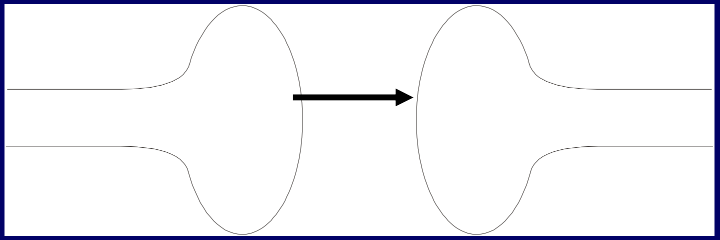
Synaptic plasticity

- **Activity-dependent changes in synaptic strength.**
- **Changes in innervation patterns. New synapses or deterioration of synapses.**
- **Repair/changes in the nervous system after damage.**

Synaptic transmission



Pre   Post

1. AP triggers Calcium inflow which in turn results in fusion of vesicles with the plasmamembrane.

2. Transmittor is released and diffuses over to the postsynaptic site.

3. The transmittorn activates ionotropic (or metabotropic) postsynaptic receptors.

4. The receptor activation results in a flow of ions over the plasmamembrane and therefore in voltage changes (EPSP, IPSP) that at are summated temporally and spatially at Axon hilloch (AP generation).

5. Transmittor is taken away by reuptake, diffusion and breakdown.

Receptor-Ion exemples

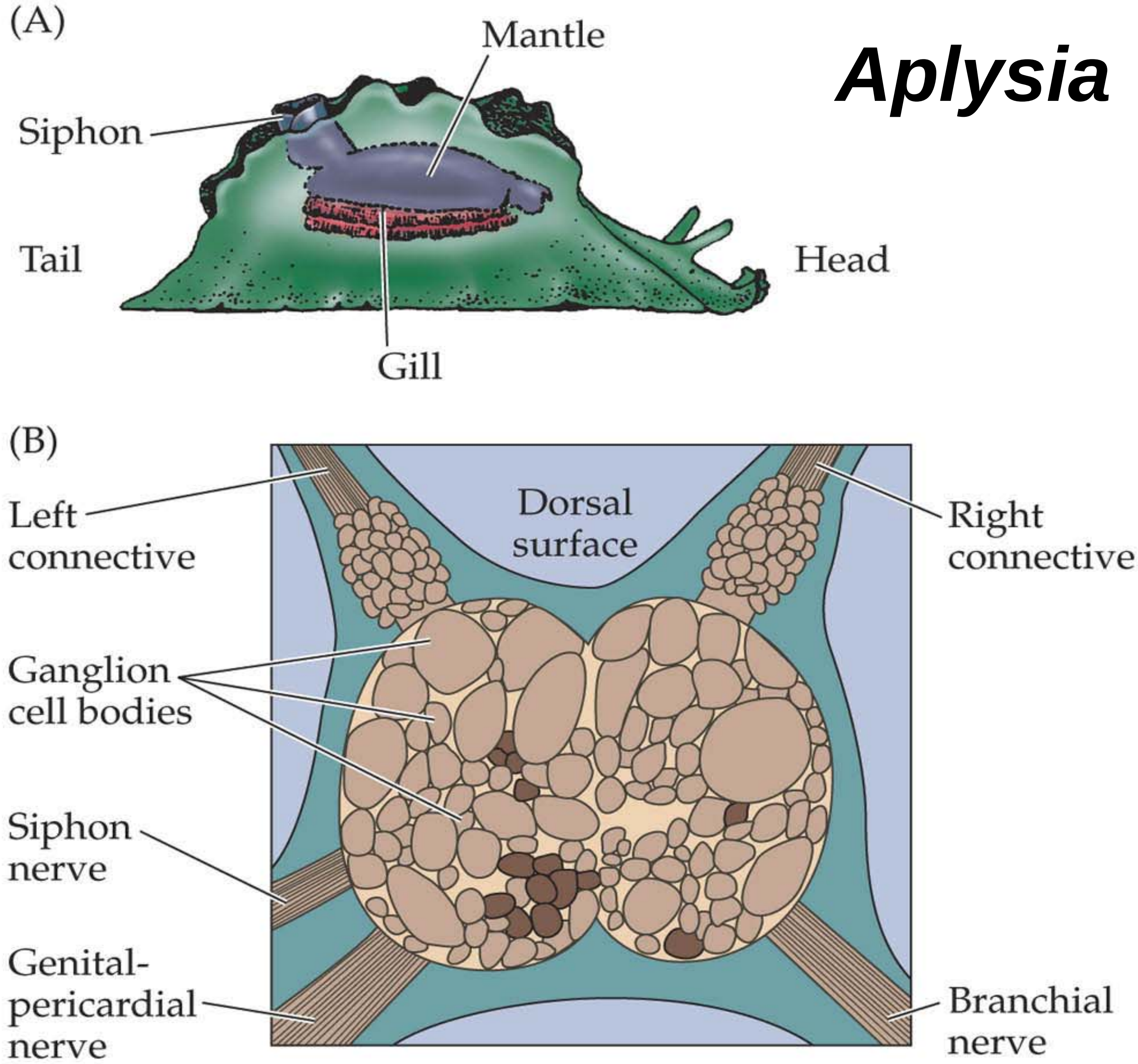
- **$GABA_A$**: Cl^-
- **nAChR**: Na^+, K^+, Ca^{2+}
- **AMPA:** Na^+, K^+, (Ca^{2+})
- **NMDA**: Na^+, K^+, Ca^{2+}

The size of the EPSP/IPSP is dependent on:

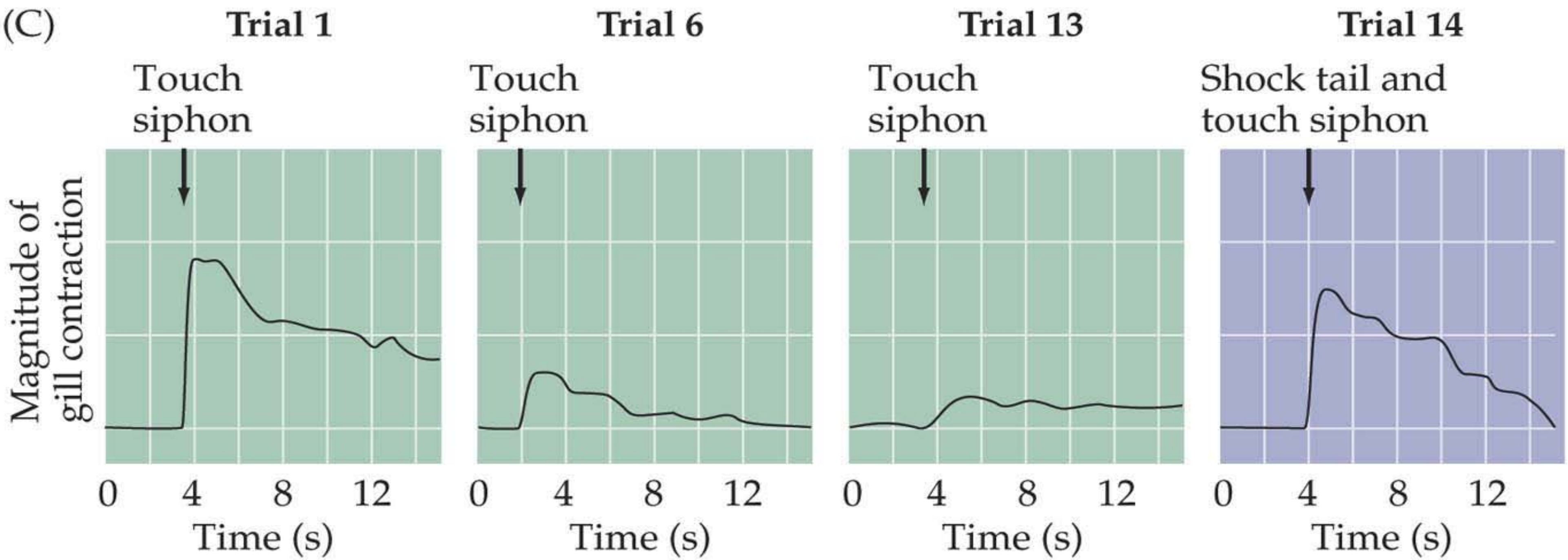
- How likely it is that TM is released by a presynaptic AP.
- How many TM molecules that are present in a vecicle.
- How much TM that is broken down in the synaptic cleft.
- How likely it is that an ion channel is opened when TM binds to a receptor.
- How many ion channels/receptors that are present in the postsynaptic membrane.
- The ion channel conductance.
- The input resistance of the postsynaptic cell.

Many of these factors are dynamically controlled and can be modulated by for instances phosphorylation of receptors.

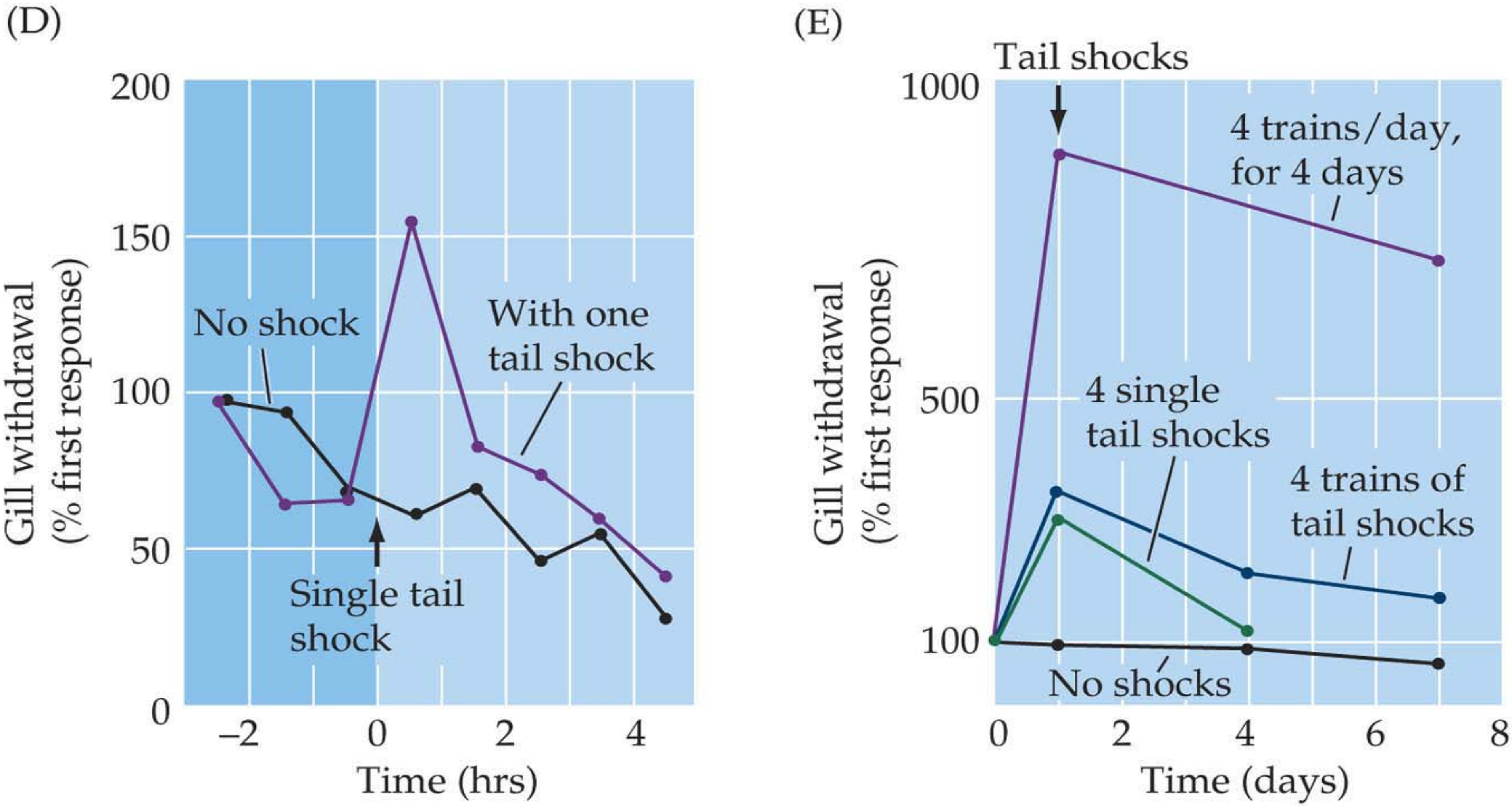
Aplysia


(A)
Mantle
Siphon
Tail
Head
Gill
(B)
Dorsal surface
Left connective
Right connective
Ganglion cell bodies
Siphon nerve
Genital-pericardial nerve
Branchial nerve

