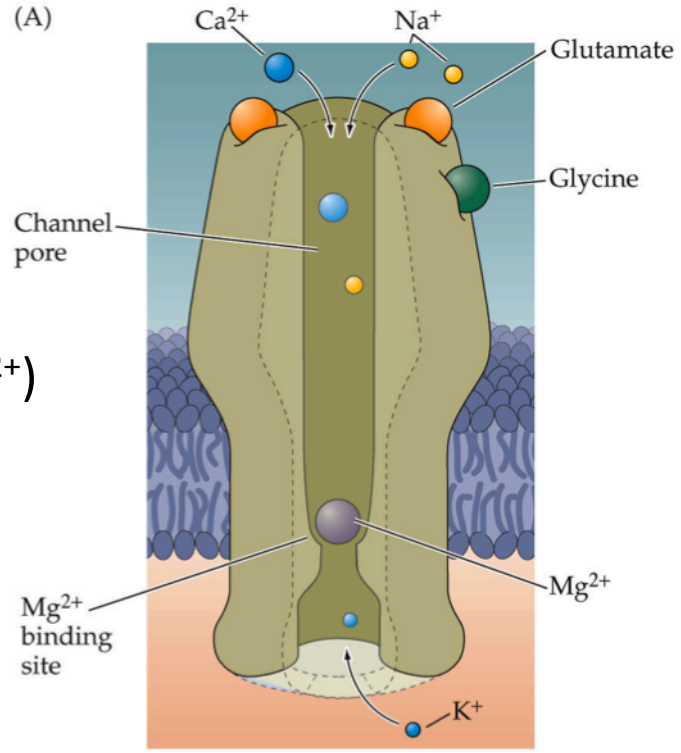
NMDA



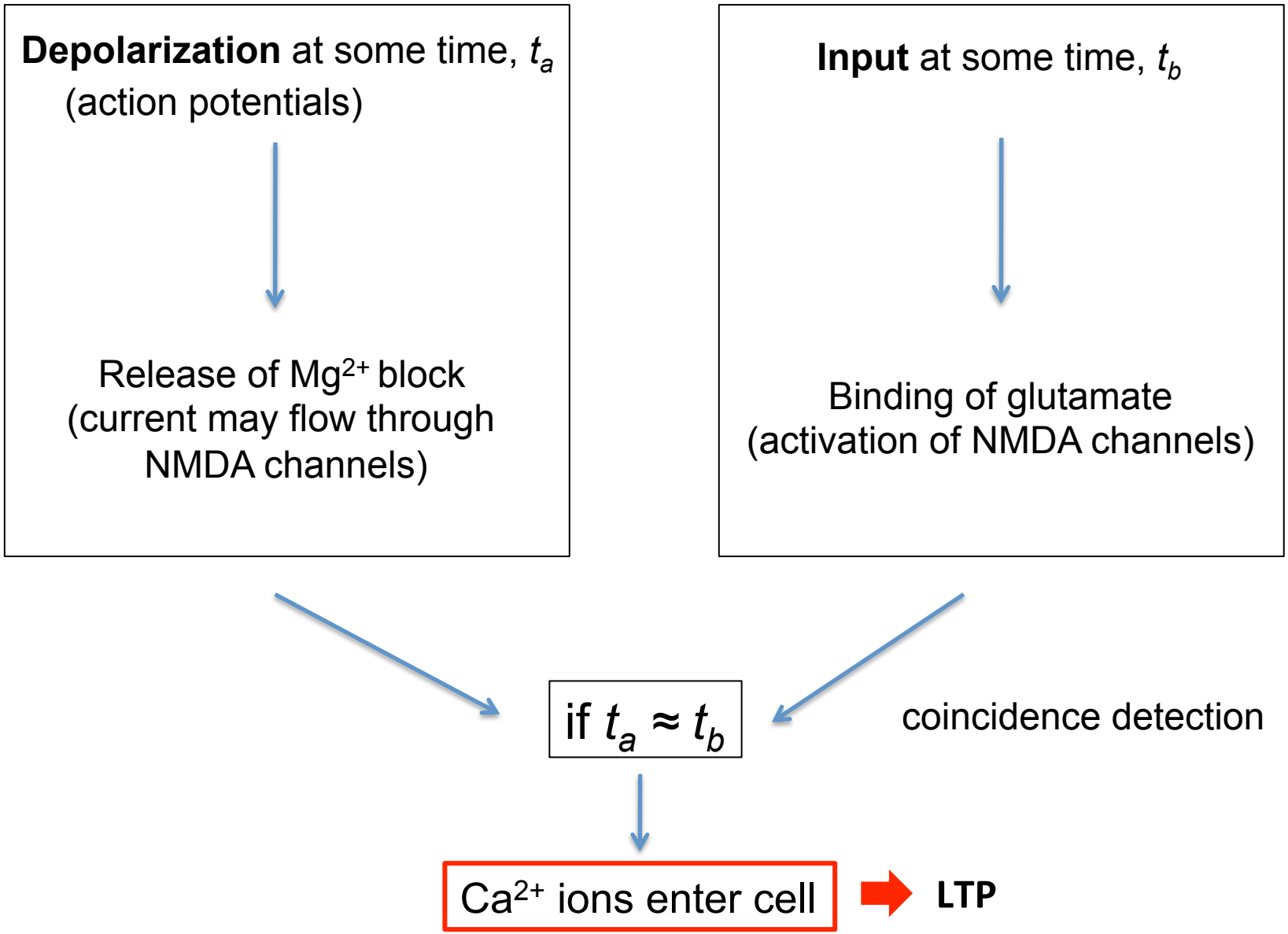
What's so special about **NMDA Receptors**?

① Blocked by magnesium ions (Mg^{2+})

② Relatively permeable to calcium ions (Ca^{2+})



Ca^{2+} ⇨ intracellular signal cascade ⇨ strengthen synapses


Depolarization at some time, t_a
(action potentials)
Release of Mg^{2+} block
(current may flow through
NMDA channels)
Input at some time, t_b
Binding of glutamate
(activation of NMDA channels)
if $t_a \approx t_b$
coincidence detection
Ca^{2+} ions enter cell
LTP

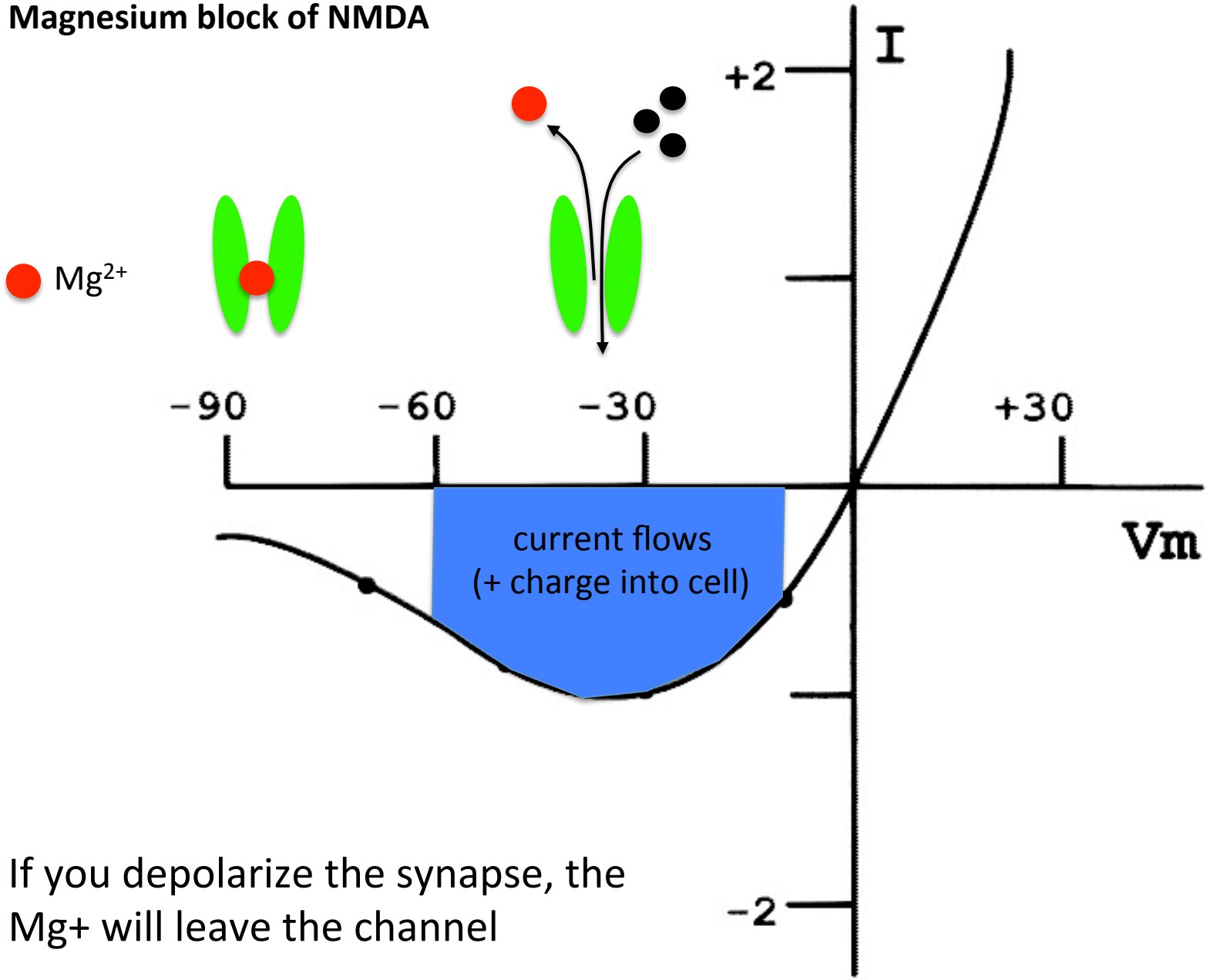
How do you get Mg^{++} out of the channel?

Why is it in there in the first place?