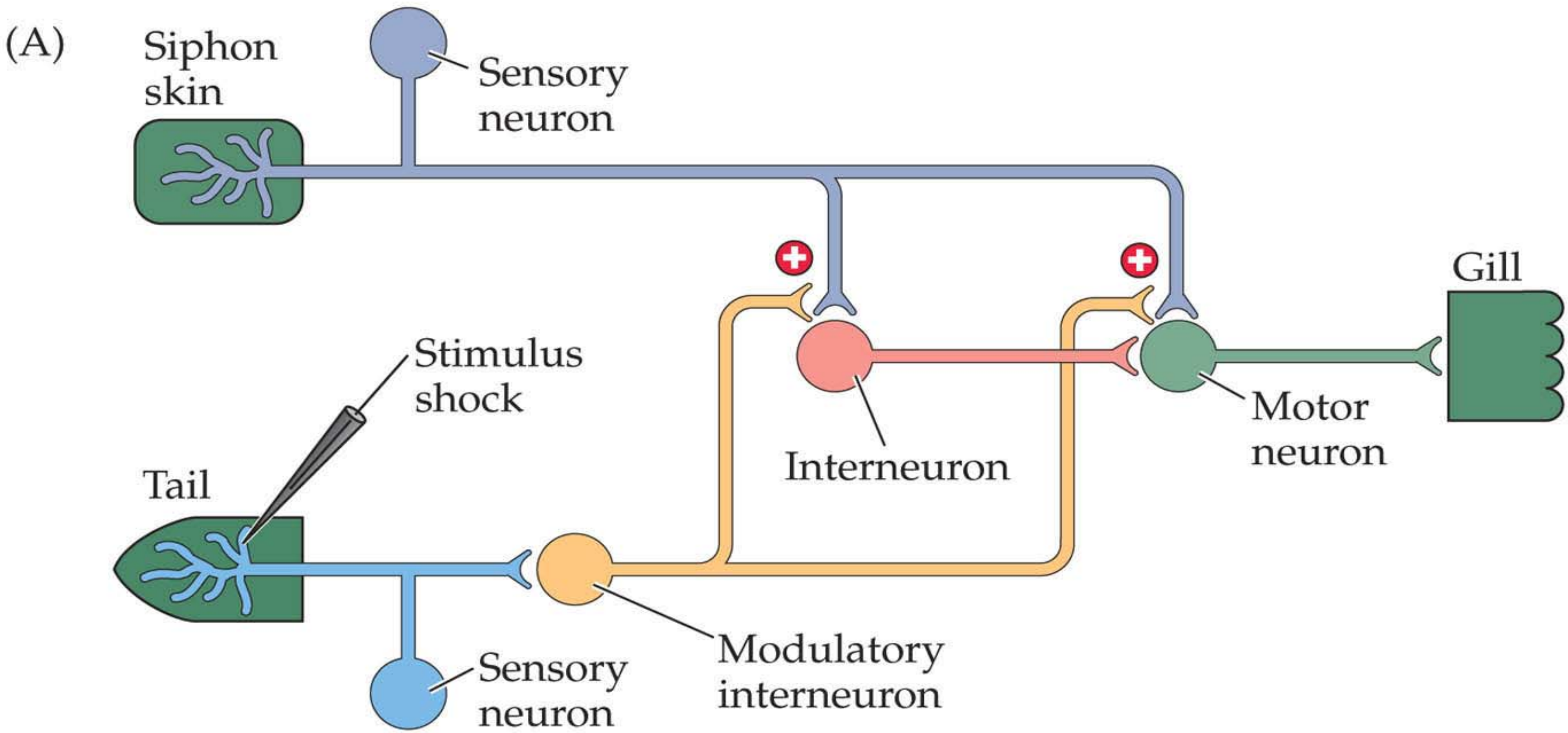
Habituation & Sensitation



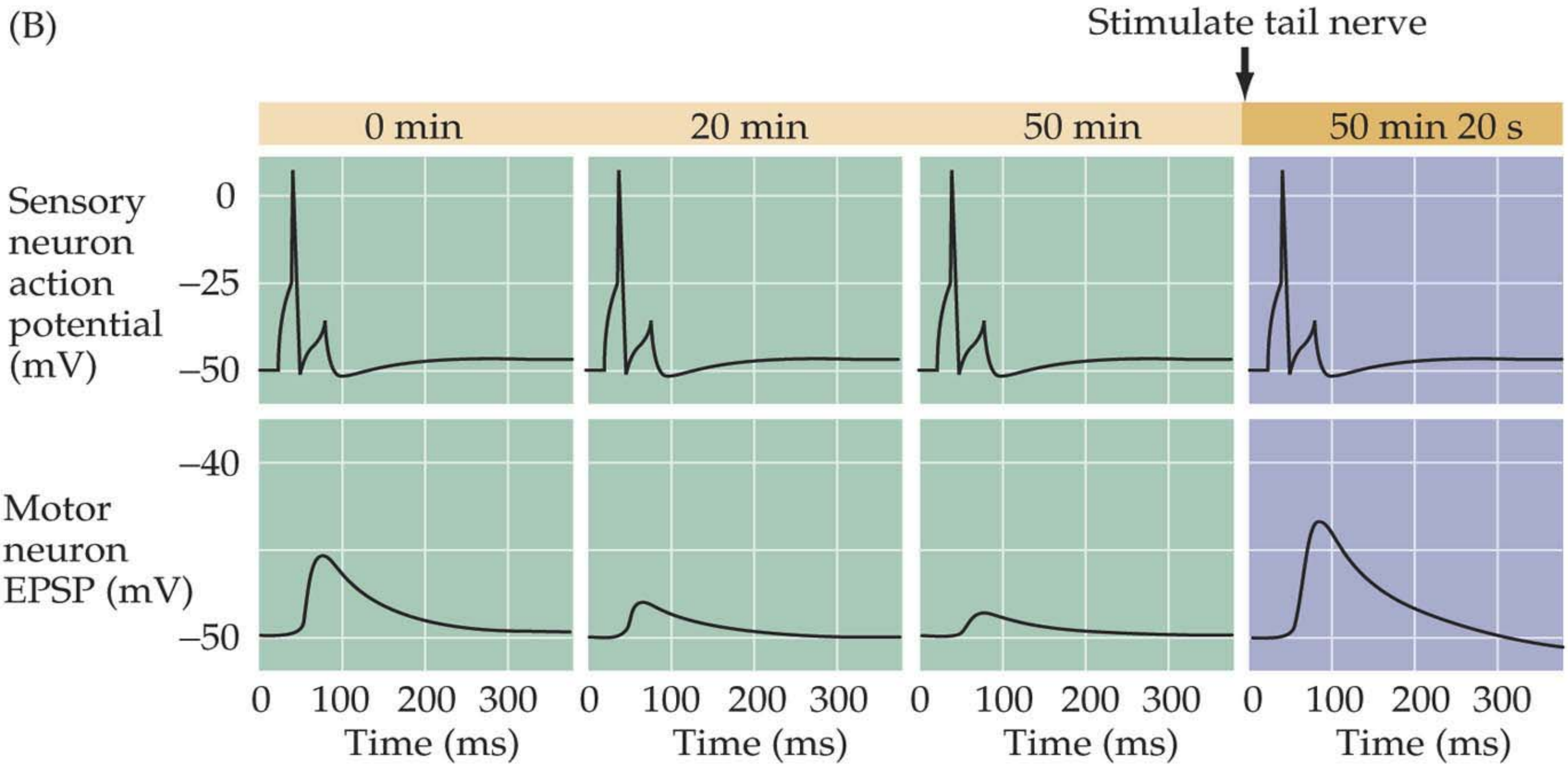
NEUROSCIENCE, Third Edition, **Figure 24.1 (Part 2)**

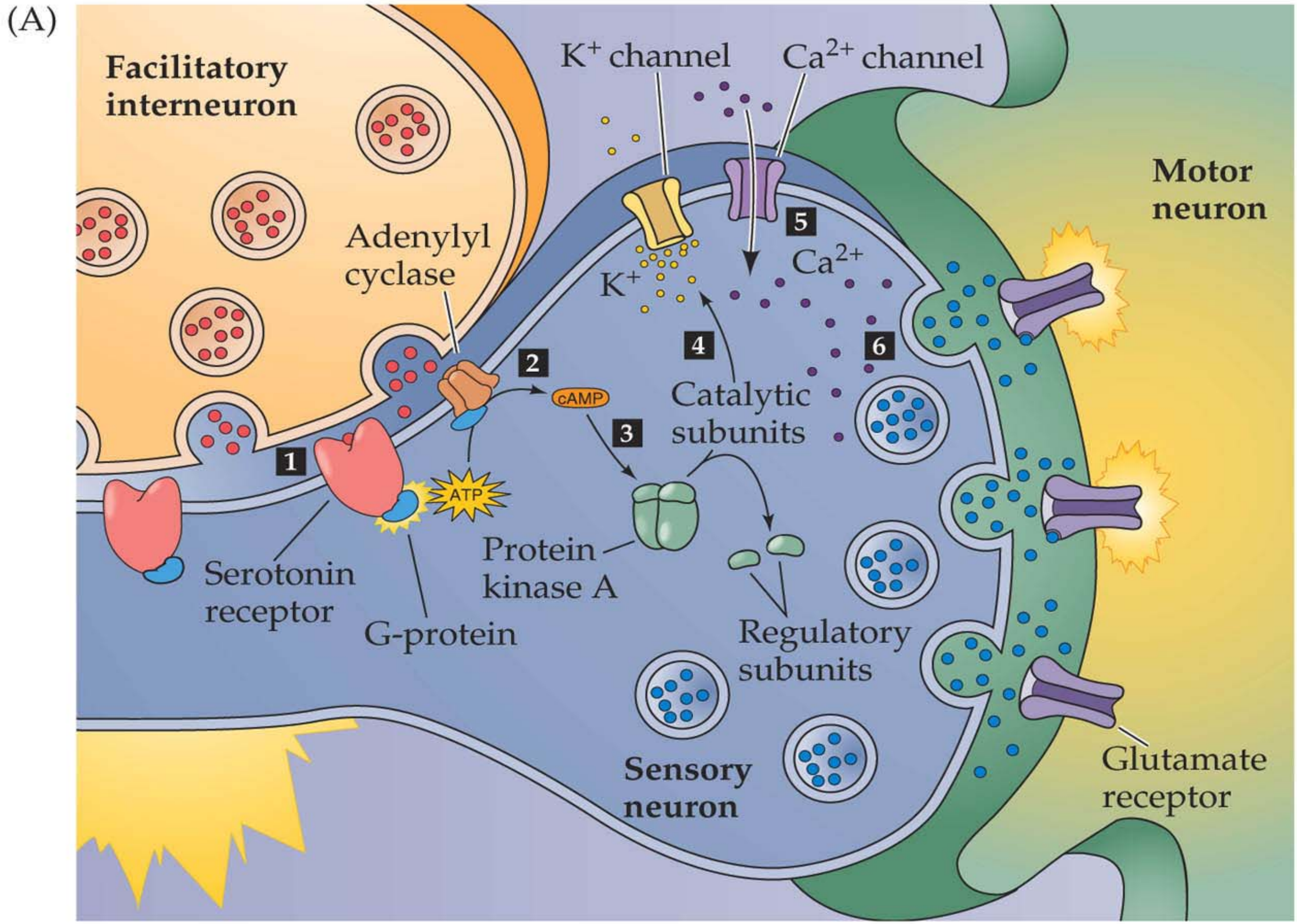


NEUROSCIENCE, Third Edition, **Figure 24.1 (Part 3)**

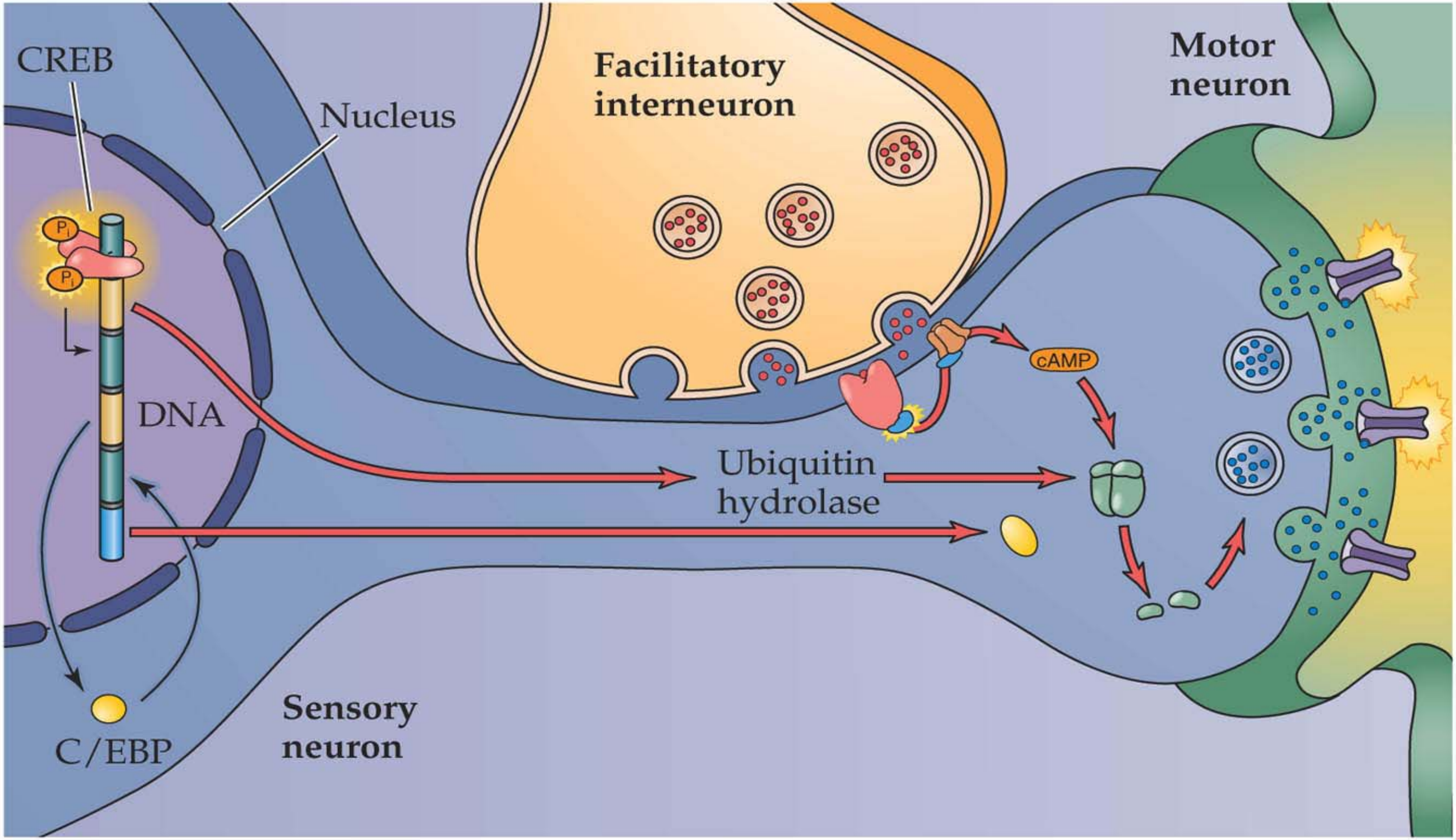


NEUROSCIENCE, Third Edition, **Figure 24.2 (Part 1)**


(B)
Stimulate tail nerve
0 min
20 min
50 min
50 min 20 s
Sensory neuron action potential (mV)
0
–25
–50
Motor neuron EPSP (mV)
–40
–50
0 100 200 300
Time (ms)


(A)
Facilitatory interneuron
K+ channel
Ca2+ channel
Motor neuron
5
Adenylyl cyclase
K+
Ca2+
4
6
2
cAMP
Catalytic subunits
3
1
ATP
Protein kinase A
Serotonin receptor
G-protein
Regulatory subunits
Sensory neuron
Glutamate receptor

(B)

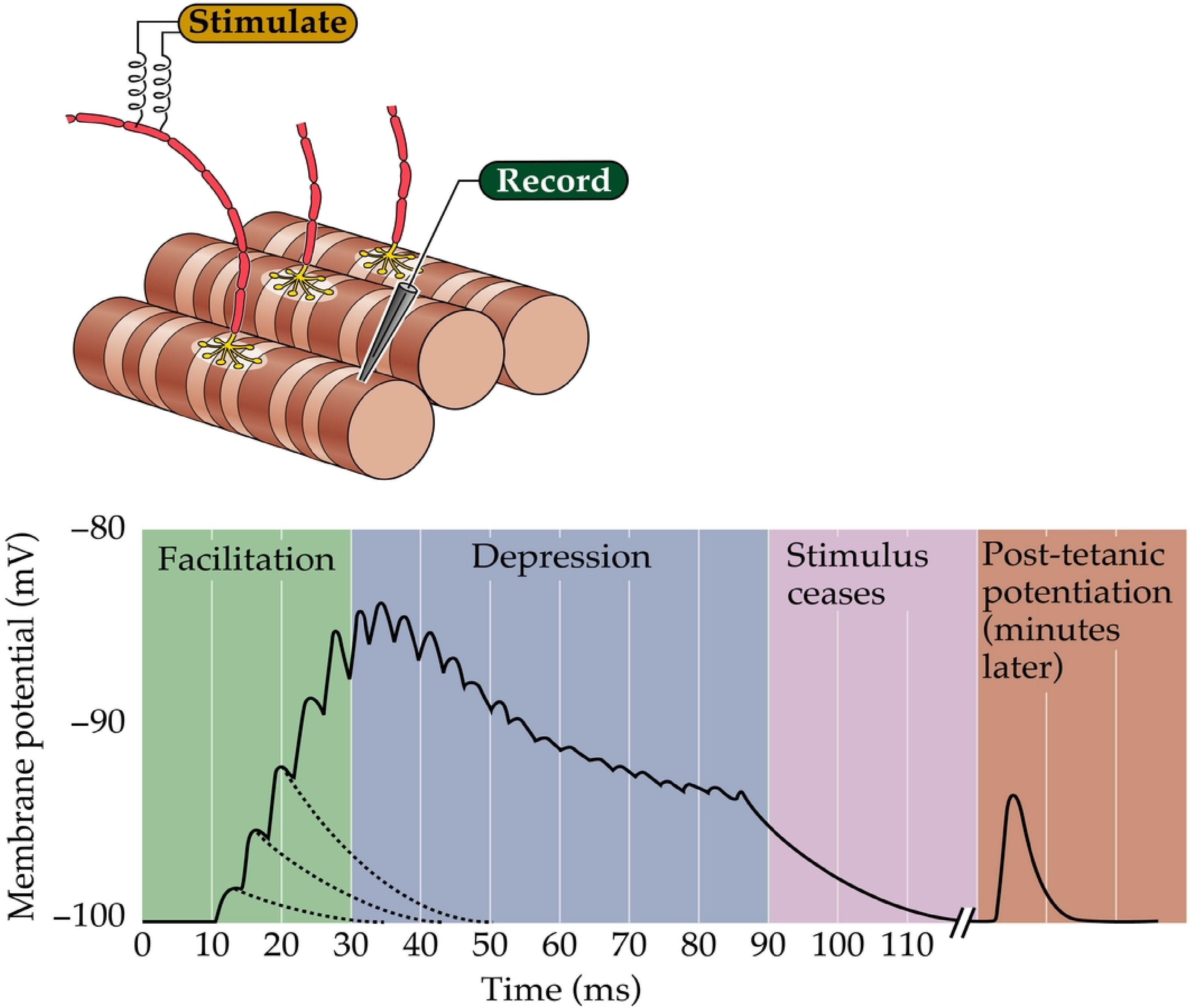


NEUROSCIENCE, Third Edition, **Figure 24.3 (Part 2)**

Activity-dependent synaptic plasticity

- Short-term synaptic plasticity
- Long-term synaptic plasticity
- Long-term potentiation (LTP)
- Long-term depression (LTD)
- Depotentiation