- Intracellular concentration = 0.5 mM
- Extracellular concentration = 2 mM

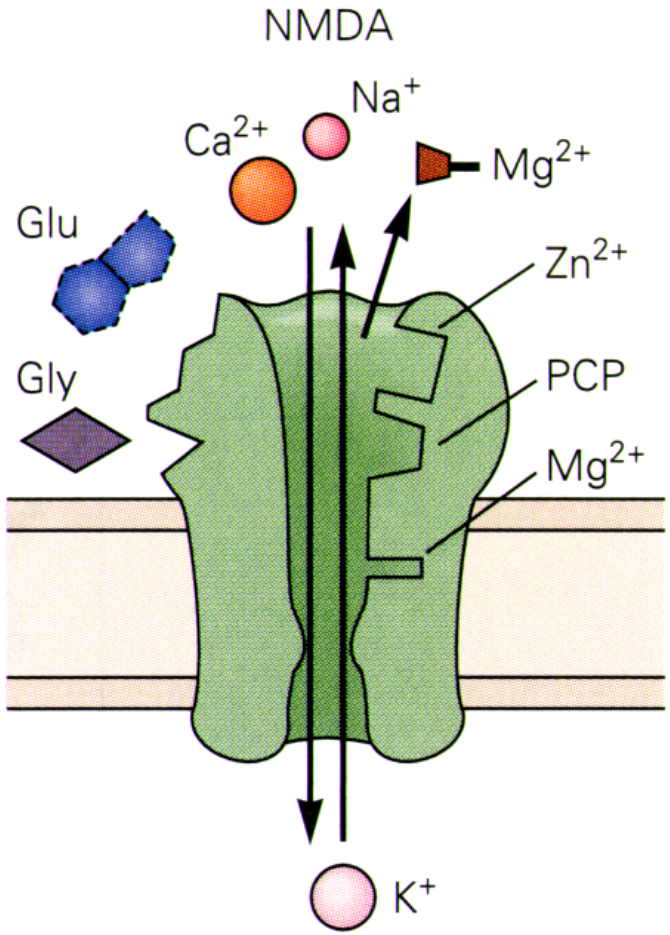
Why else?

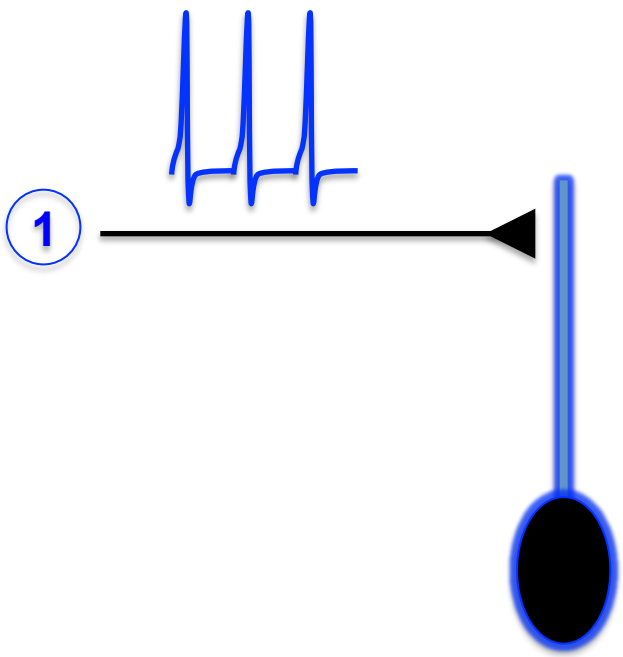
Magnesium block of NMDA



If you depolarize the synapse, the Mg+ will leave the channel

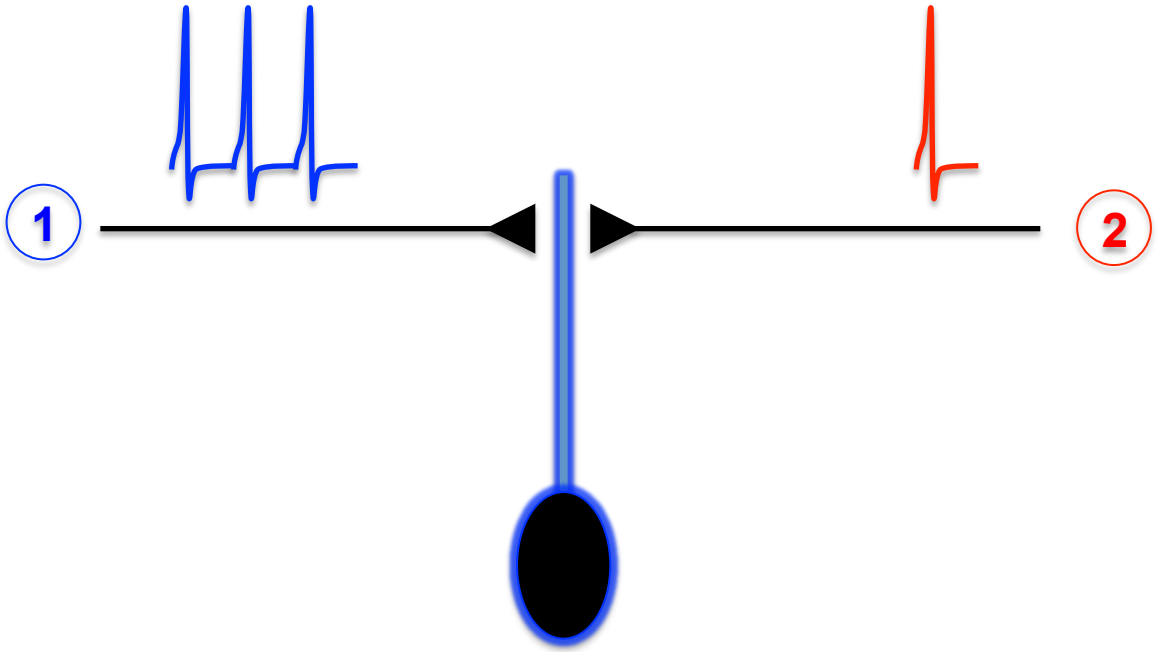
With the Mg+ block gone, the synapse is ready to be activated





Neurotransmitter + Depolarization = Ca^{2+} enters cell

Calcium signaling leads to strengthening of synapses

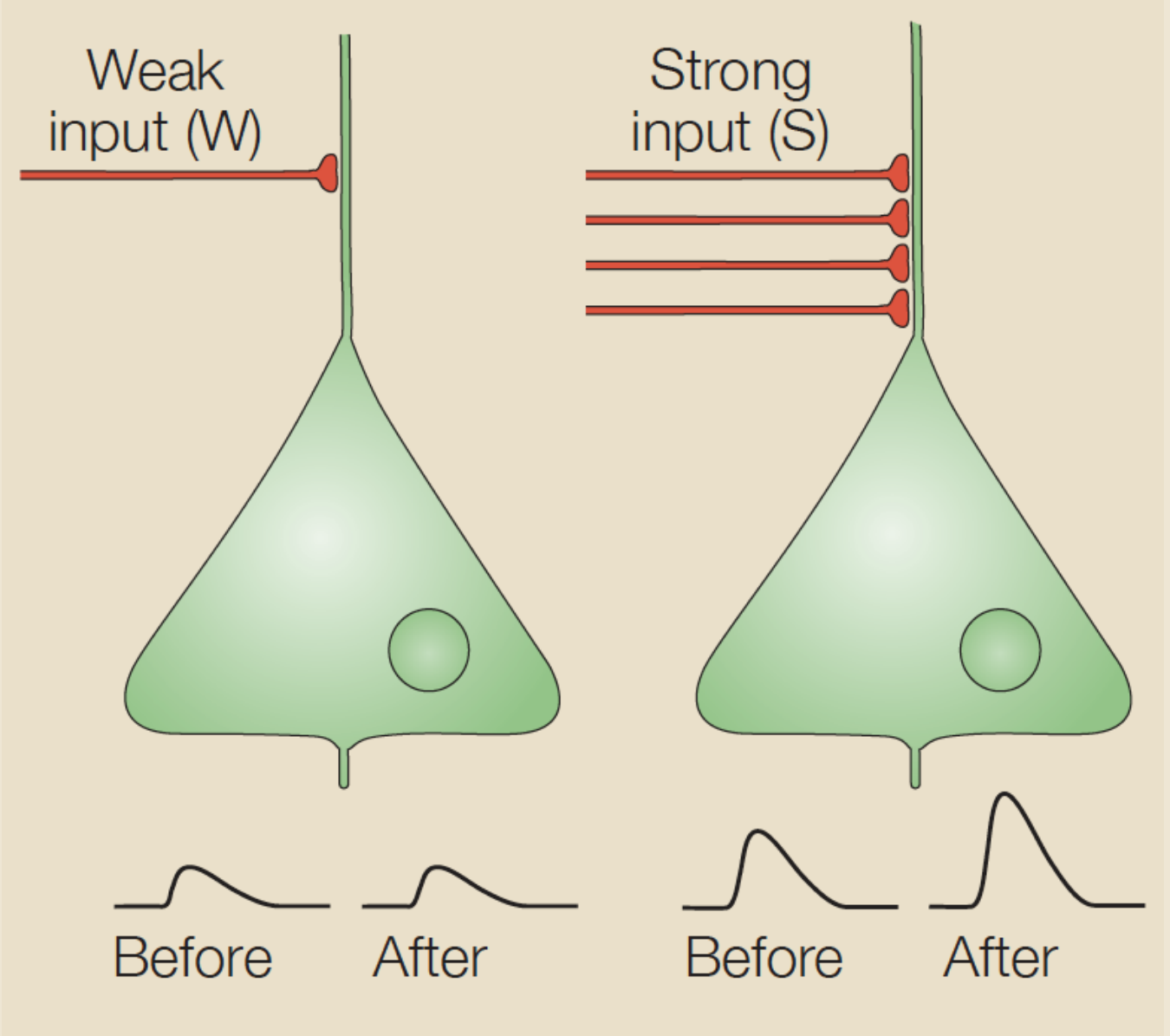


Same process can strengthen neighboring synapses

Associations can form…

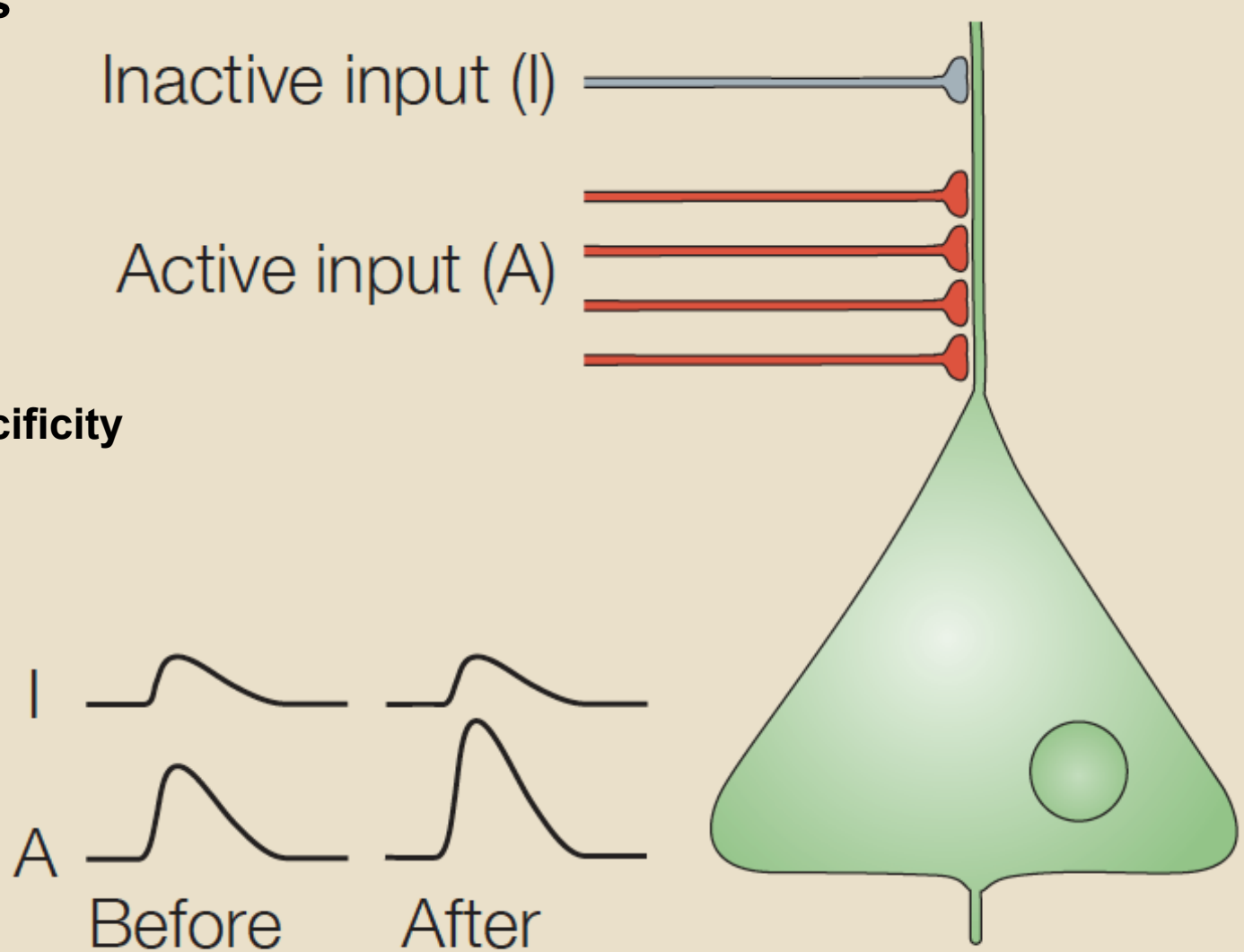
LTP Properties

1. Cooperativity



Malenka, 2003

LTP Properties

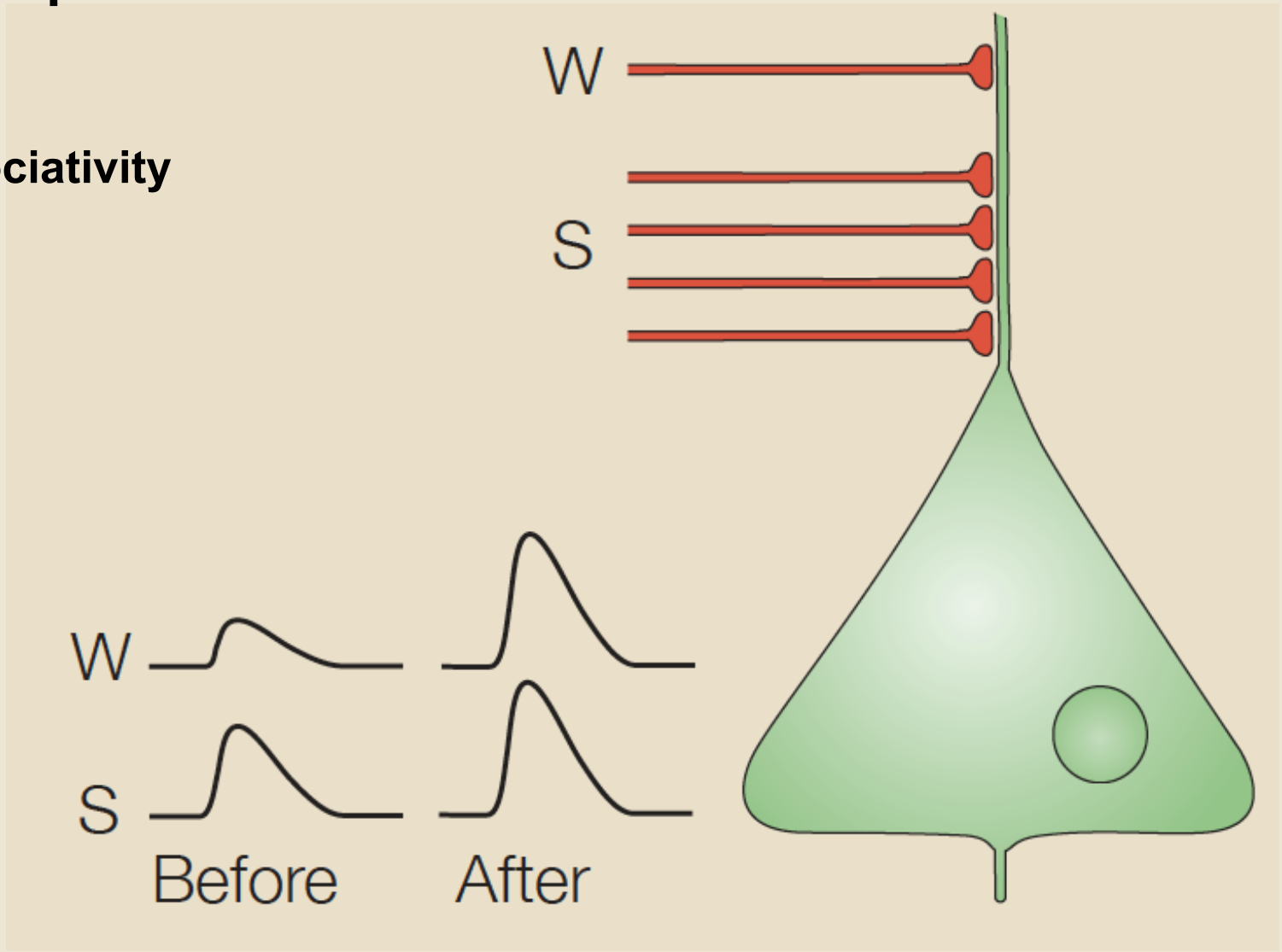


2. Synapse specificity

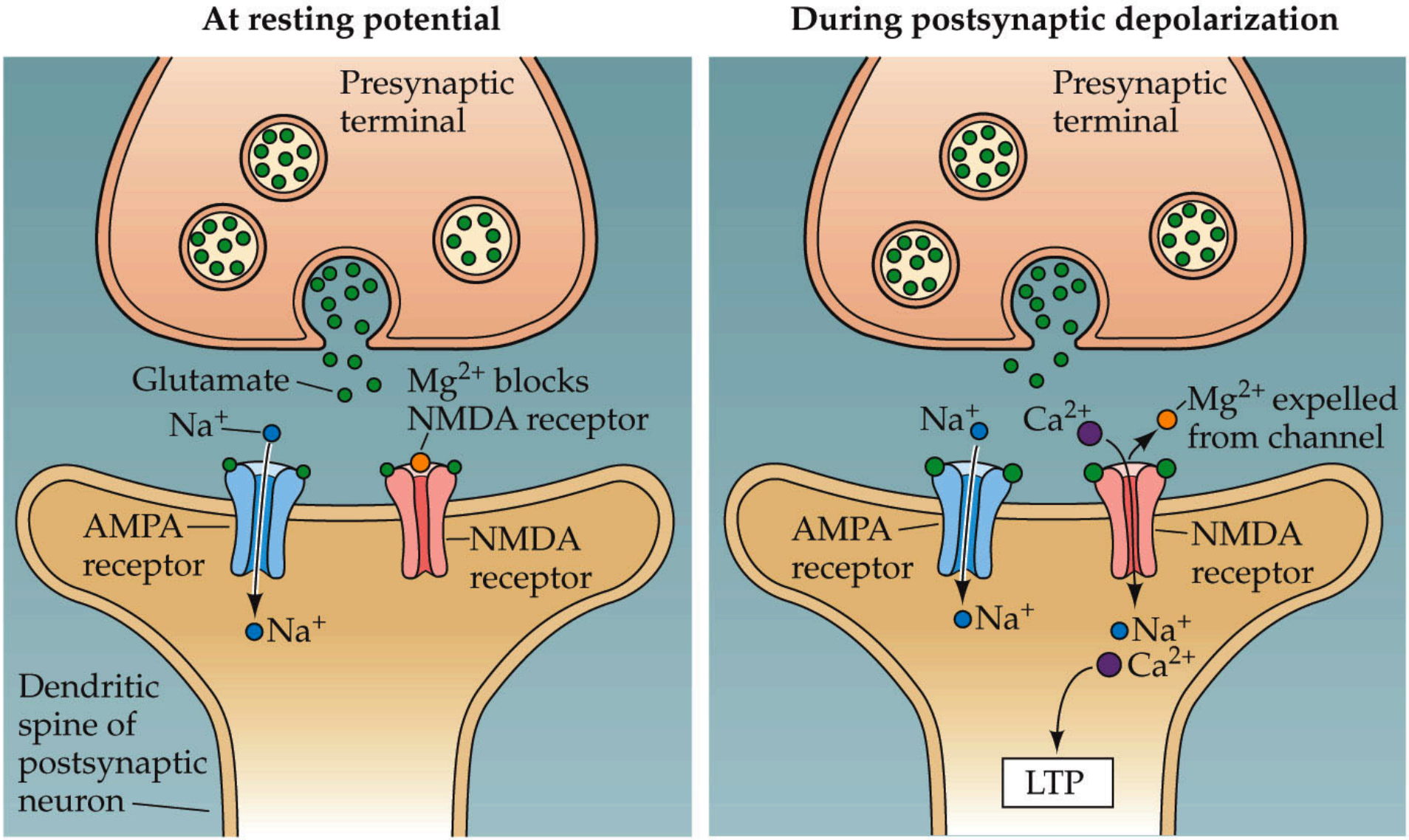
Malenka, 2003

LTP Properties

3. Associativity

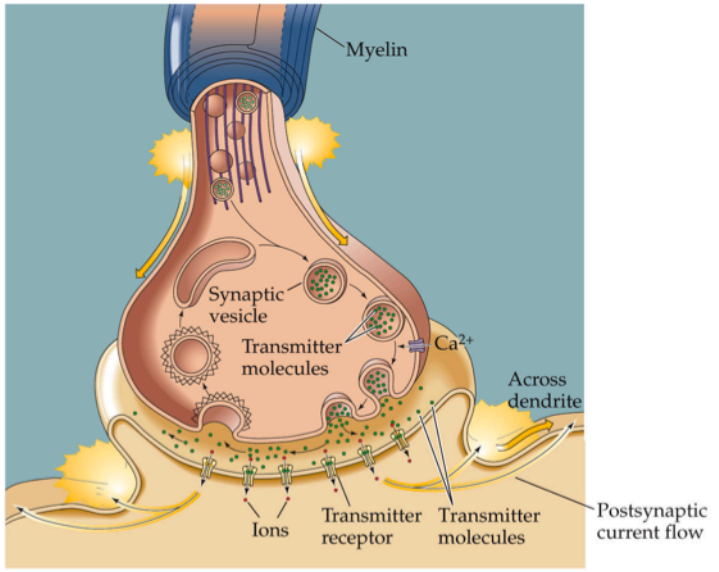


Malenka, 2003


At resting potential
Presynaptic terminal
Glutamate
Mg^{2+} blocks NMDA receptor
Na^+
AMPA receptor
NMDA receptor