- Glutamatergic


Stimulate
Record
Facilitation
Depression
Stimulus ceases
Post-tetanic potentiation (minutes later)
Membrane potential (mV)
−80
−90
−100
0
10
20
30
40
50
60
70
80
90
100
110
Time (ms)

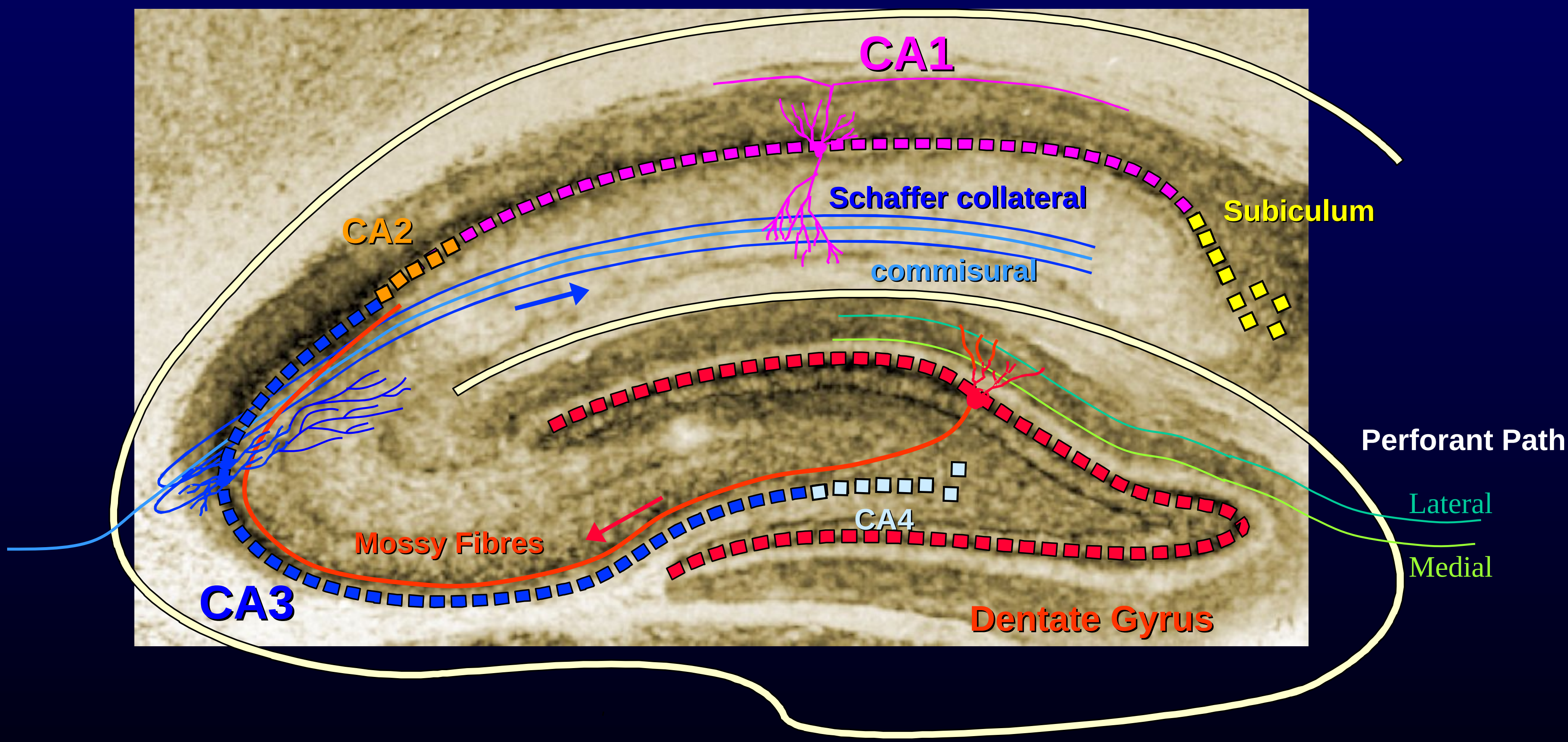
Activity-dependent long-term synaptic plasticity

- Changes in the postsynaptic response as a function of the activity pattern of the pre- and postsynaptic cells and how these patterns relate to each other.

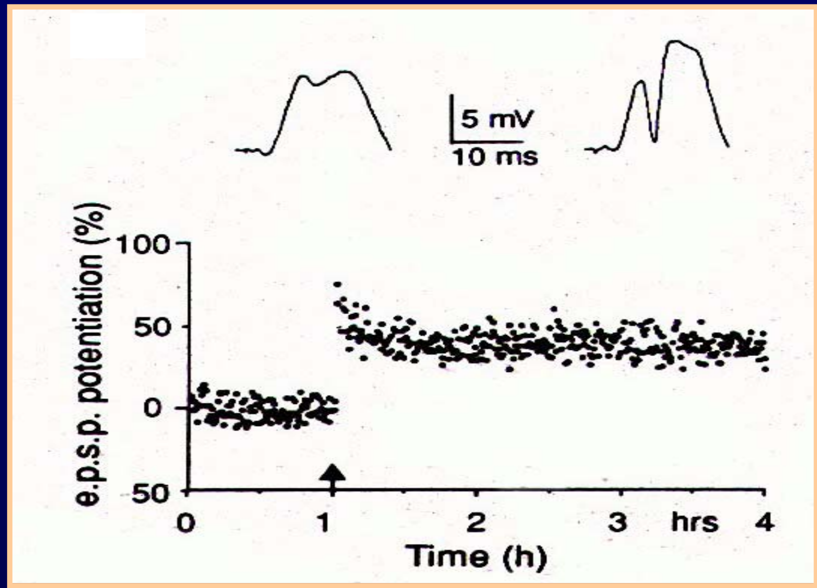
- Can involve both pre- and postsynaptic changes.

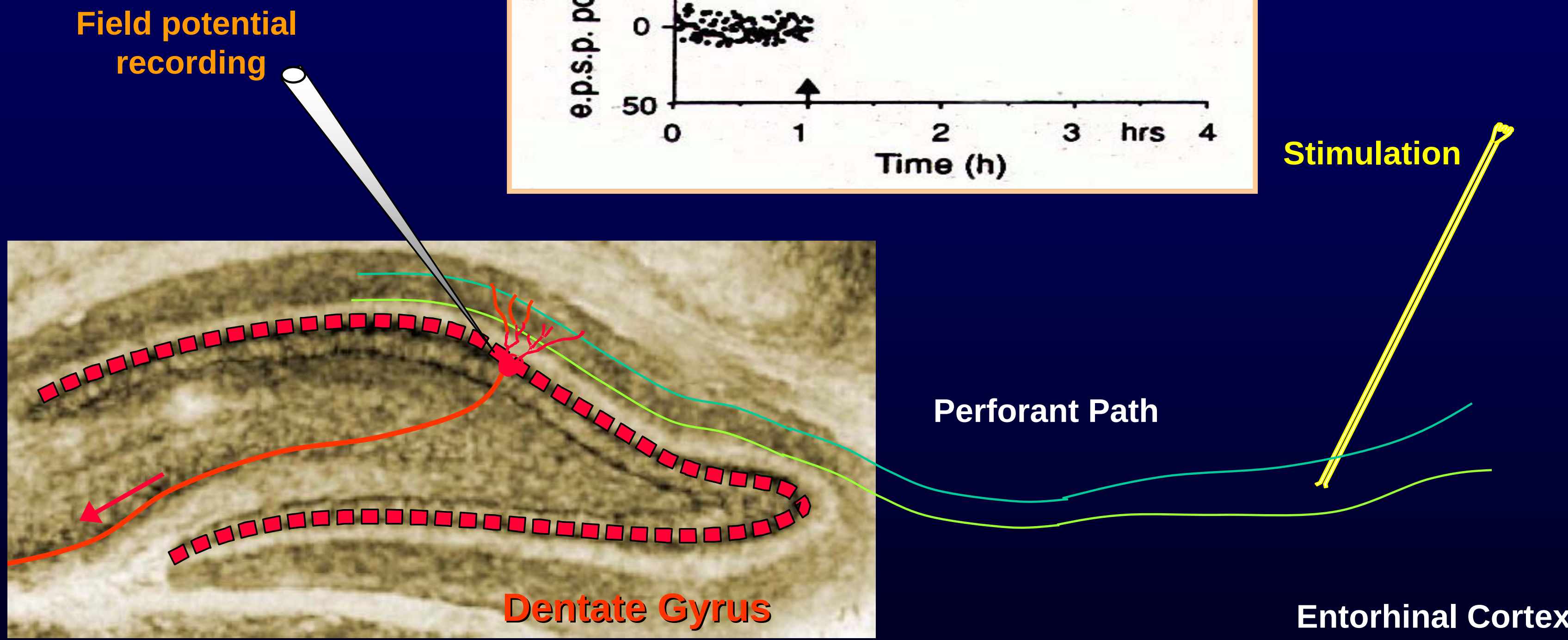
- Is differentially expressed at different synapses.

Major pathways in hippocampal slices



The Discovery of LTP

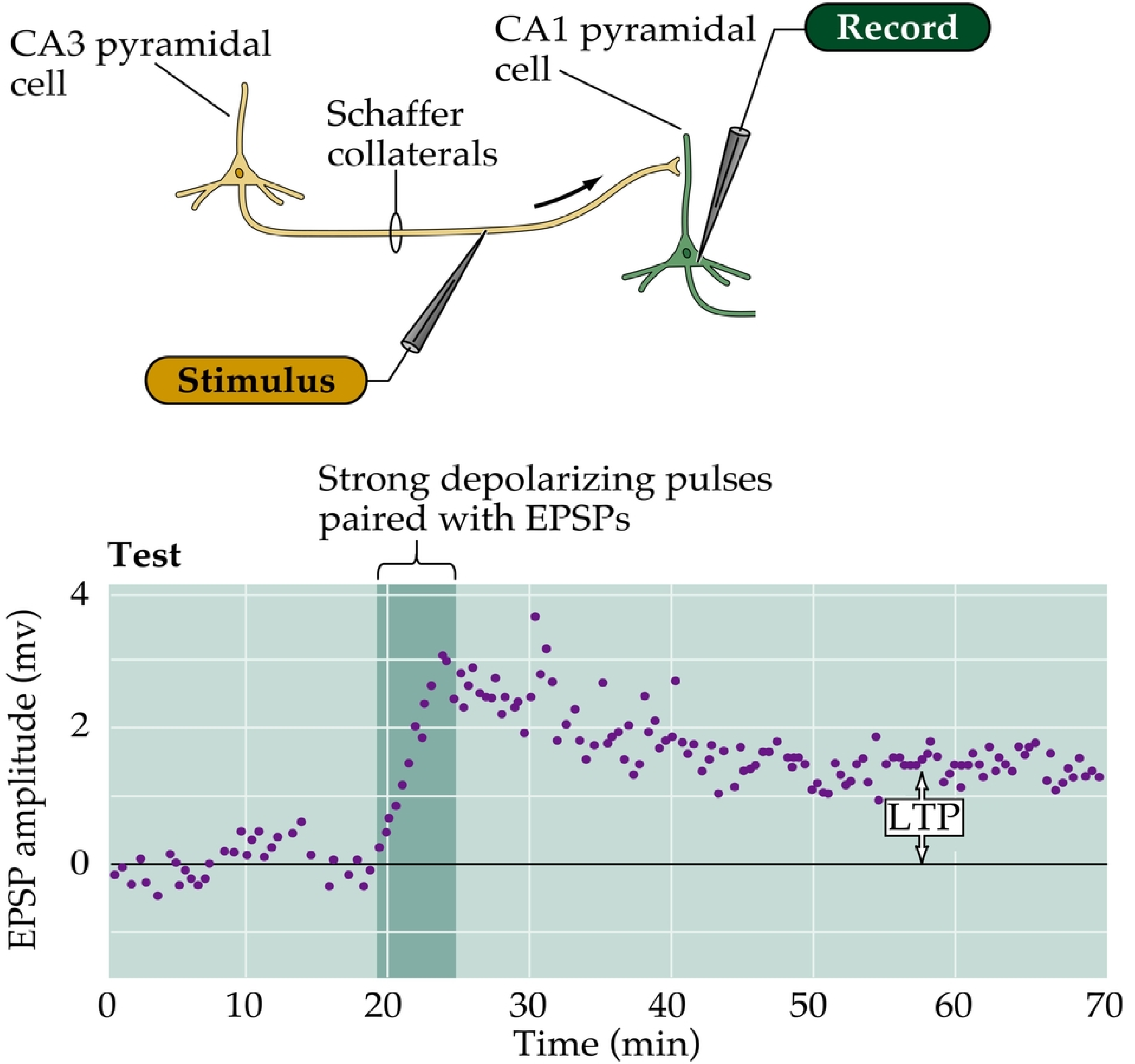




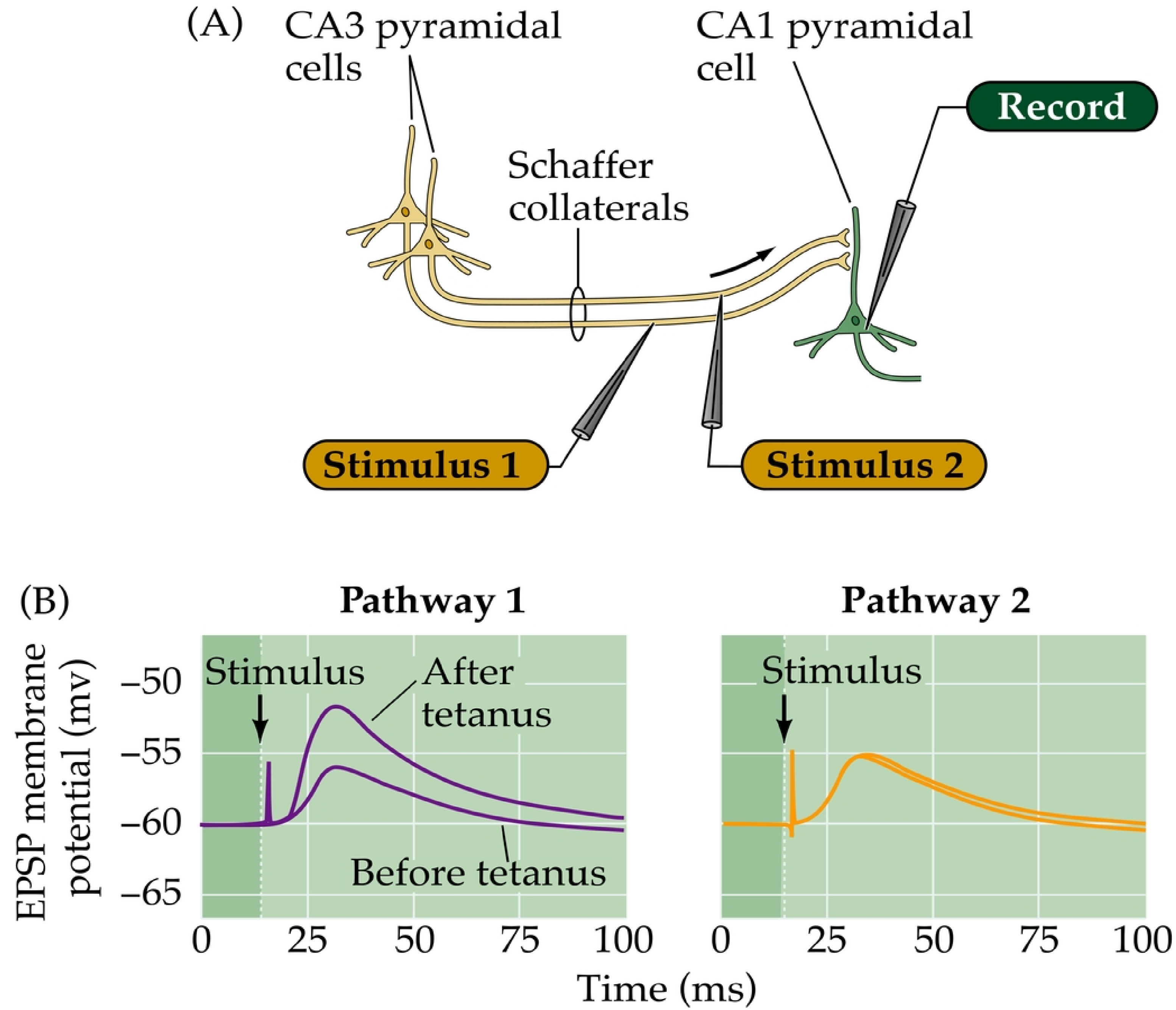
Bliss & Lomo (1973) *J. Physiol* **232;** 331-356