Na^+
Dendritic spine of postsynaptic neuron
During postsynaptic depolarization
Presynaptic terminal
Na^+
Ca^{2+}
Mg^{2+} expelled from channel
AMPA receptor
NMDA receptor
Na^+
Na^+
Ca^{2+}
LTP

Modifying synaptic strength

- Pre-synaptic
  - Change in Ca^{++} channel #
  - Change in size of synapse
  - Change in # of vesicles (docked, primed, total)
  - Change in neurotransmitter production
  - Change in NT reuptake
  - Change in NT degradation
- Post-synaptic
  - Change in # of receptors
  - AMPAfication of synapses
  - Change in size of synapse

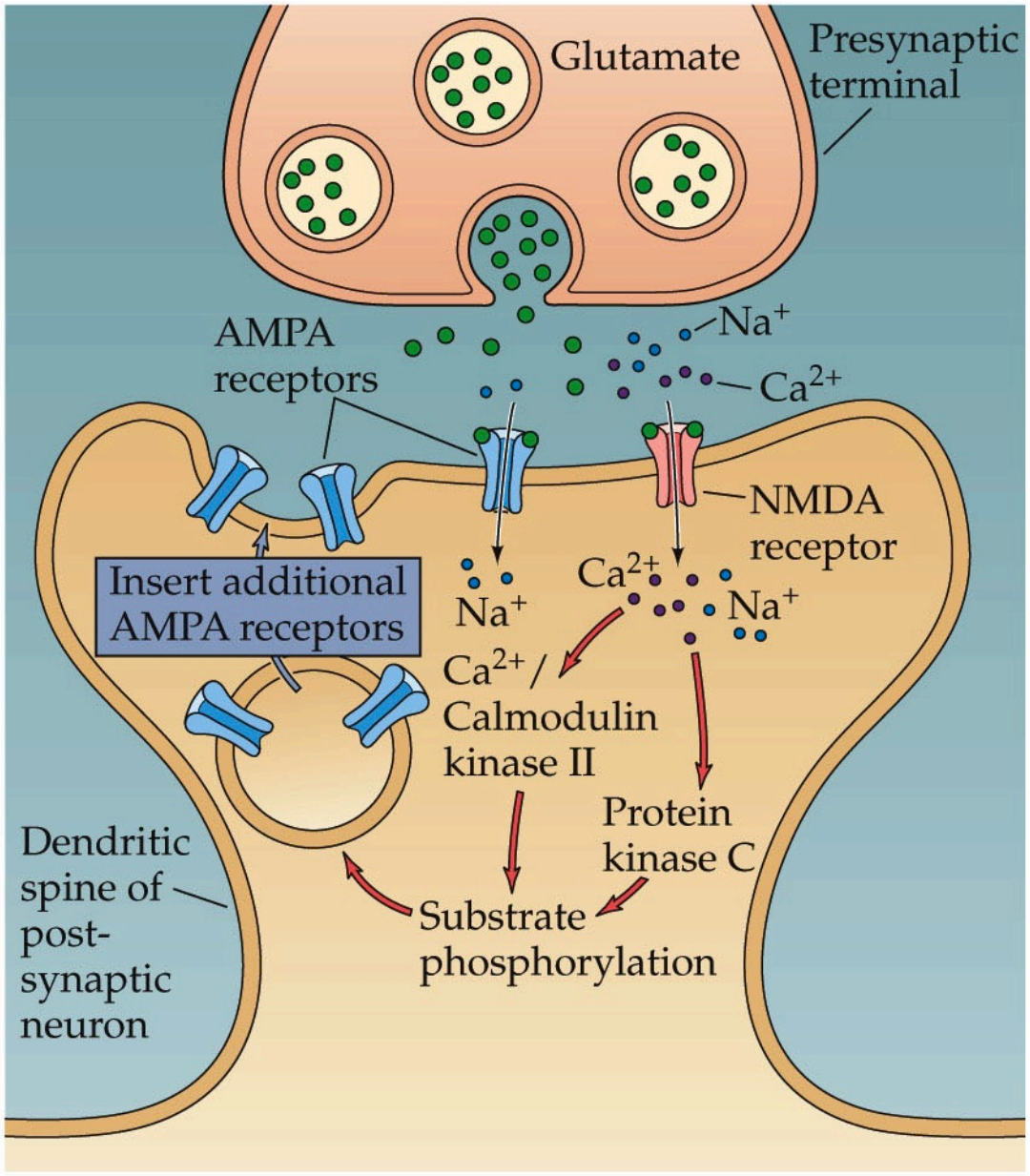


What are the consequences of the intracellular signaling?