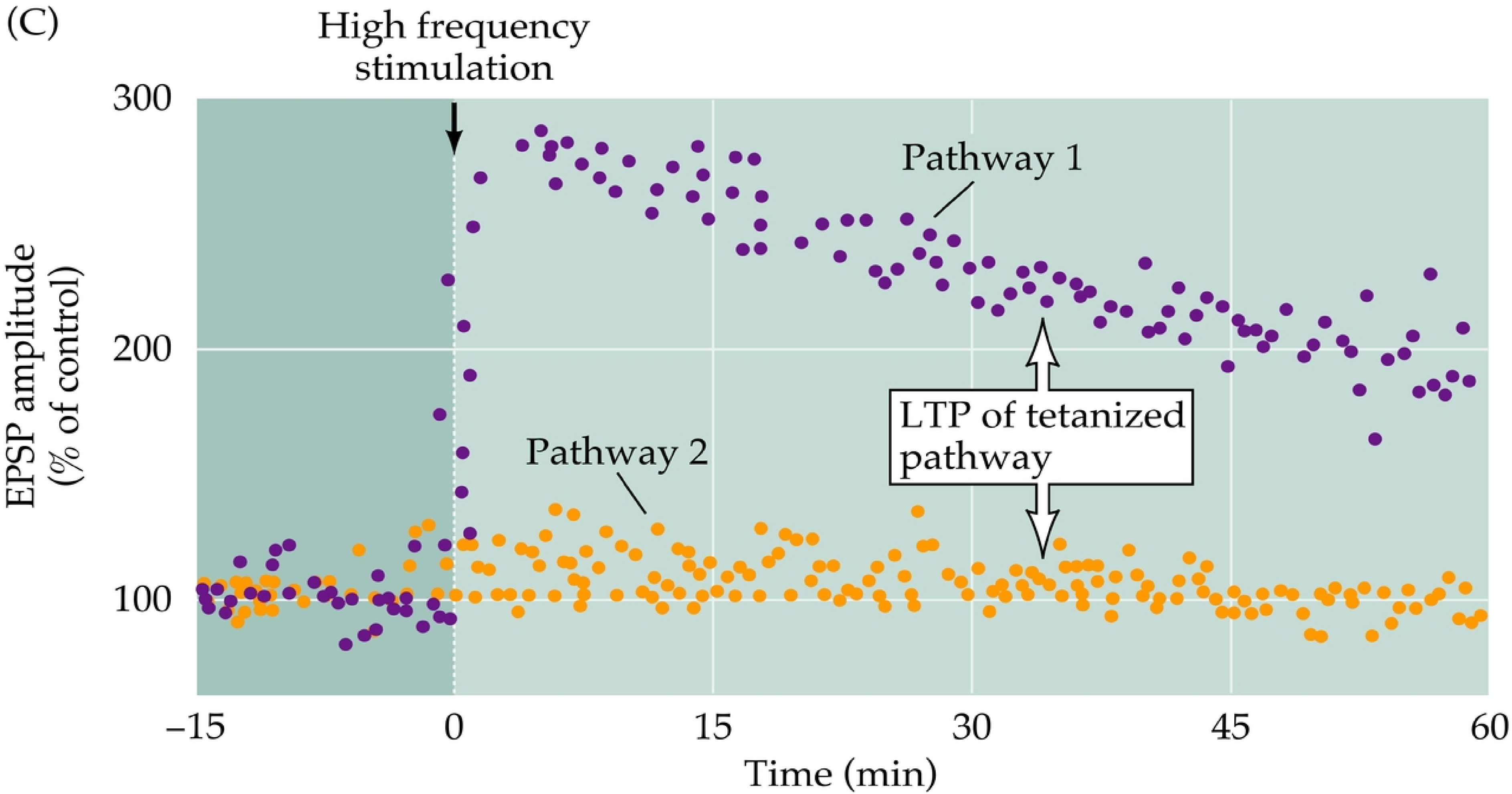
Bliss & Gardner-Medwin (1973) *J. Physiol* **232;** 357-374

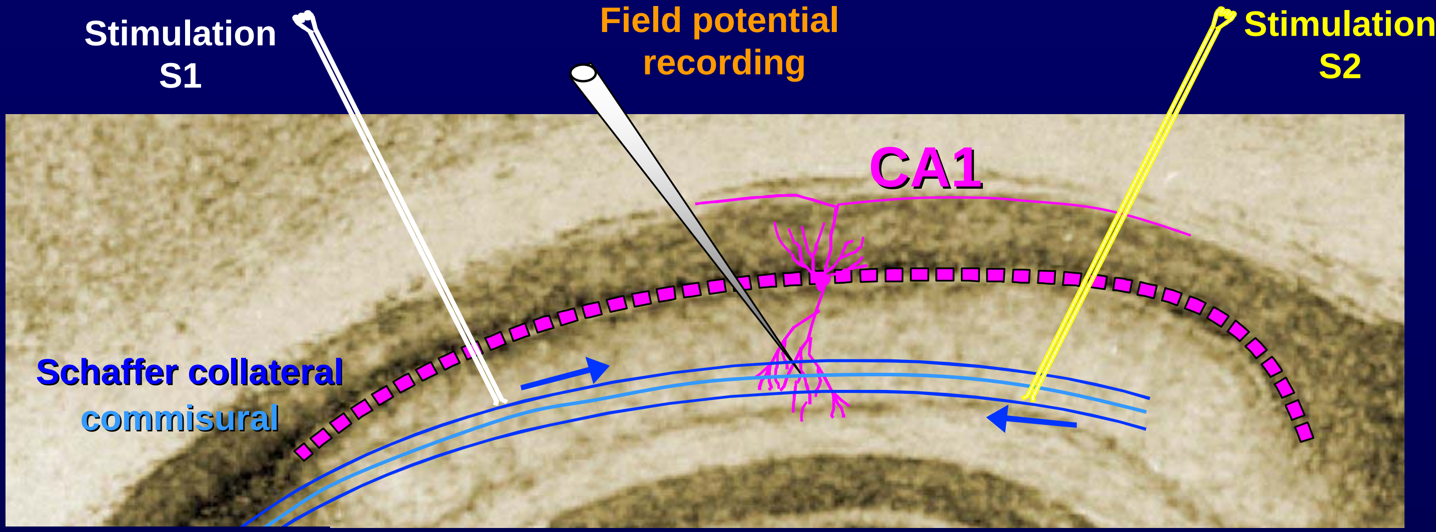
Basic properties of LTP

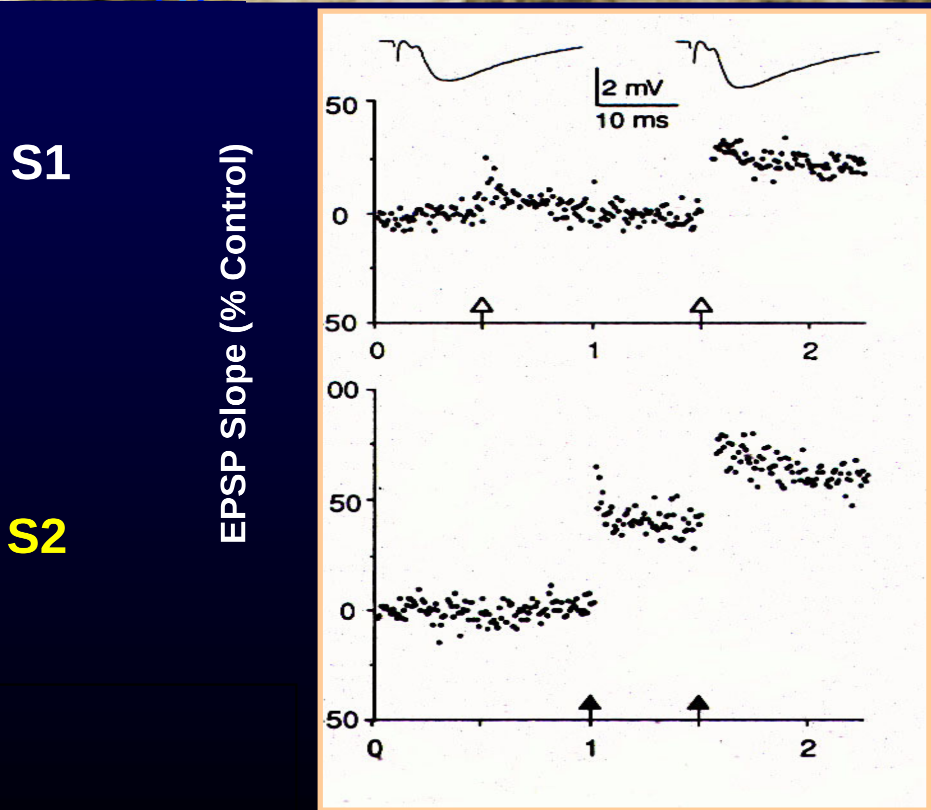


CA3 pyramidal cell
Schaffer collaterals
CA1 pyramidal cell
Record
Stimulus
Strong depolarizing pulses paired with EPSPs
Test
EPSP amplitude (mv)
4
2
0
LTP
0
10
20
30
40
50
60
70
Time (min)


(A)
CA3 pyramidal cells
CA1 pyramidal cell
Record
Schaffer collaterals
Stimulus 1
Stimulus 2
(B)
Pathway 1
Pathway 2
EPSP membrane potential (mv)
–50
–55
–60
–65
Stimulus
After tetanus
Before tetanus
Stimulus
0
25
50
75
100
0
25
50
75
100
Time (ms)


(C)
High frequency stimulation
Pathway 1
Pathway 2
LTP of tetanized pathway
300
200
100
EPSP amplitude (% of control)
–15
0
15
30
45
60
Time (min)