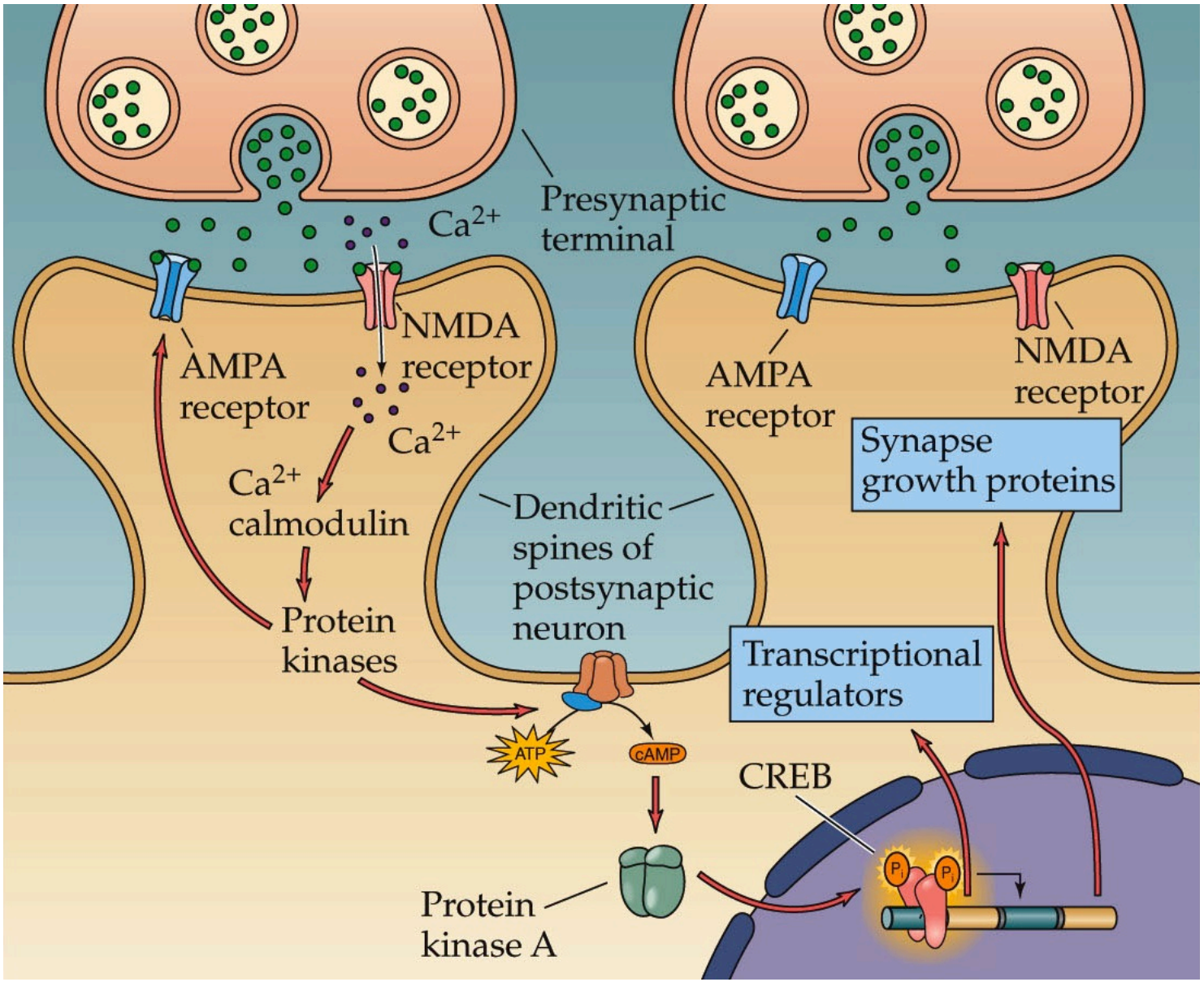
Presynaptic cell

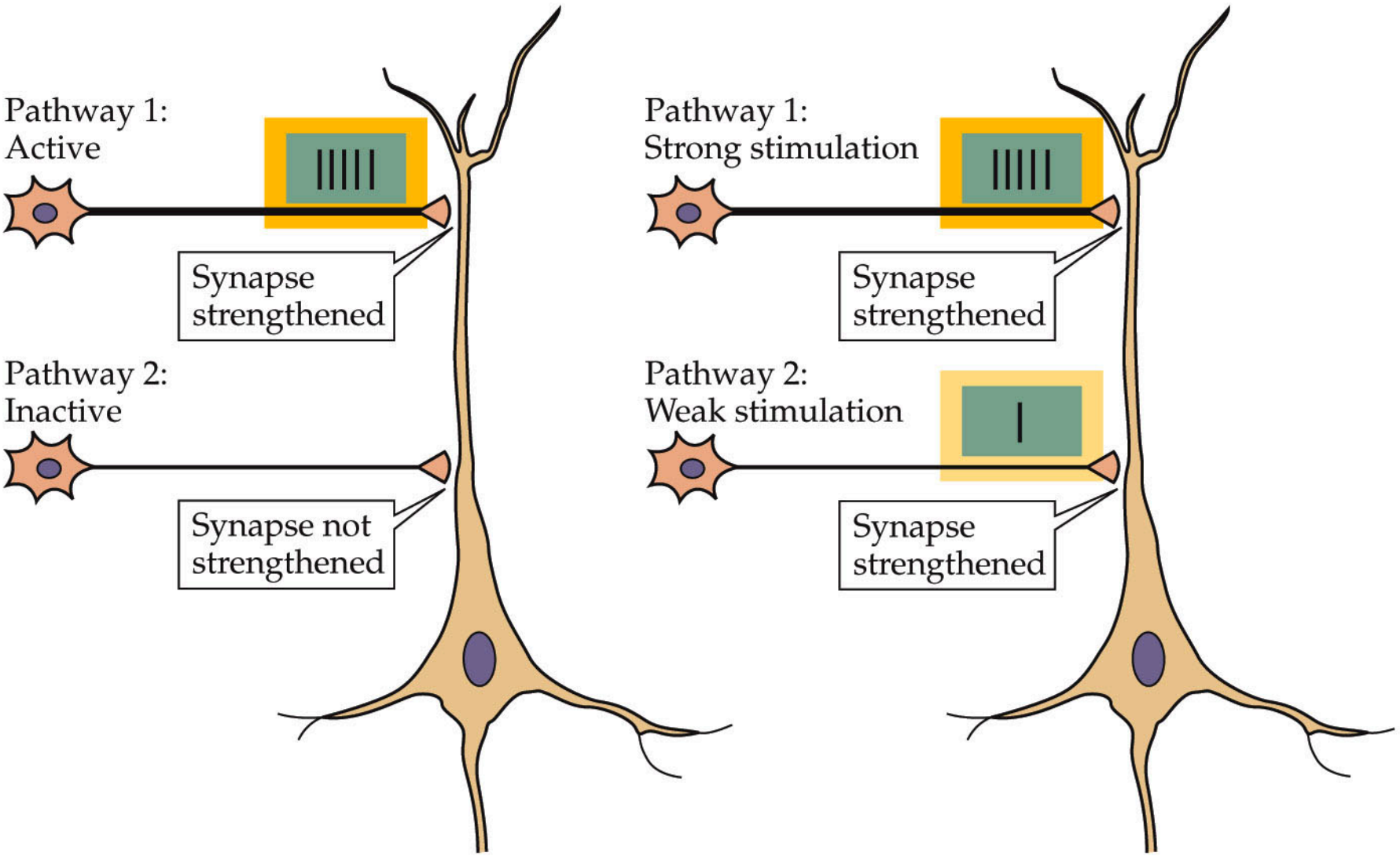
Postsynaptic cell

↑ AMPA Receptors

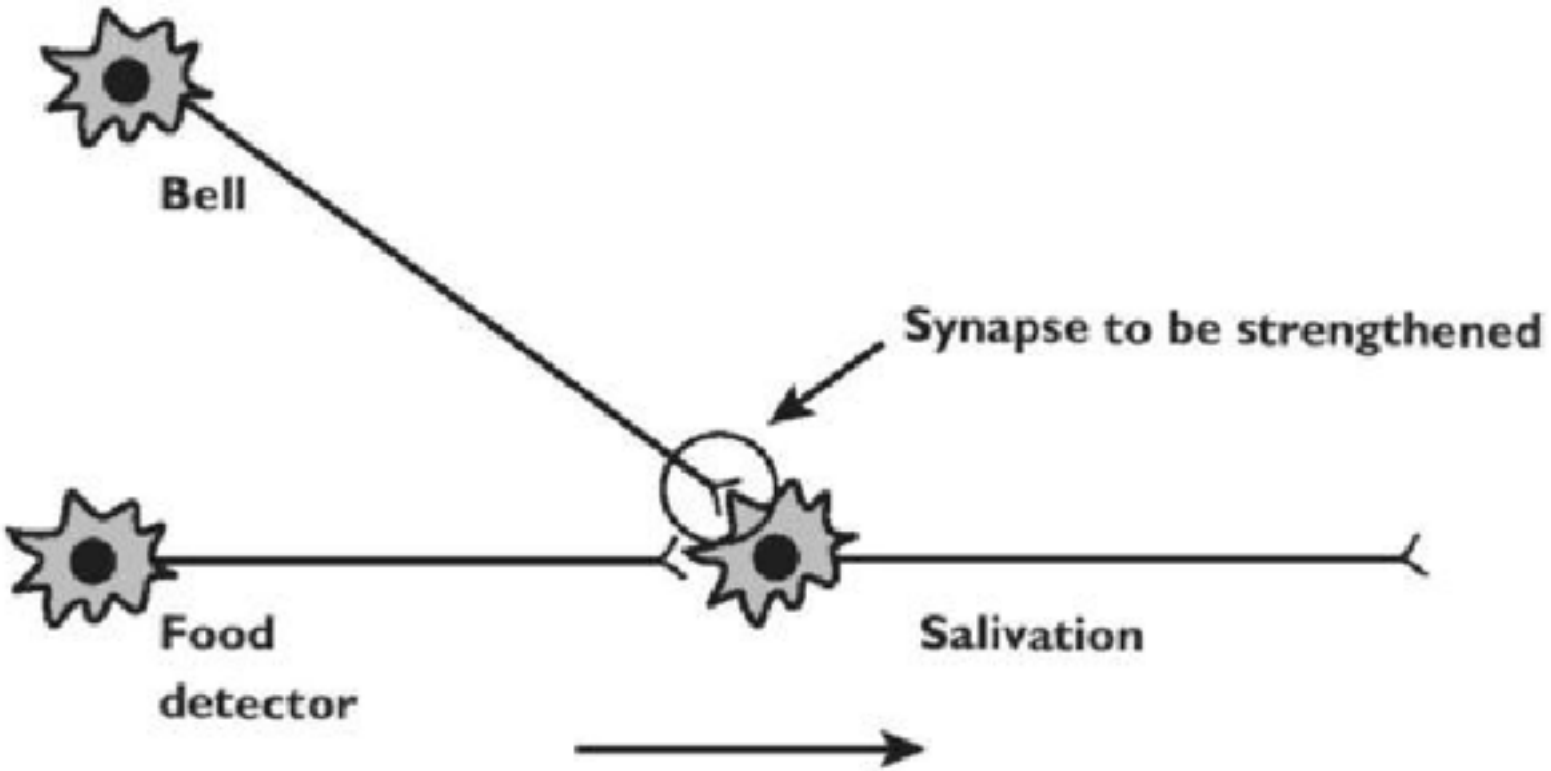


Short-term **Long-term**



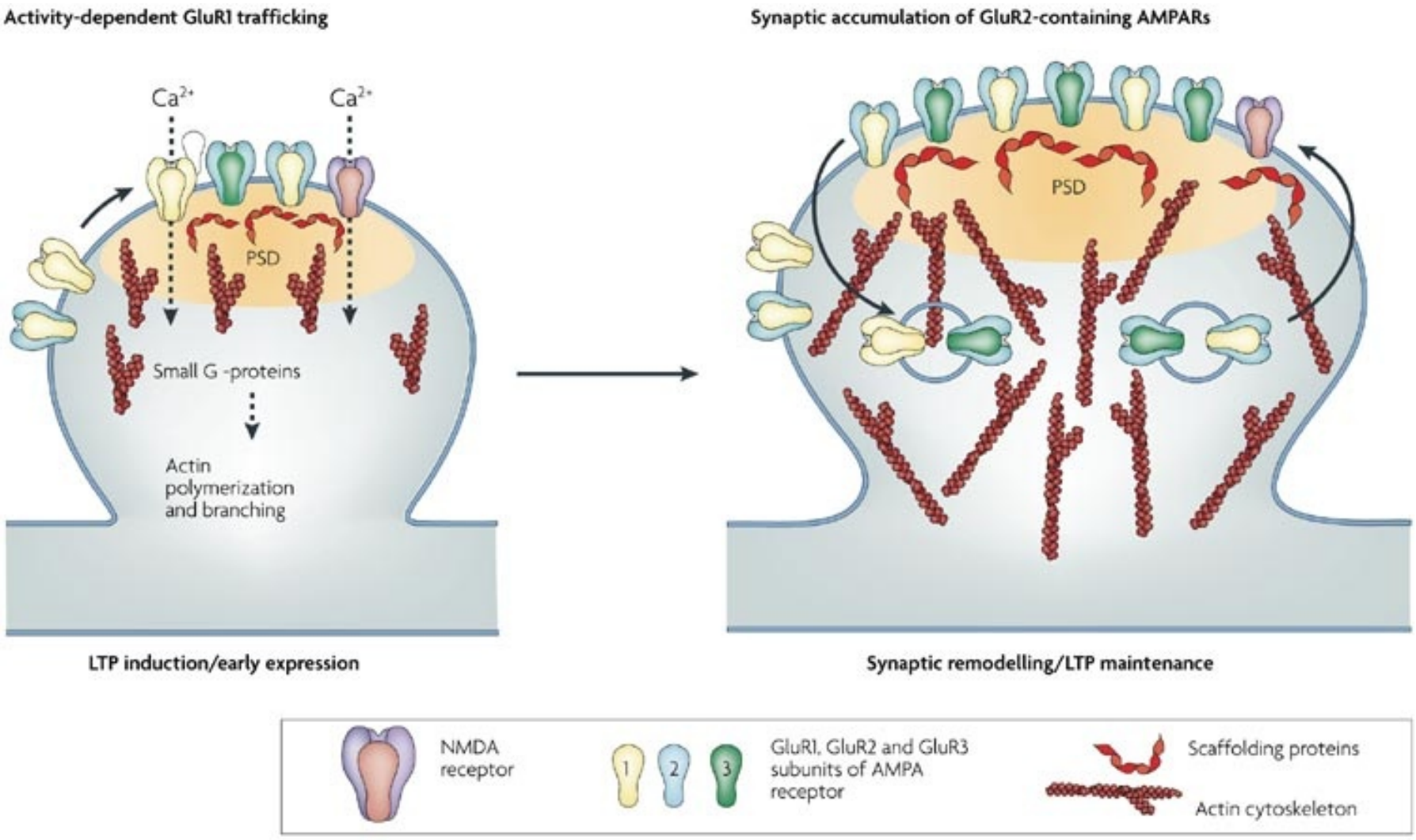

Pathway 1:
Active
Synapse
strengthened
Pathway 2:
Inactive
Synapse not
strengthened
Pathway 1:
Strong stimulation
Synapse
strengthened
Pathway 2:
Weak stimulation
Synapse
strengthened

How could this work in the brain?