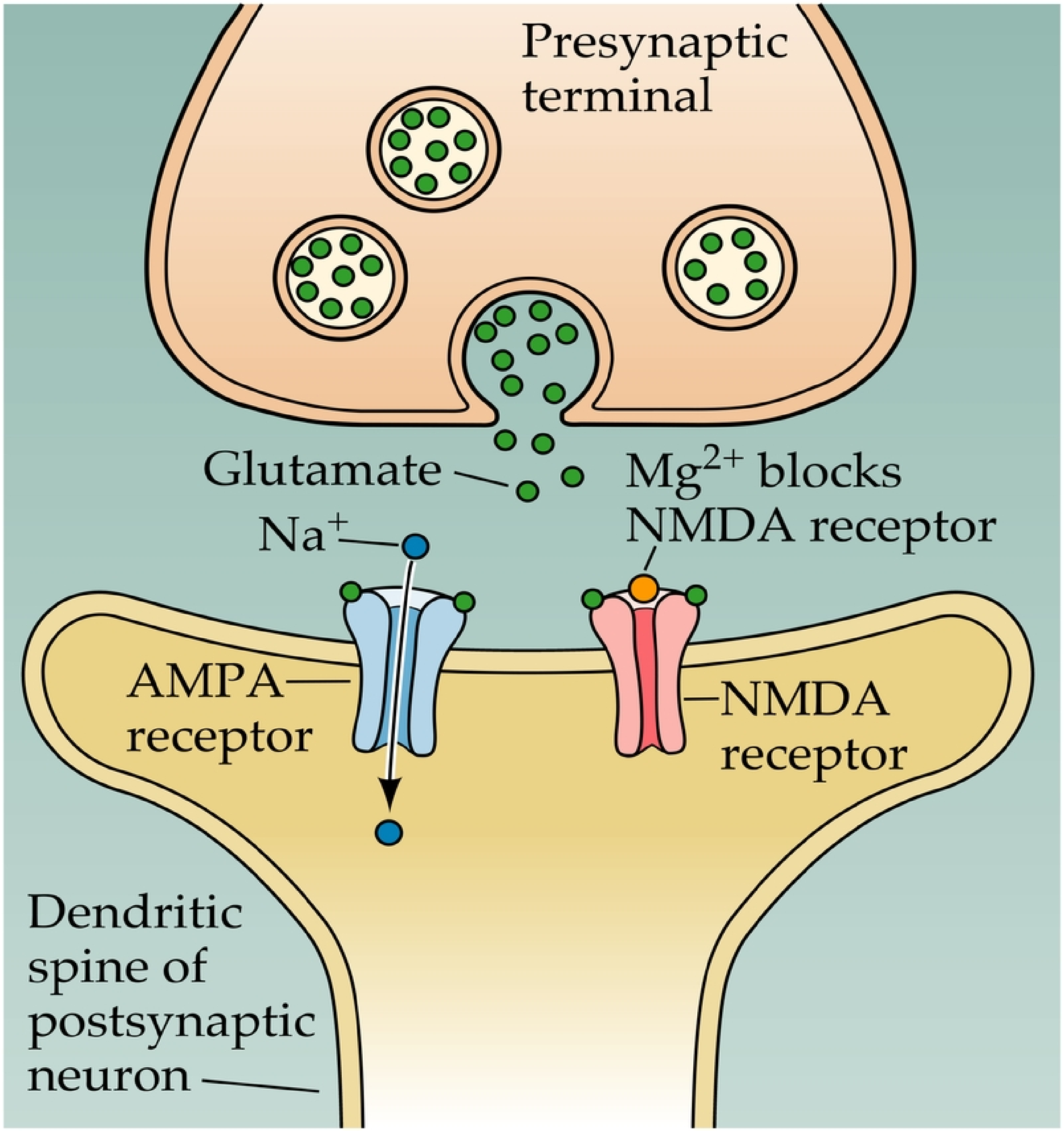


Input specificity, co-operativity & associativity

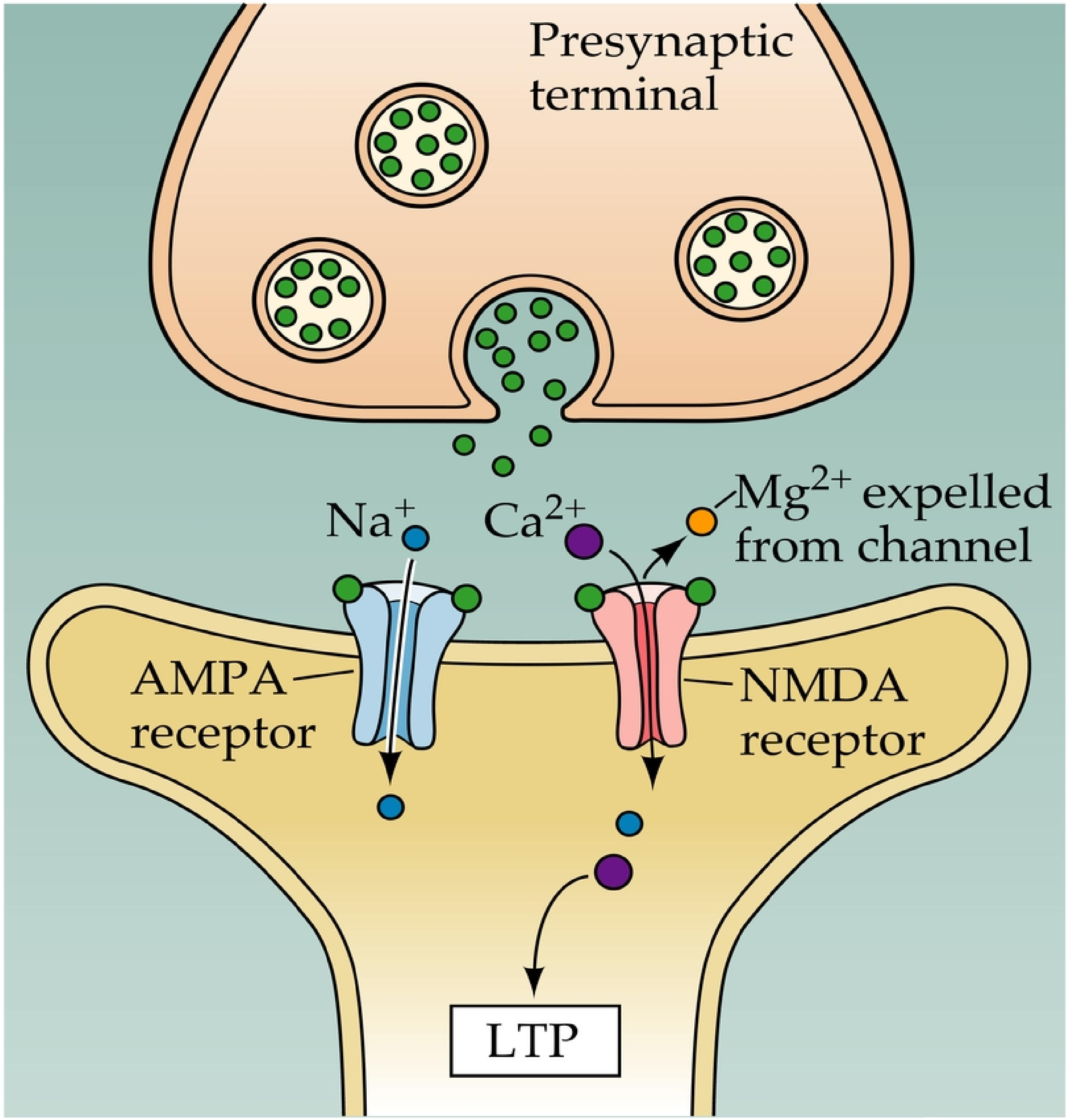
Bliss & Lomo (1973) *J. Physiol* **361;** 31-39

Mechanism of induction of NMDA receptor-dependent LTP

At resting potential

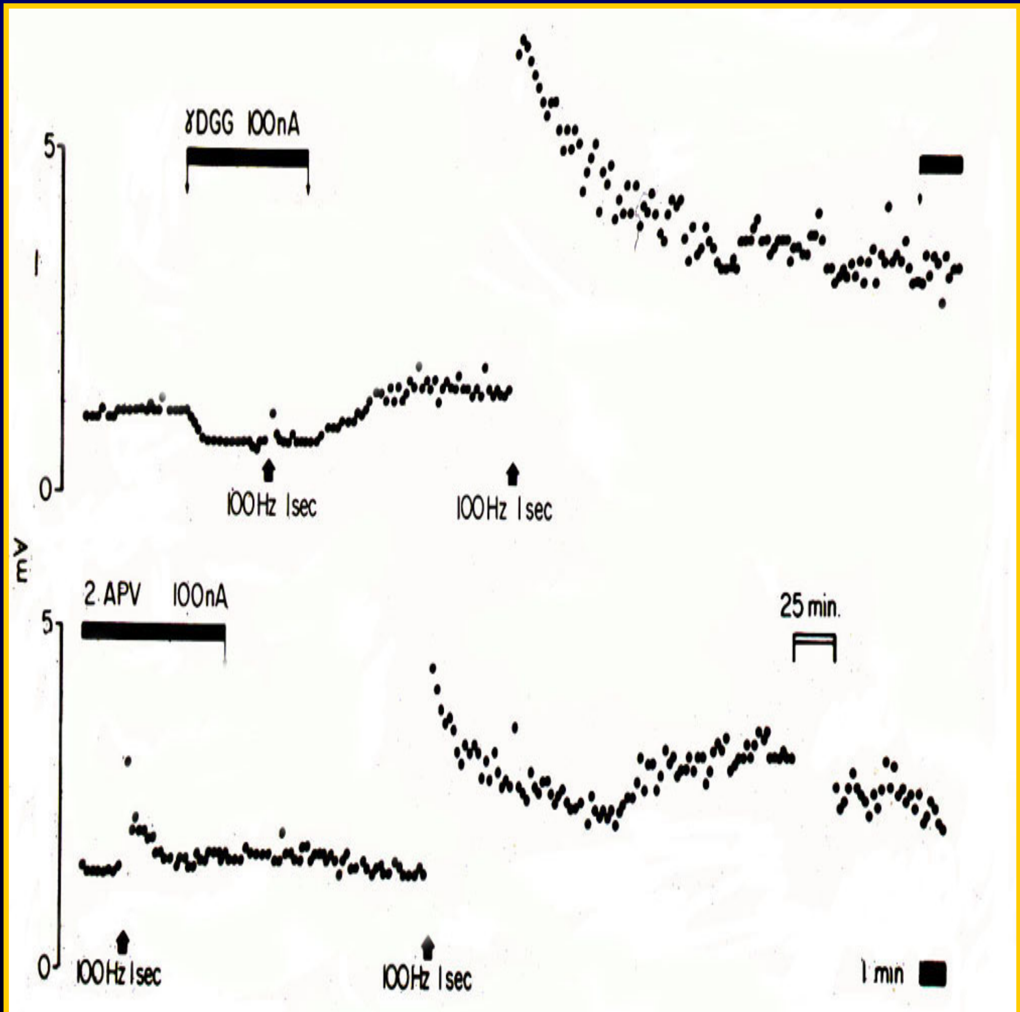


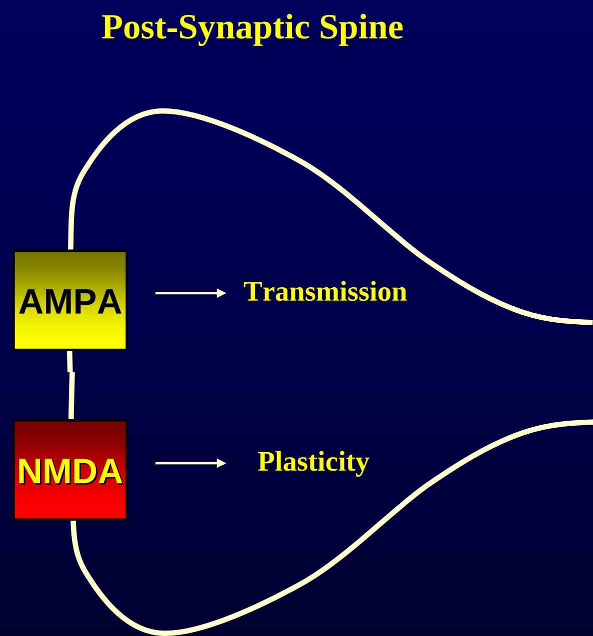
During depolarization



AMPA receptors mediate a modifiable synaptic response

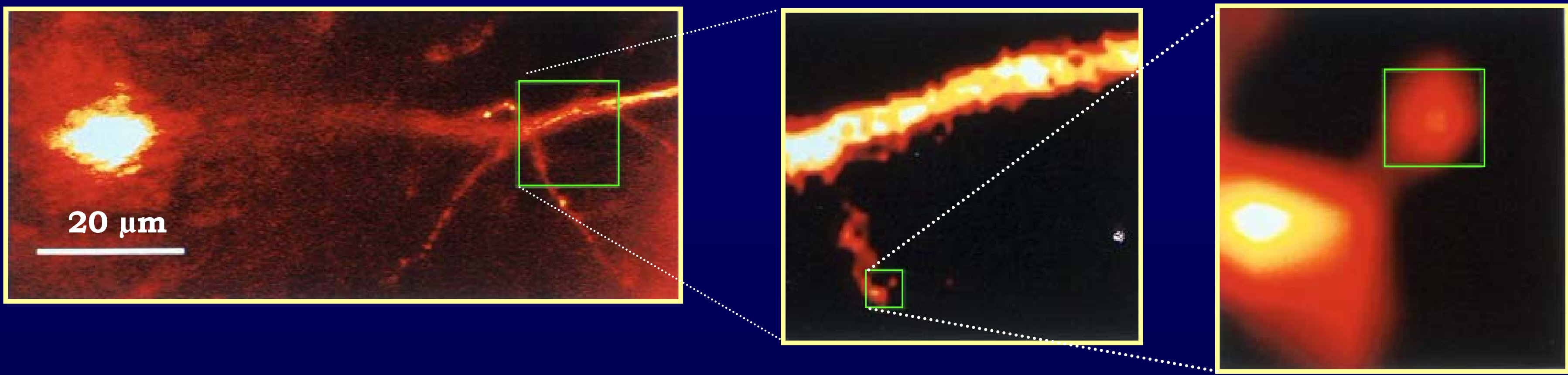
NMDA receptors are necessary for the induction of LTP

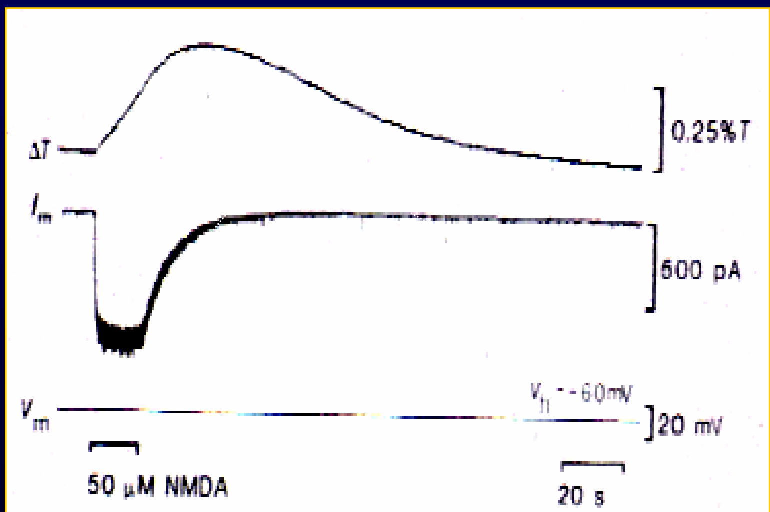




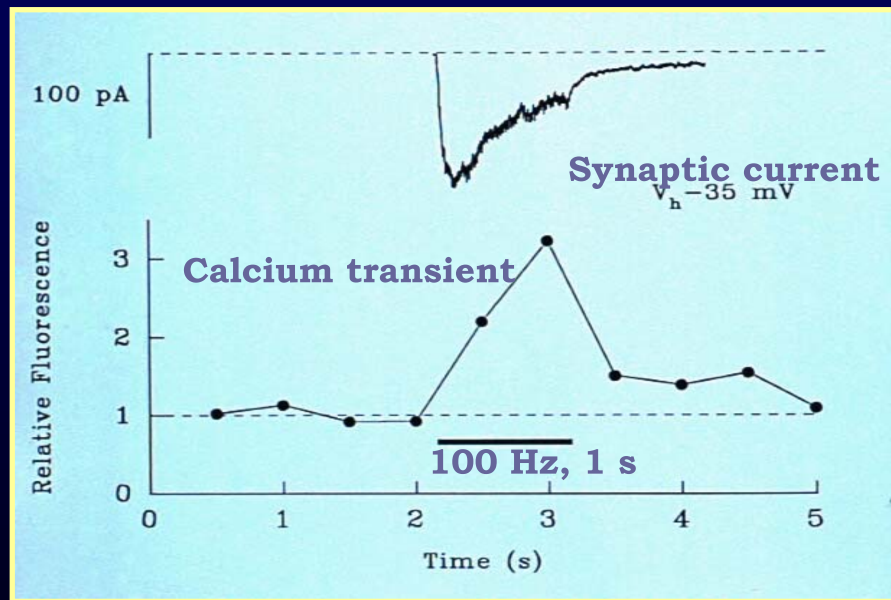
from: Collingridge, Kehl & McLennan (1983) *J. Physiol.* **334;** 33-46

Ca^{2+} permeation through NMDA receptors

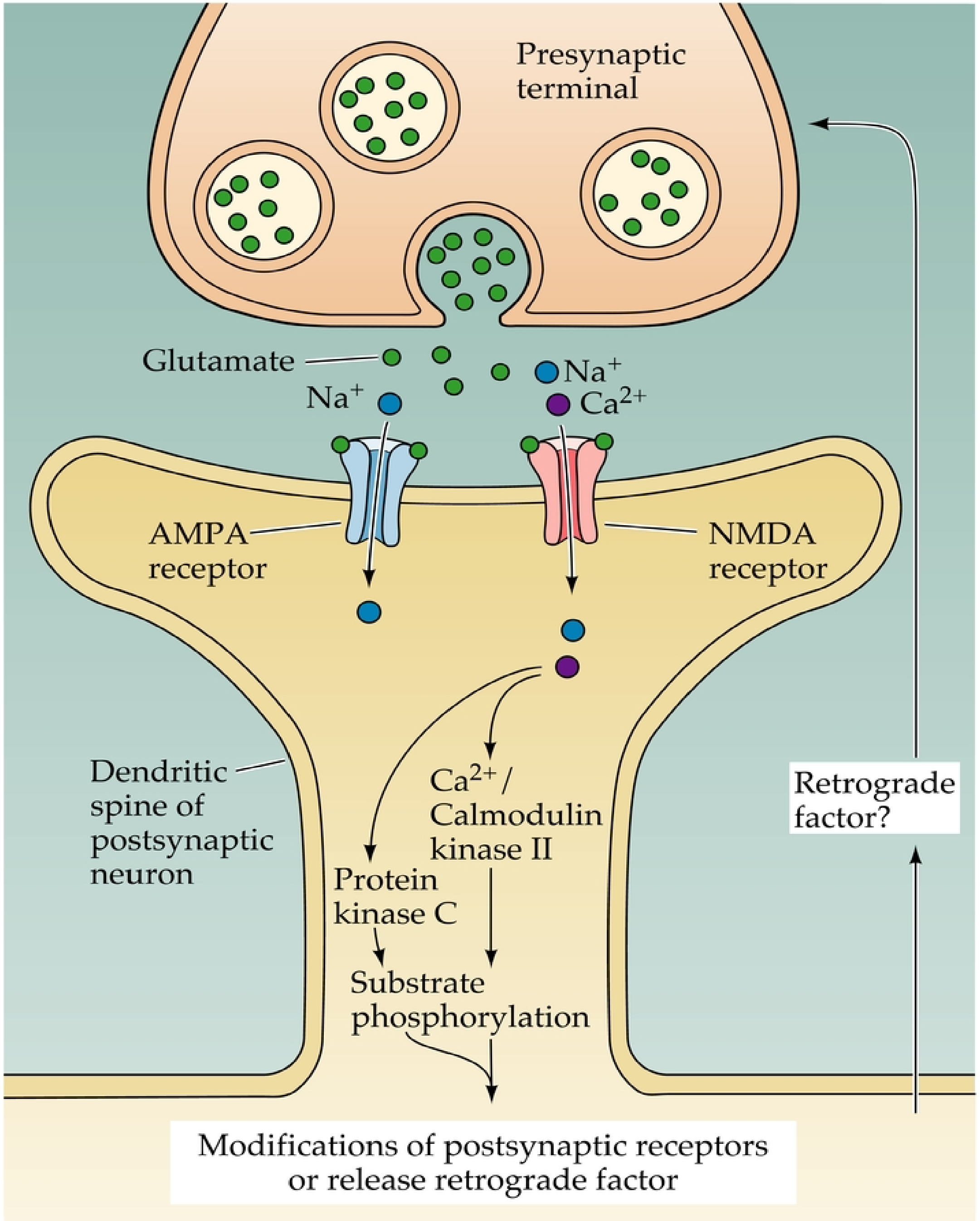




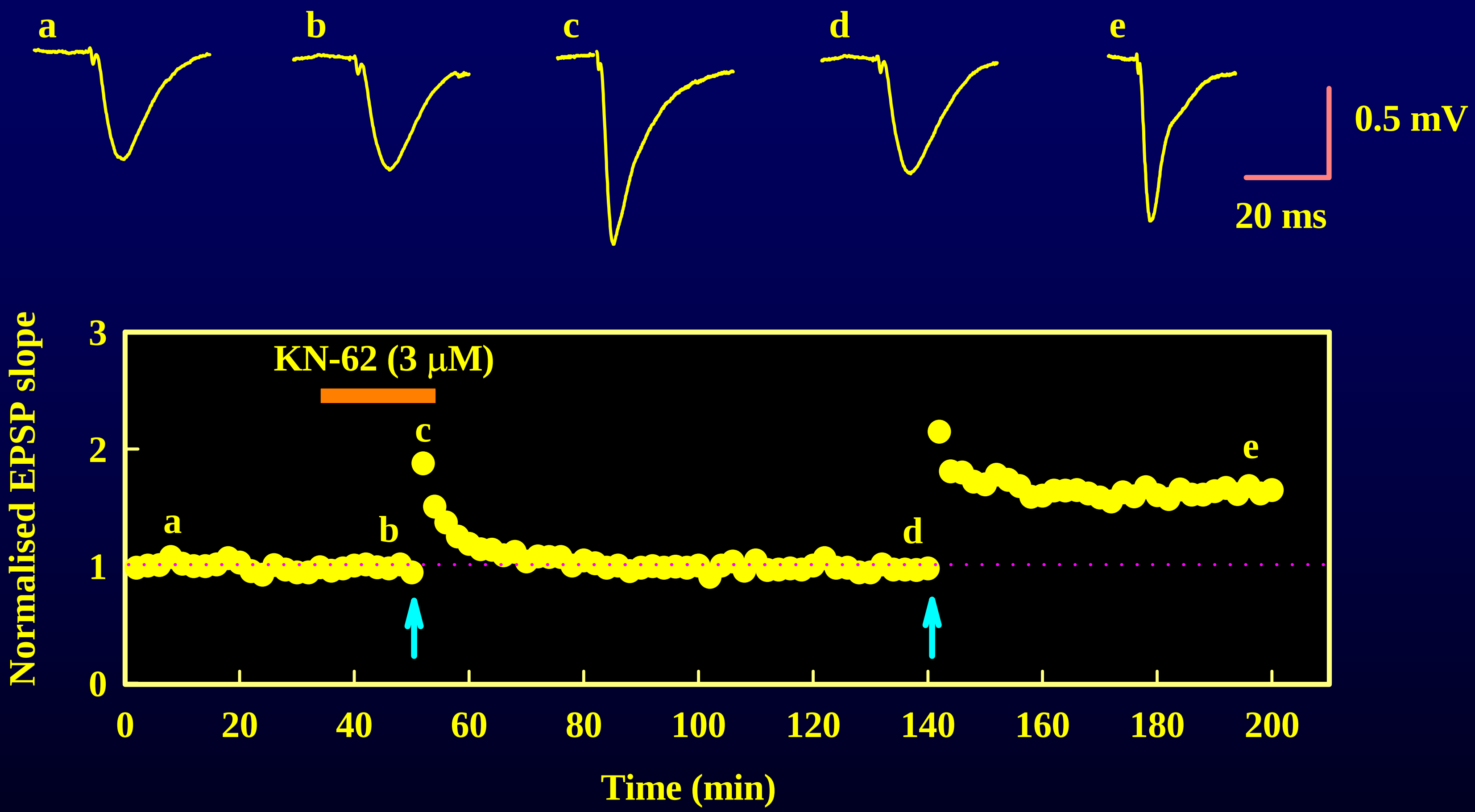
from: MacDermott *et al*, (1986) *Nature* **321;** 519-522



from: Bliss & Collingridge, (1993) *Nature* **361;** 31-39
(data from : Alford *et al*, (1993) *J. Physiol.* **469;** 693-716)


Presynaptic terminal
Glutamate
Na+
Na+
Ca2+
AMPA receptor
NMDA receptor
Dendritic spine of postsynaptic neuron
Ca2+ / Calmodulin kinase II
Protein kinase C
Substrate phosphorylation
Retrograde factor?
Modifications of postsynaptic receptors or release retrograde factor

KN-62 blocks the induction of LTP in hippocampal CA1 neurons



from : Bortolotto & Collingridge, (1998) *Neuropharmacology* **37;** 535-544
after: Ito, Hikada & Sugiyama (1991) *Neurosci. Lett.* **121;** 119-121

Signalling mechanisms following the synaptic activation of NMDA receptors

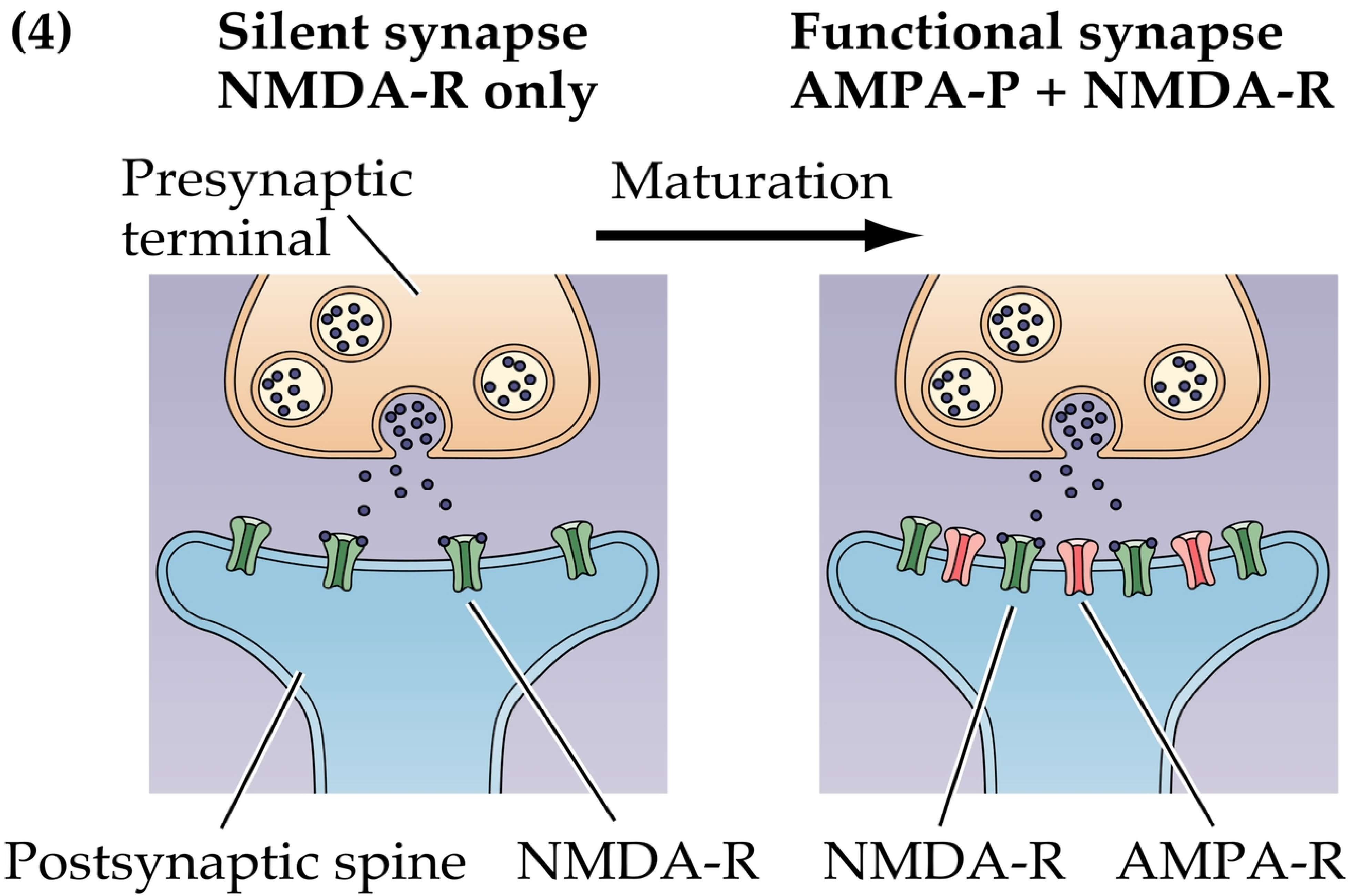
- a transient rise in [Ca^{2+}] in dendritic spines
- activation of CaMKII

The synaptic strength increases as:

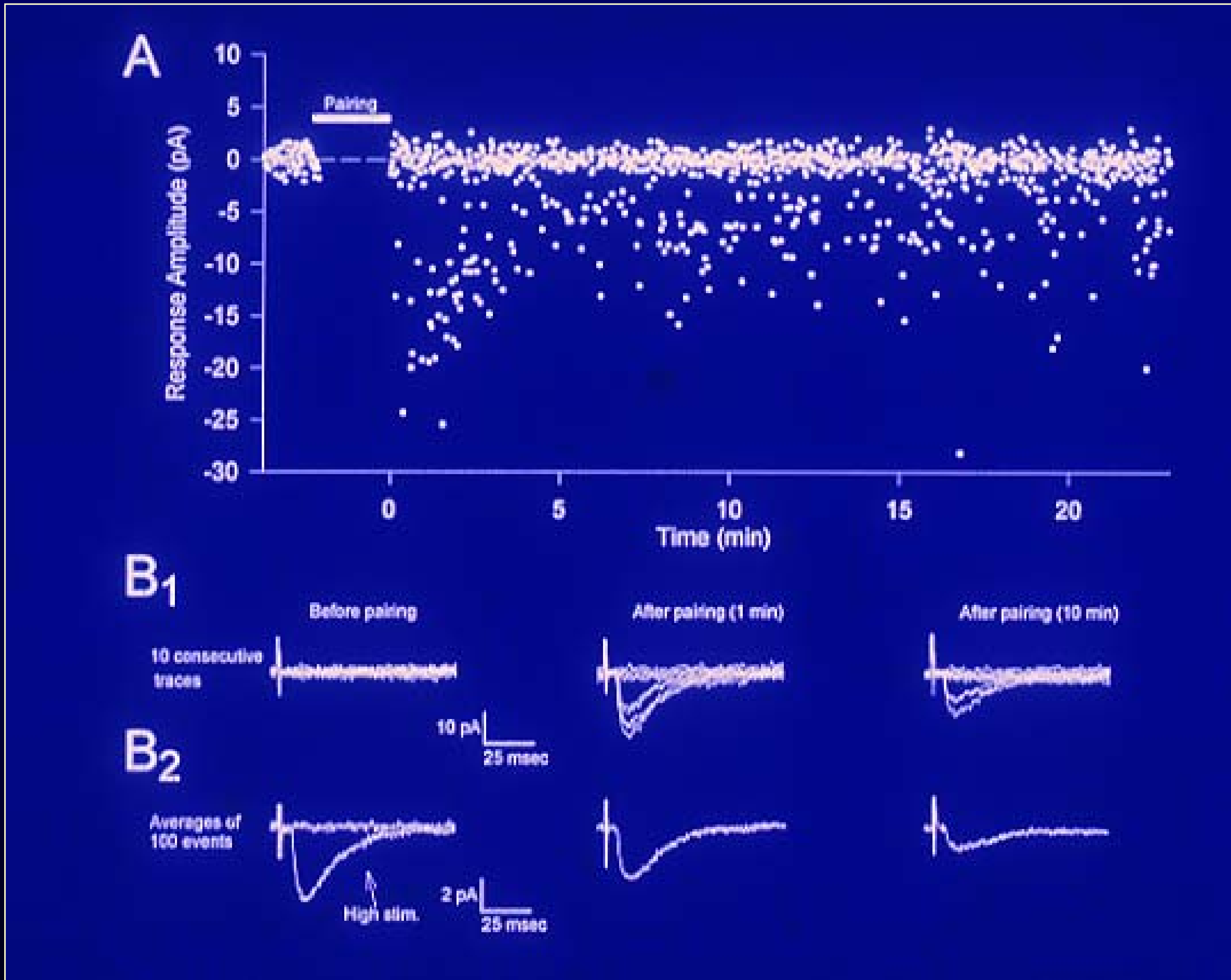
The single channel conductance of AMPA-receptors increases.

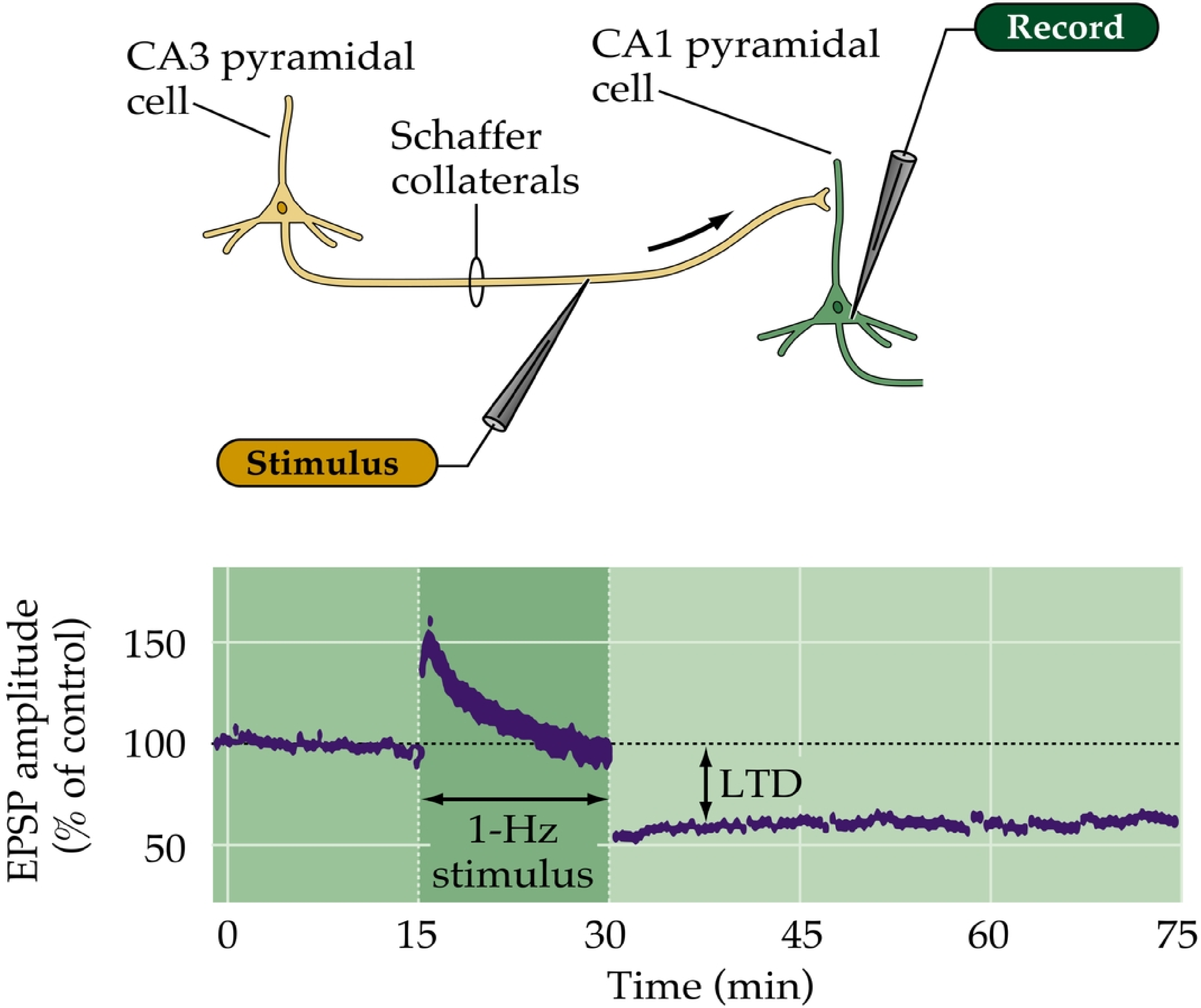
The number of AMPA-receptors in the postsynaptic cleft increases.