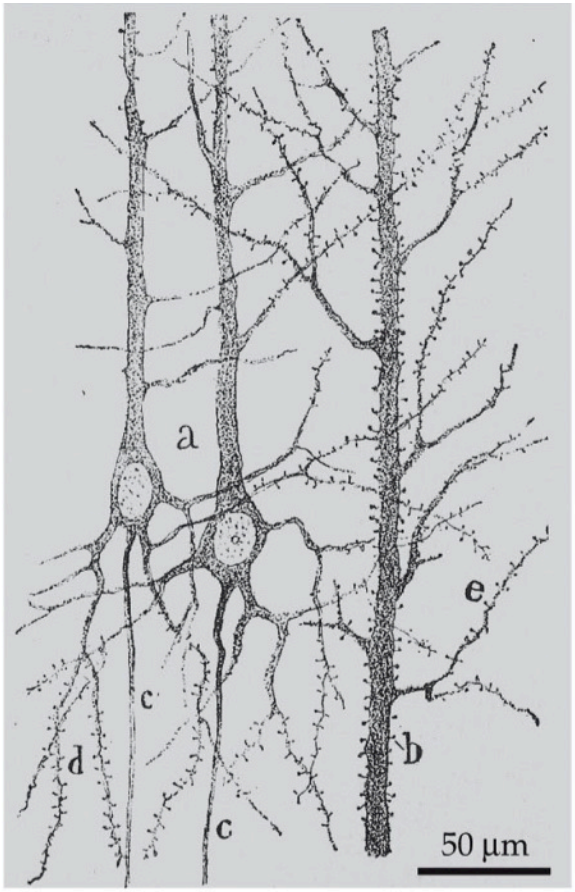


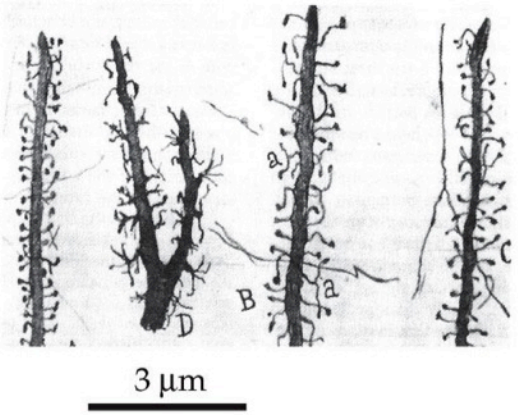
Form a connection between the neuron that represents ‘food’ and the neuron that represents the ‘bell’ sound

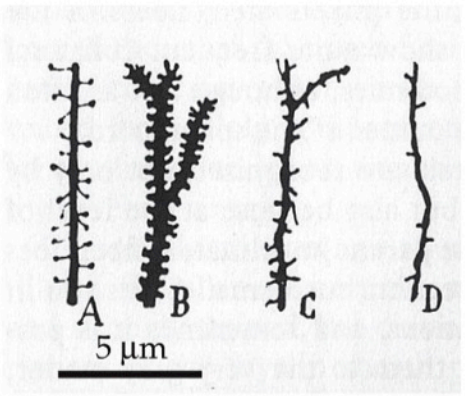
Increase the number of receptors

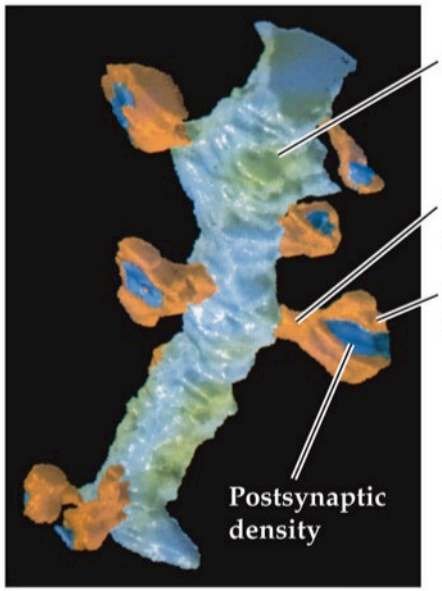


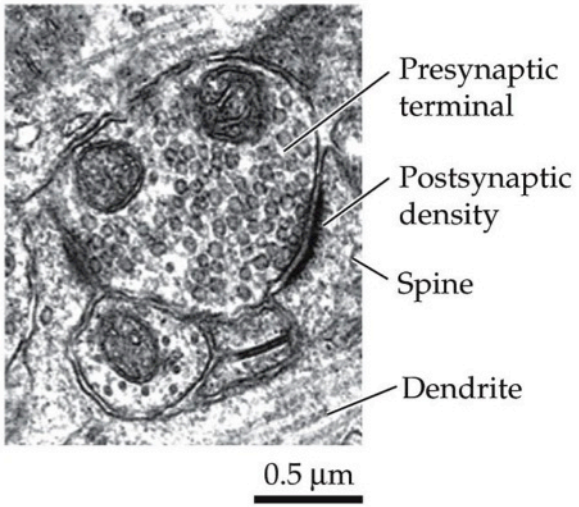
Structural plasticity – Dendritic Spines



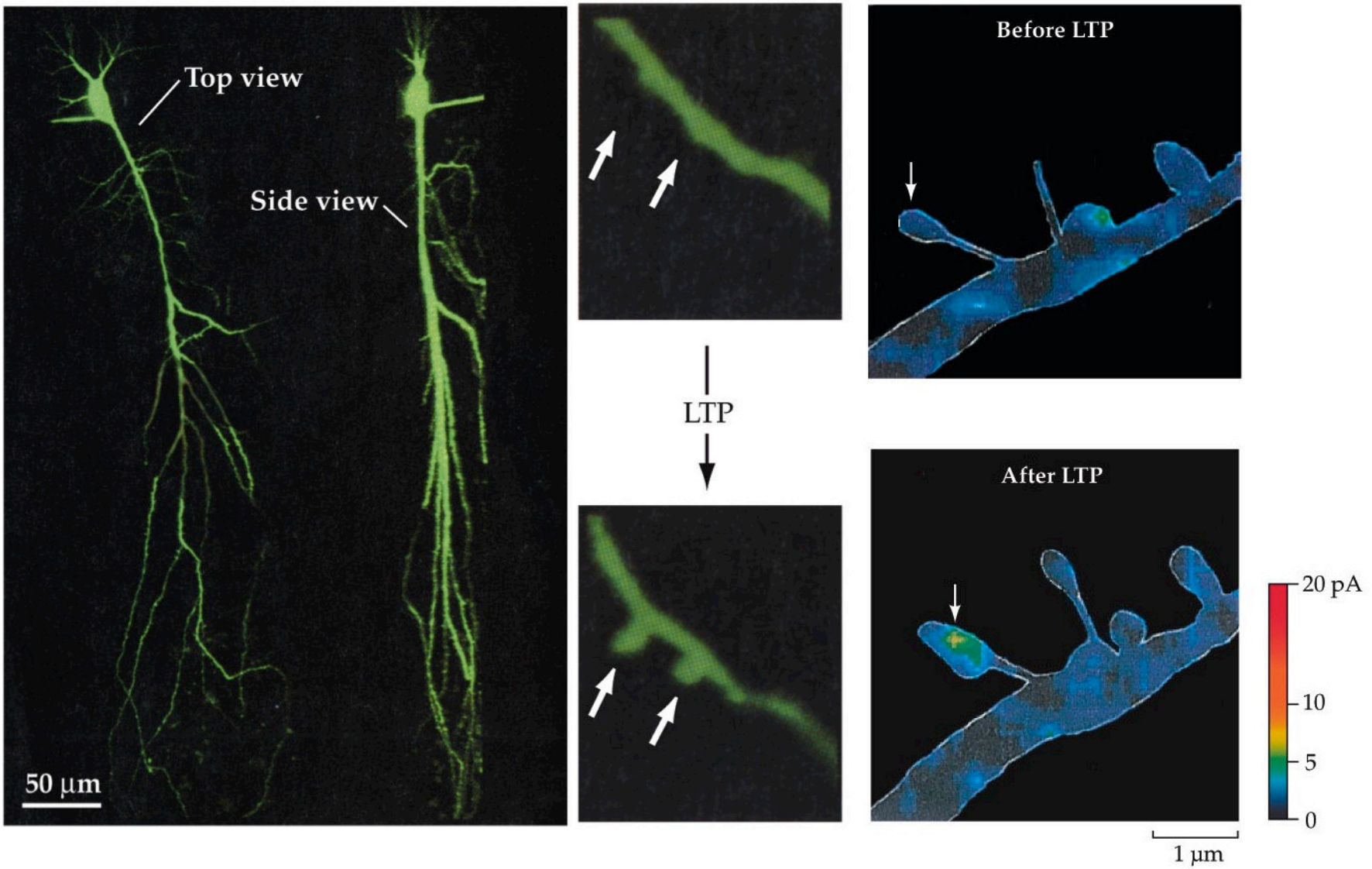








Structural plasticity – Dendritic Spines



nature Vol 462|17 December 2009|doi:10.1038/nature08577

LETTERS

Stably maintained dendritic spines are associated with lifelong memories

Guang Yang[1], Feng Pan[1] & Wen-Biao Gan[1]