The mechanisms appear to be mutually exclusive.

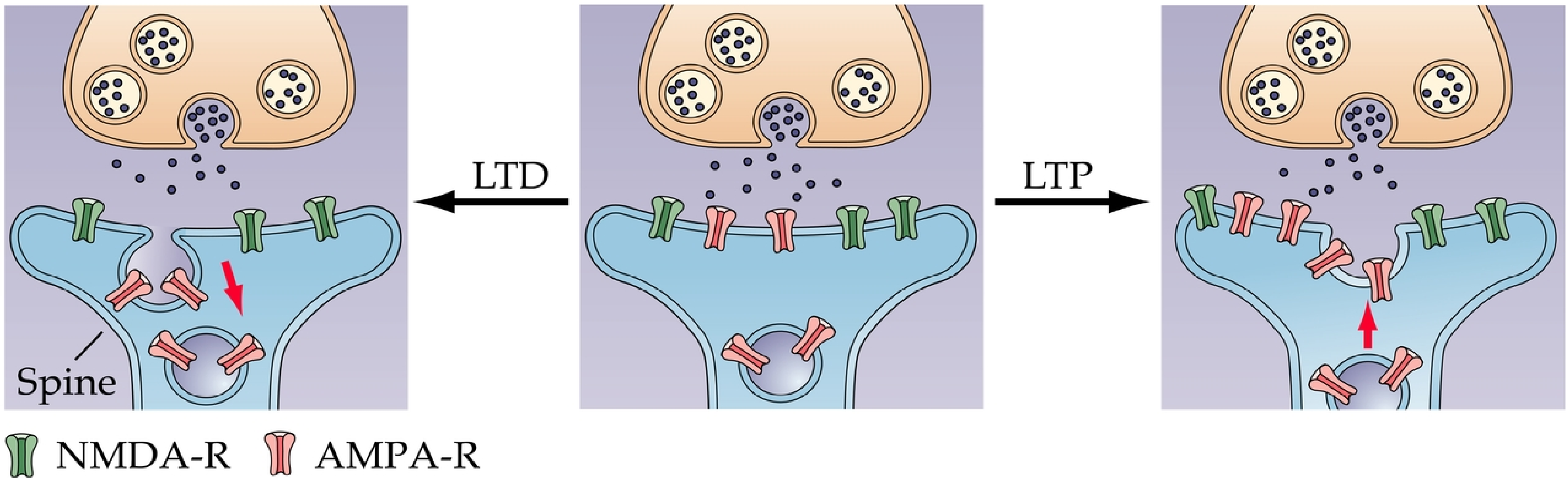

(4)
Silent synapse
NMDA-R only
Functional synapse
AMPA-P + NMDA-R
Presynaptic terminal
Maturation
Postsynaptic spine
NMDA-R
NMDA-R
AMPA-R

Evidence for the existence of silent synapses

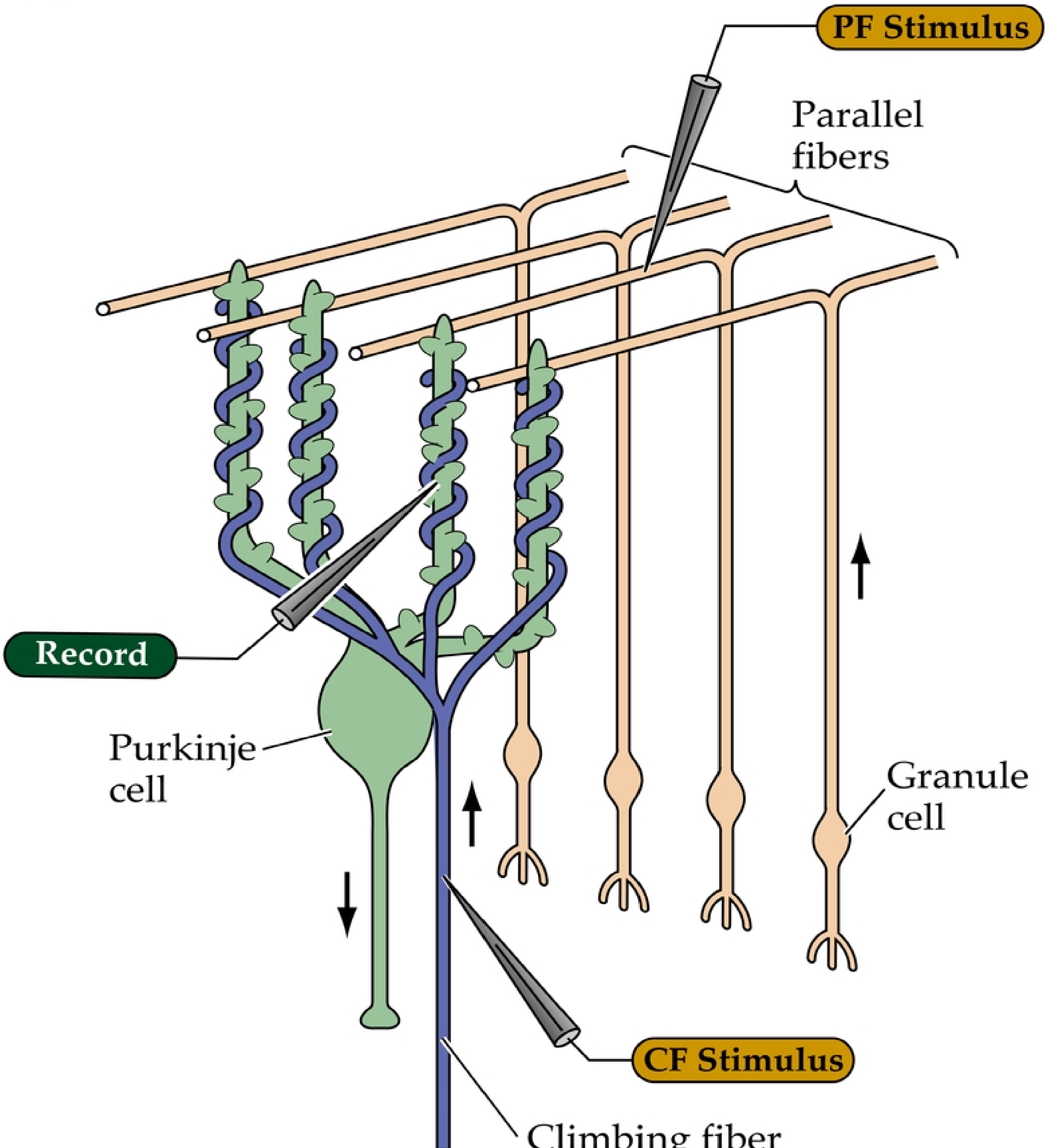


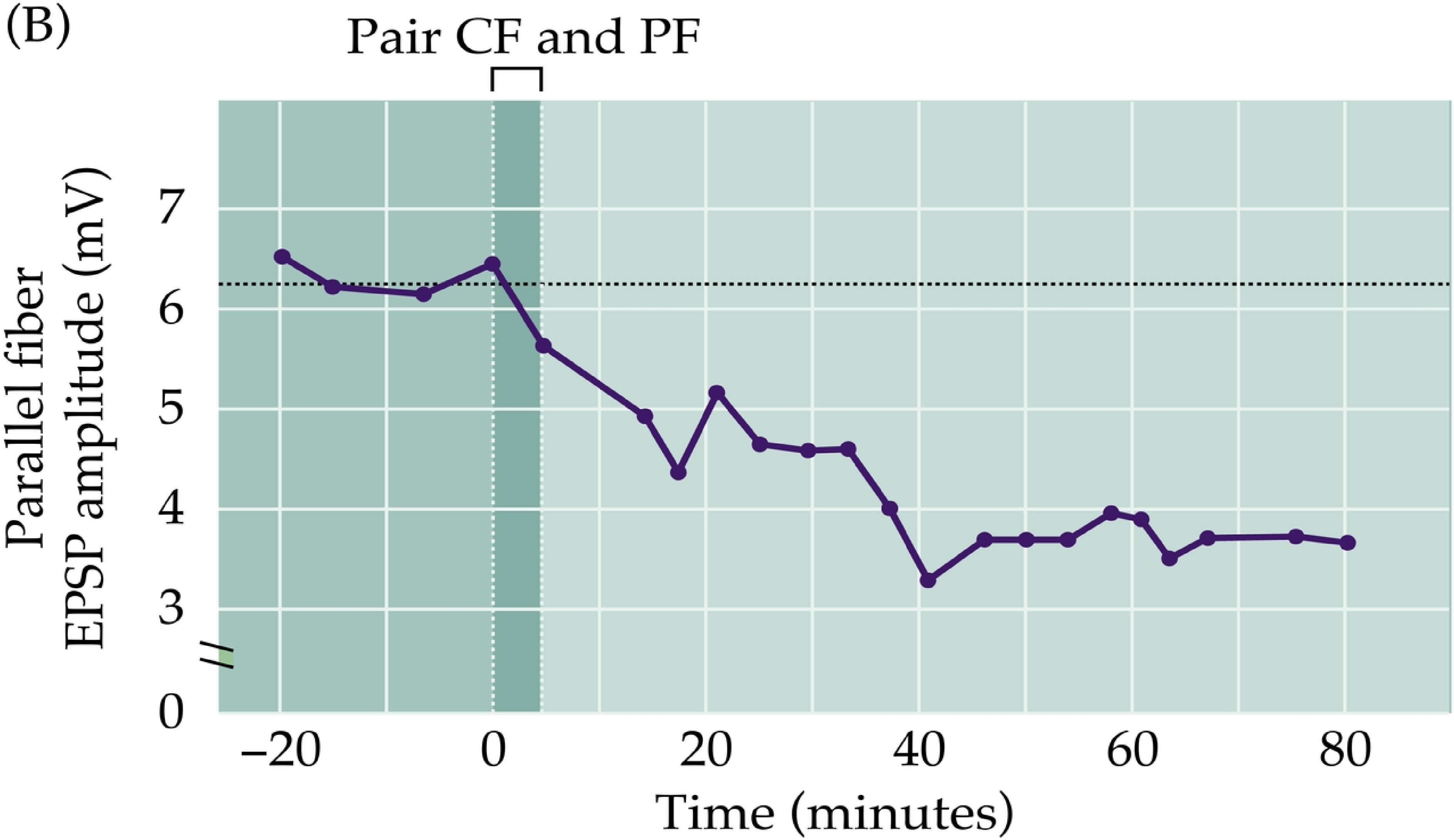

Record
CA3 pyramidal cell
CA1 pyramidal cell
Schaffer collaterals
Stimulus
EPSP amplitude (% of control)
150
100
50
LTD
1-Hz stimulus
0
15
30
45
60
75
Time (min)

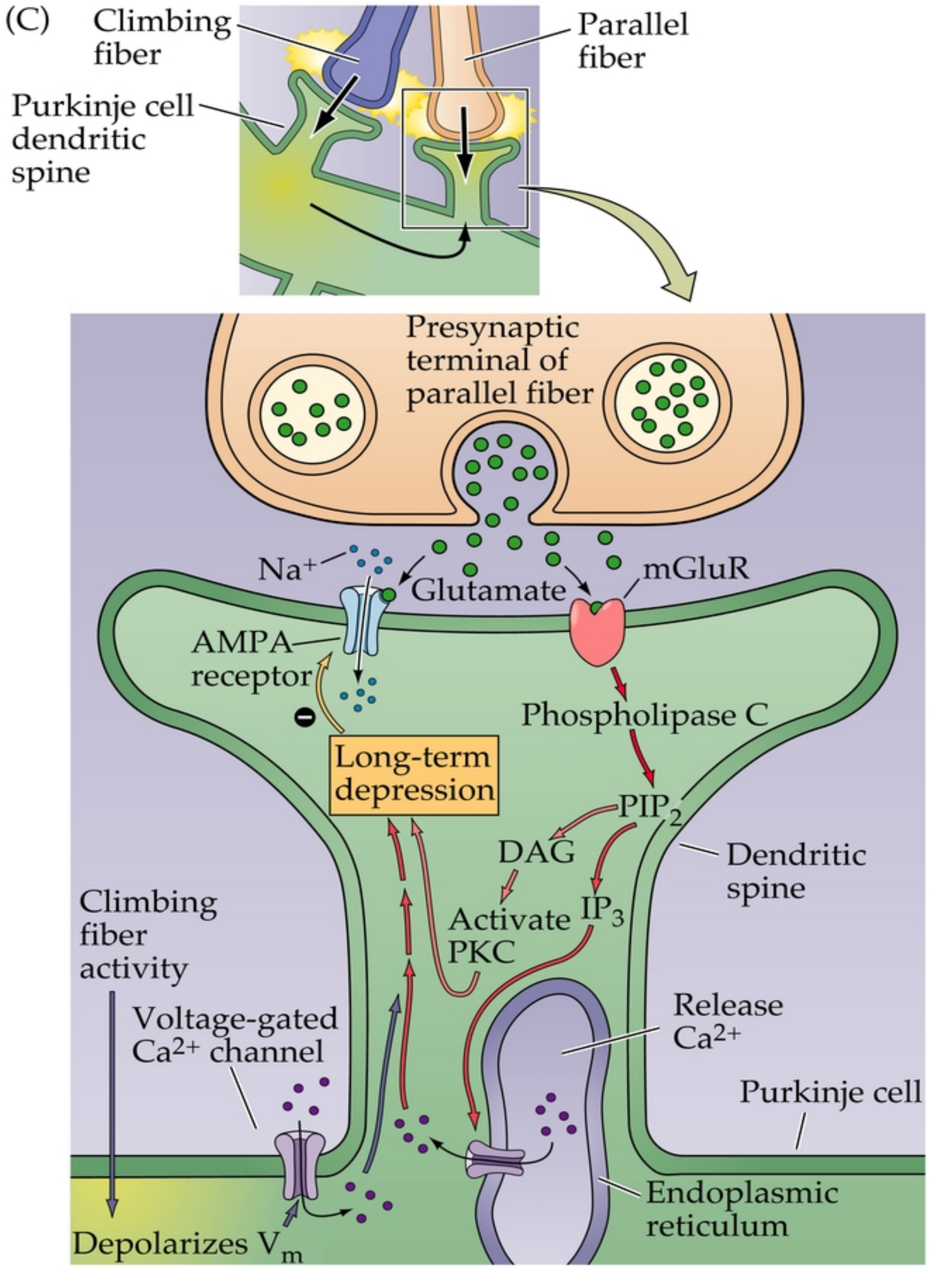
(3)