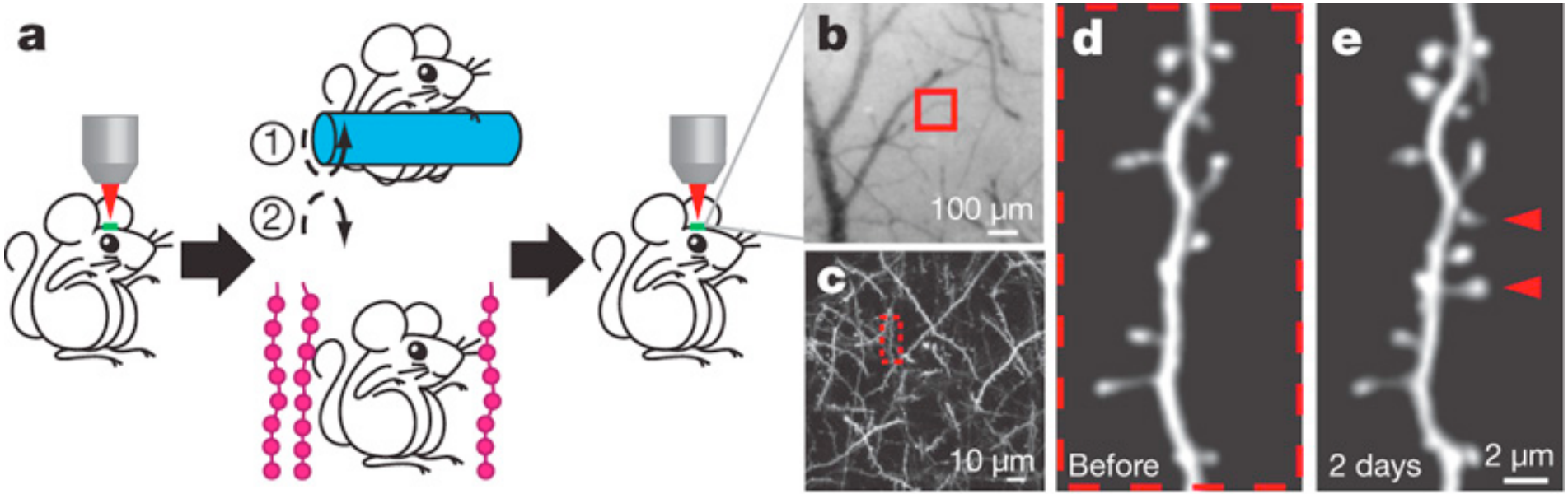


Figure 1

Motor Learning

Sensory Learning

SE: standard housing
EE: enriched housing

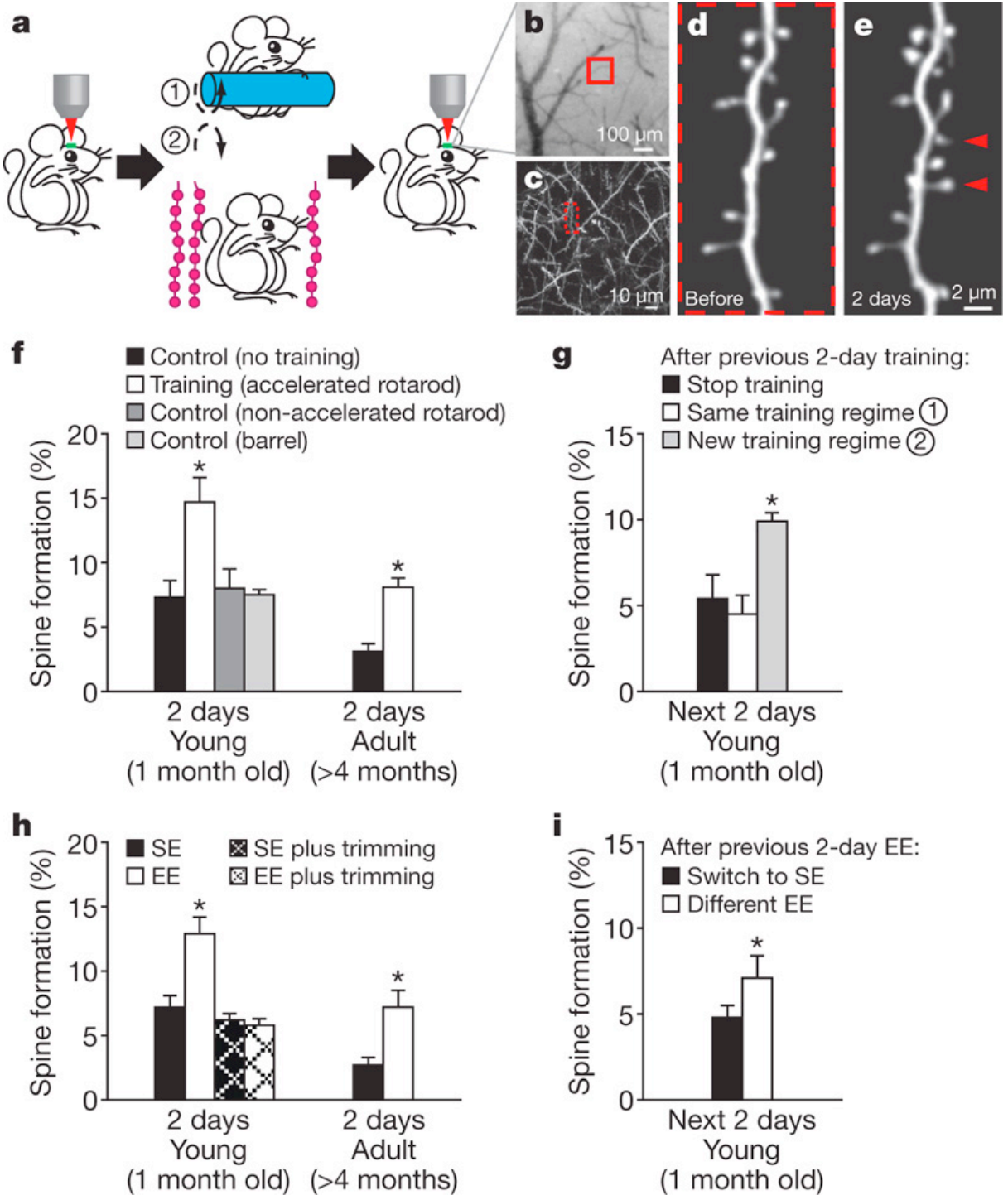


Figure 2 | A fraction of newly formed spines persists over weeks and correlates with performance after learning.

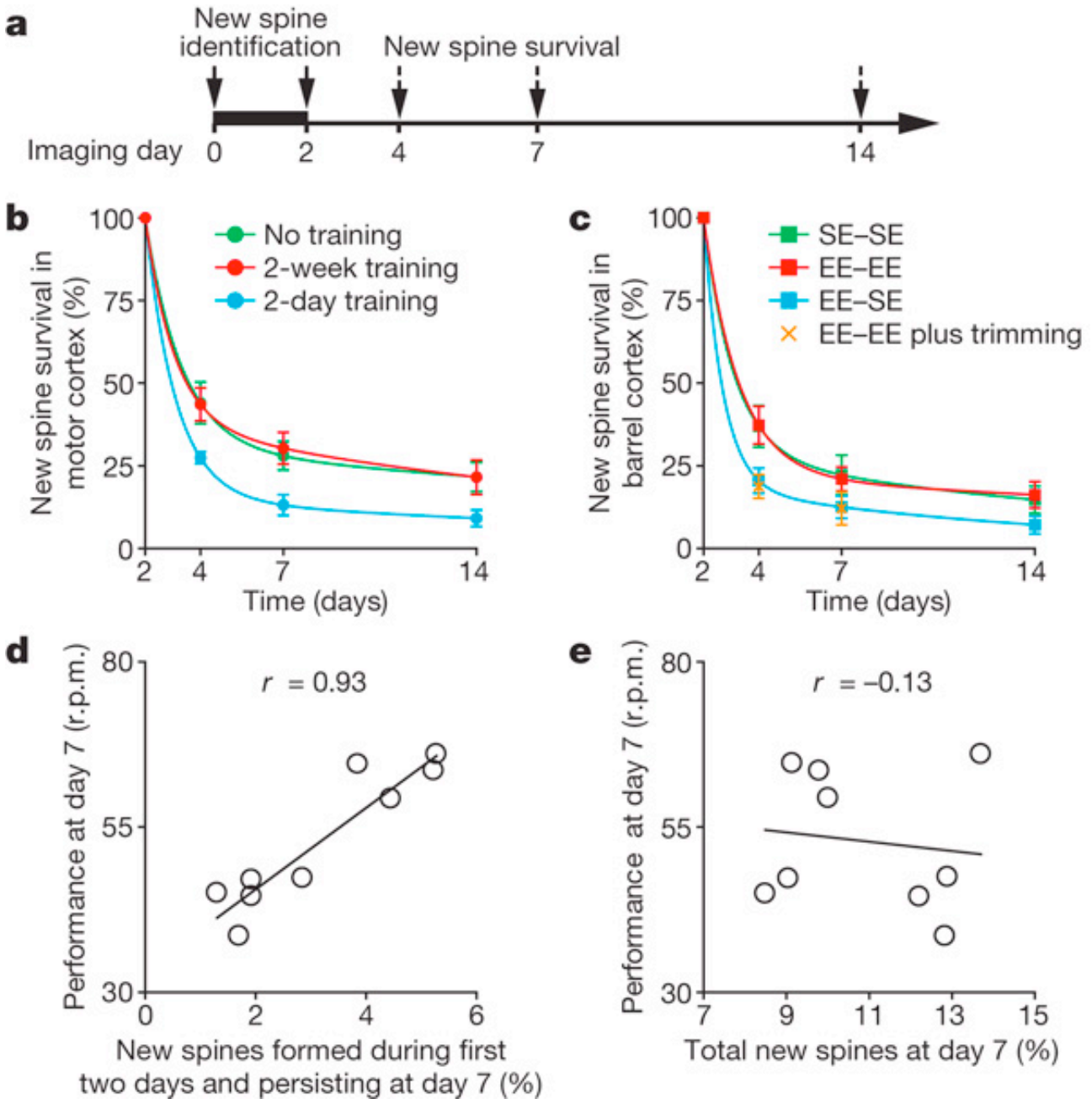


Figure 3 | Novel experience promotes spine elimination.

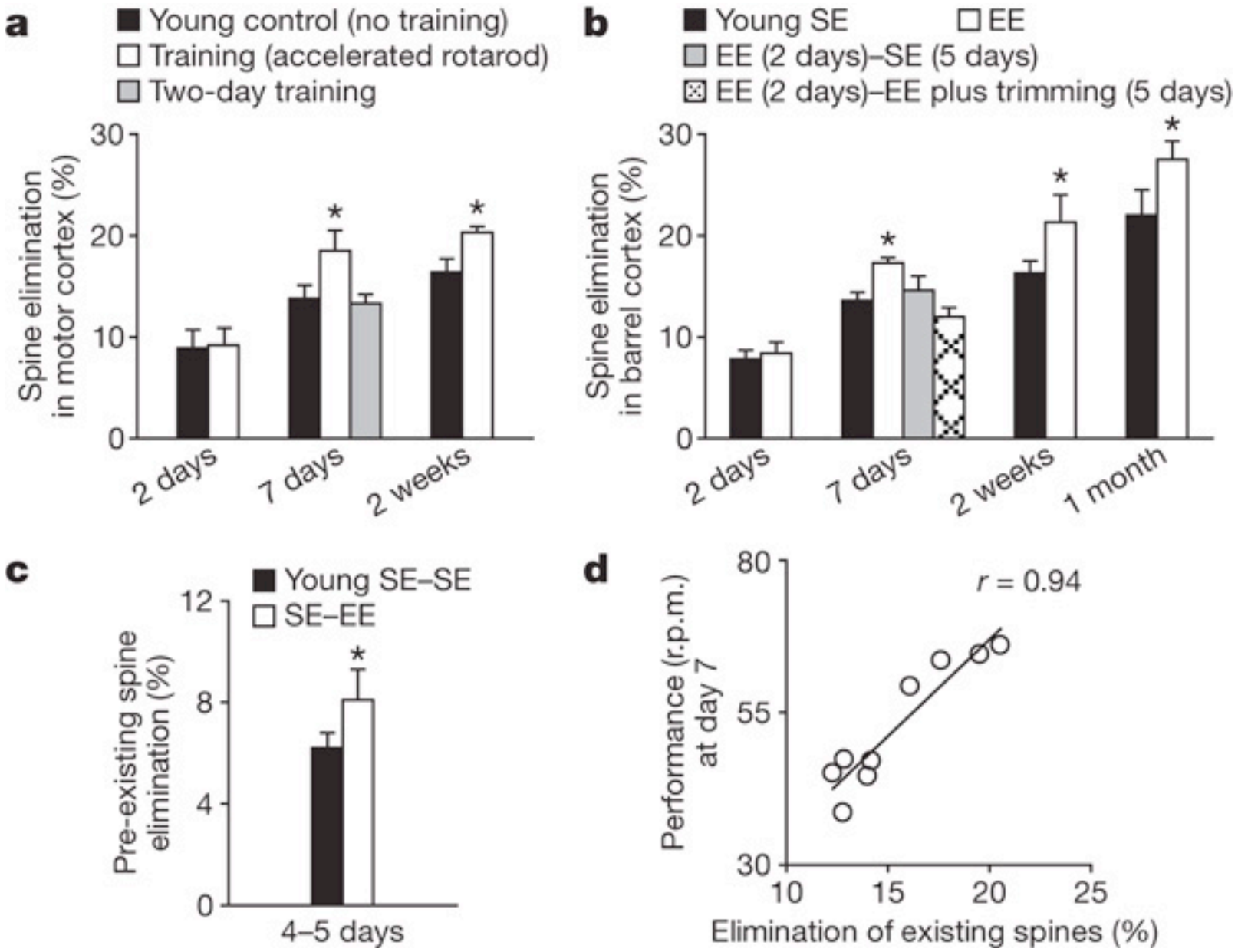
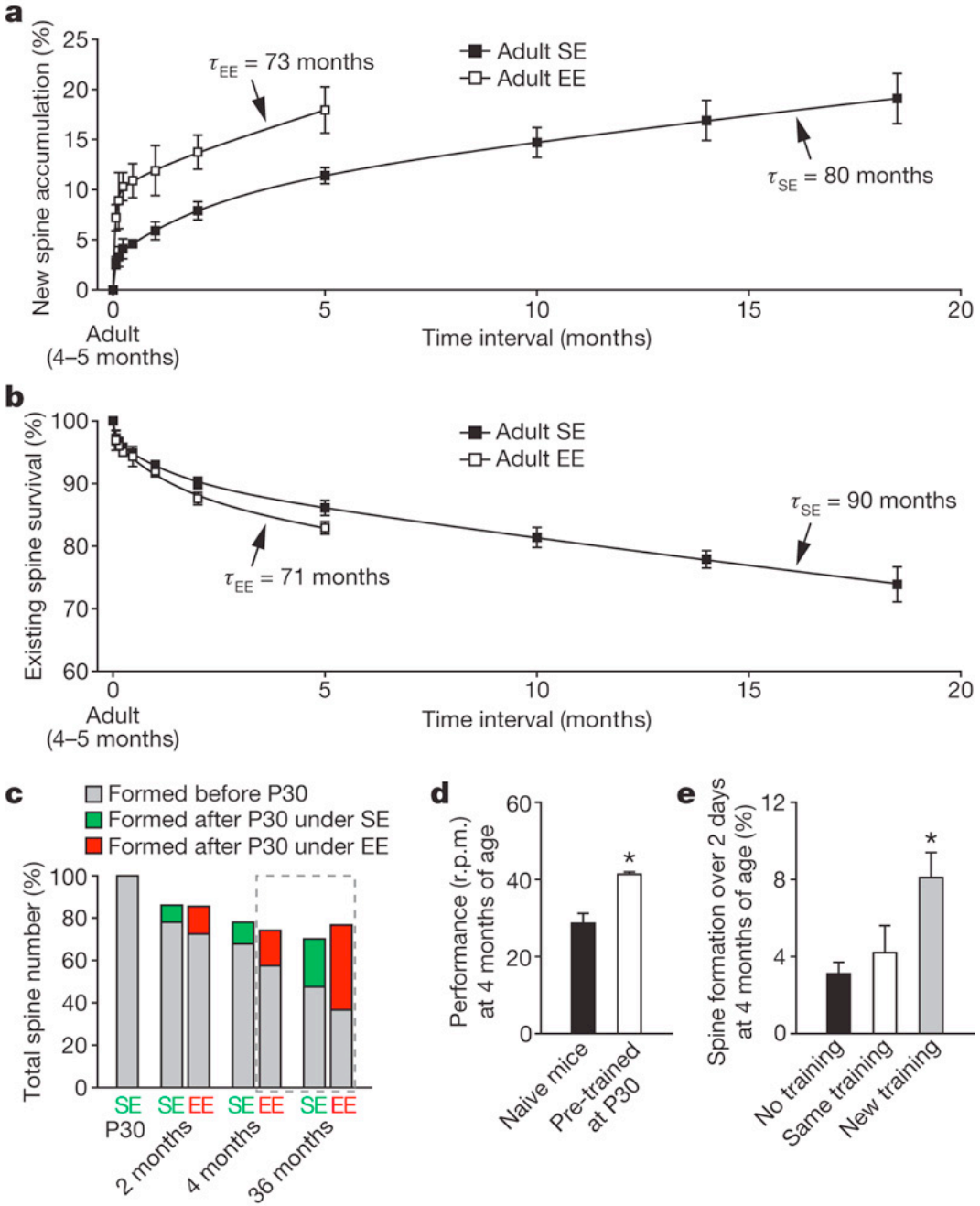
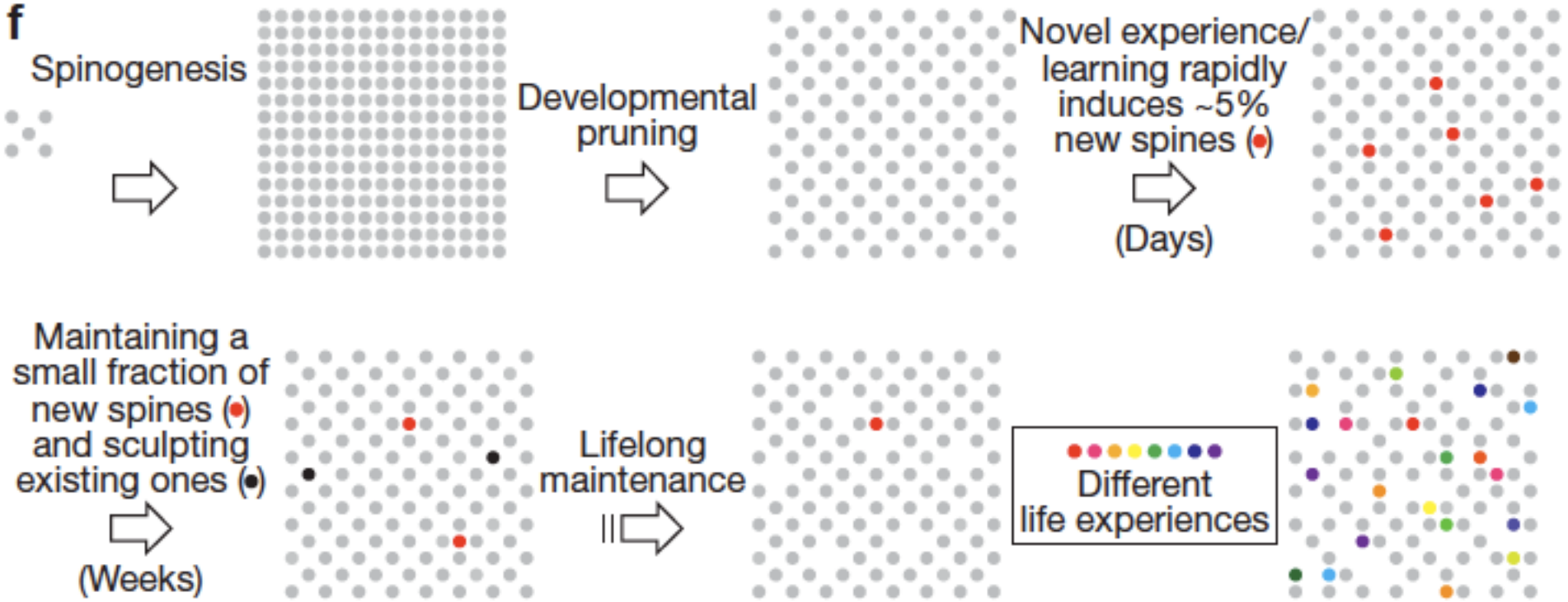


Figure 4 | Maintenance of daily formed new spines and spines formed during early development throughout life.




f
Spinogenesis
Developmental pruning
Novel experience/ learning rapidly induces ~5% new spines (•)
(Days)
Maintaining a small fraction of new spines (•) and sculpting existing ones (•)
(Weeks)
Lifelong maintenance
Different life experiences