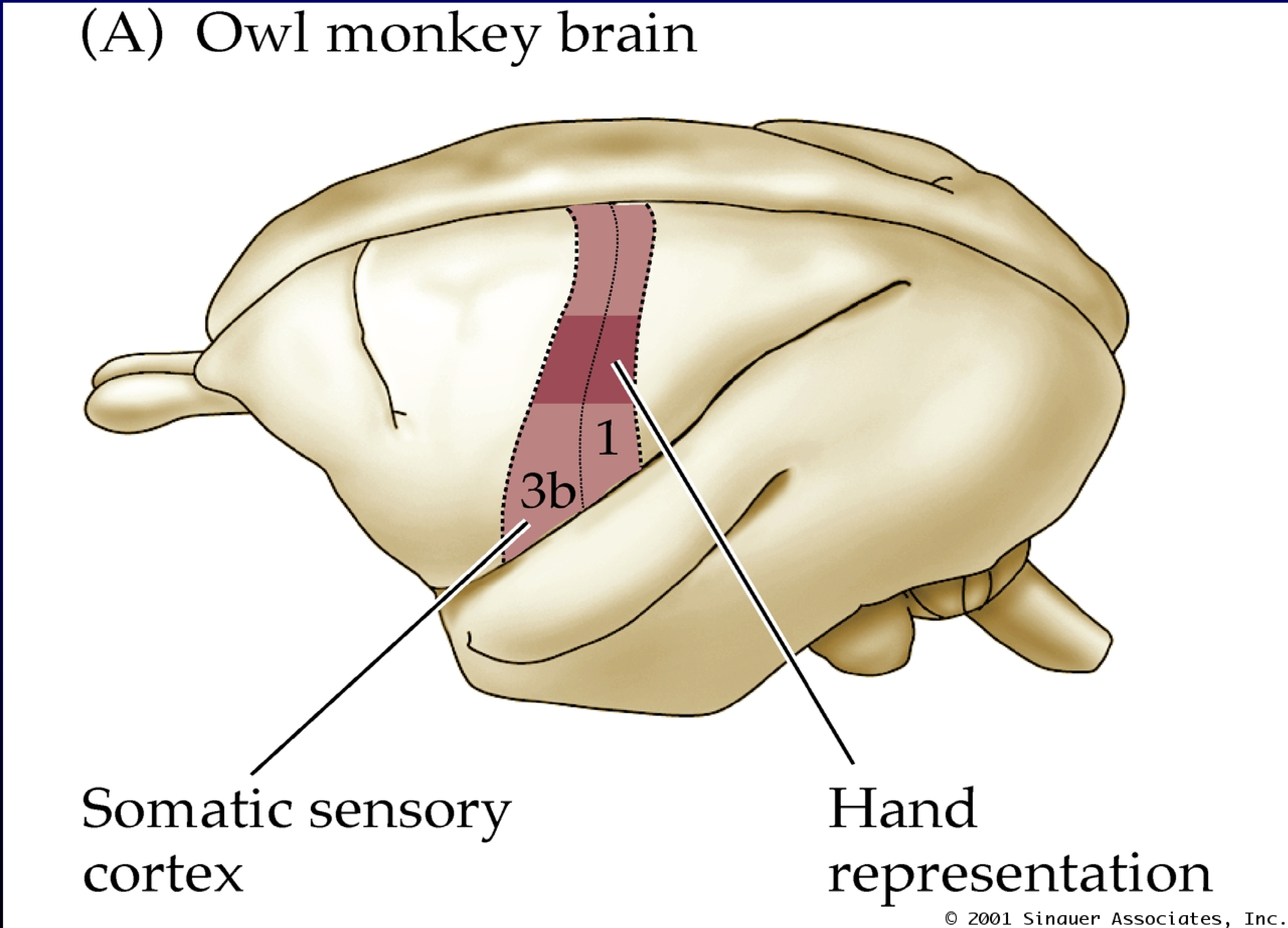
(A)

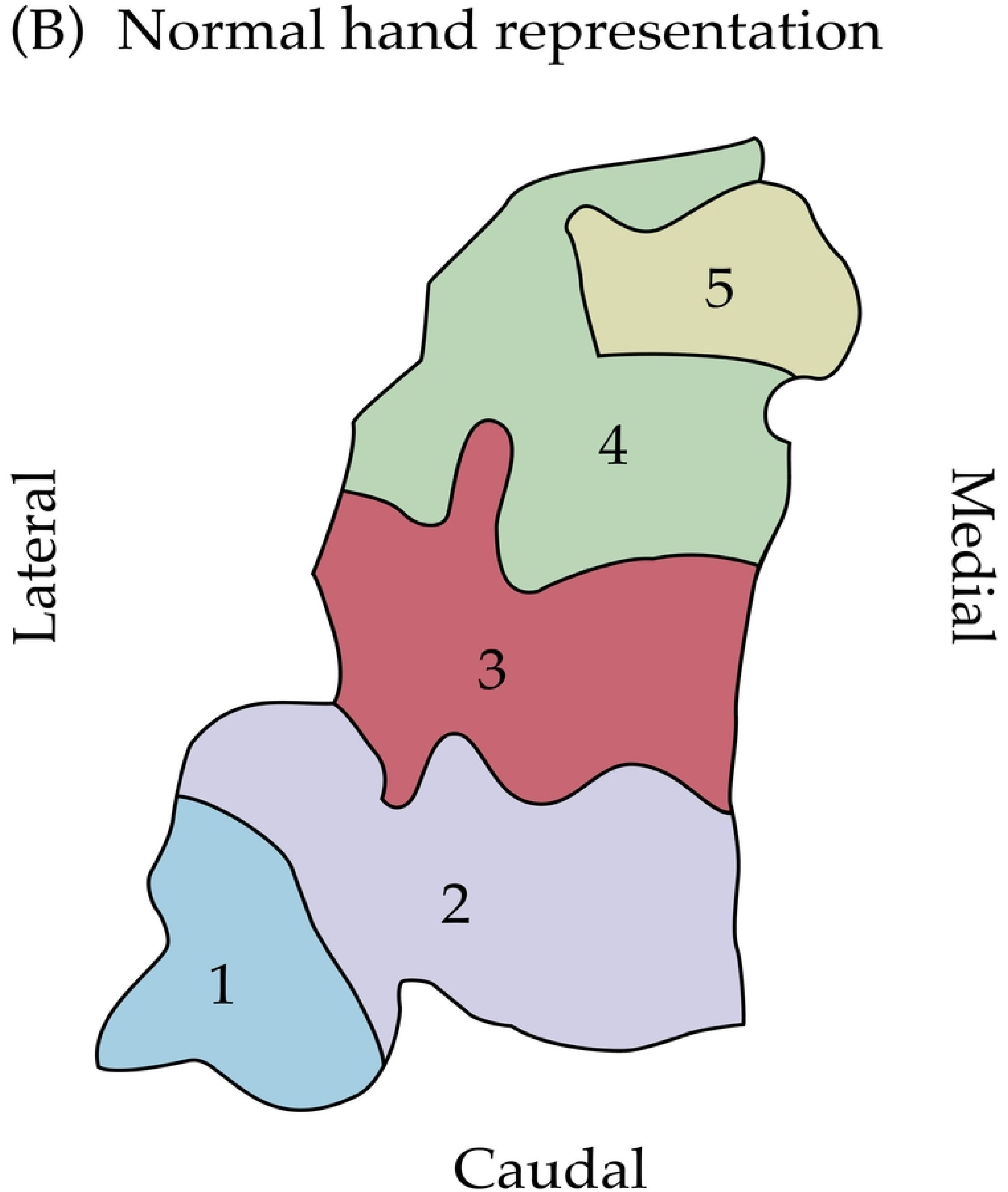

PF Stimulus
Parallel fibers
Record
Purkinje cell
Granule cell
CF Stimulus
Climbing fiber


(B)
Pair CF and PF
Parallel fiber
EPSP amplitude (mV)
7
6
5
4
3
0
–20
0
20
40
60
80
Time (minutes)

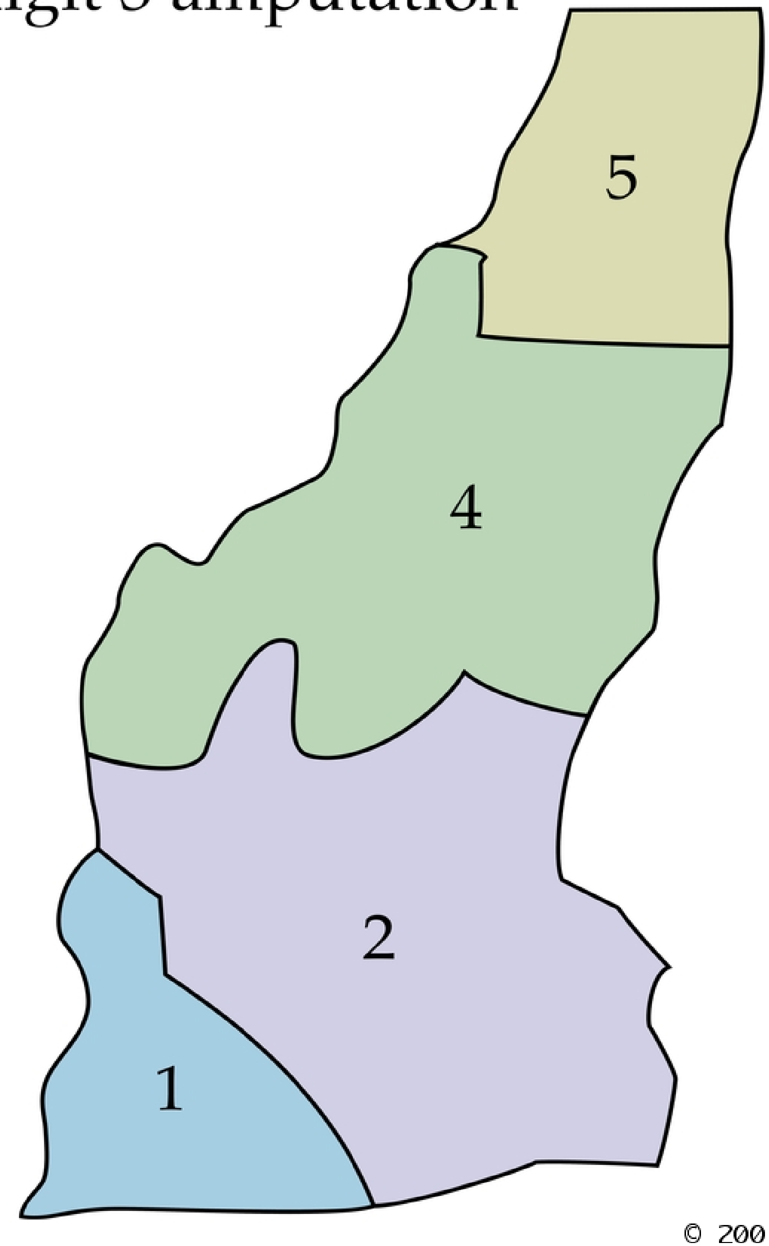

(C)
Climbing fiber
Parallel fiber
Purkinje cell dendritic spine
Presynaptic terminal of parallel fiber
Na+
Glutamate
mGluR
AMPA receptor
Phospholipase C
Long-term depression
PIP2
DAG
Dendritic spine
Activate PKC
IP3
Climbing fiber activity
Voltage-gated Ca2+ channel
Release Ca2+
Purkinje cell
Endoplasmic reticulum
Depolarizes Vm

Damage-induced alterations

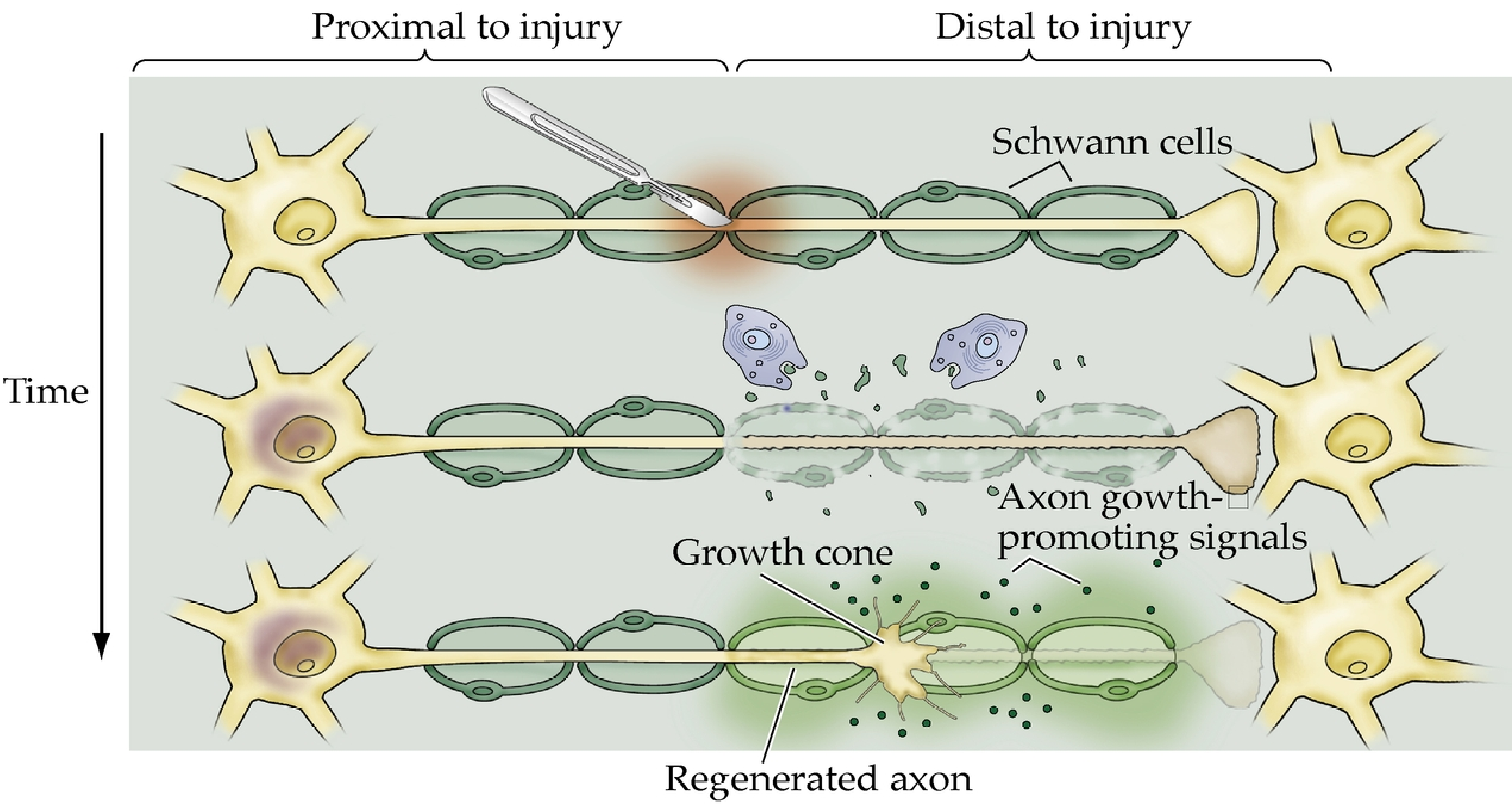

(A) Owl monkey brain
1
3b
Somatic sensory cortex
Hand representation


(B) Normal hand representation
5
4
3
2
1
Lateral
Medial
Caudal

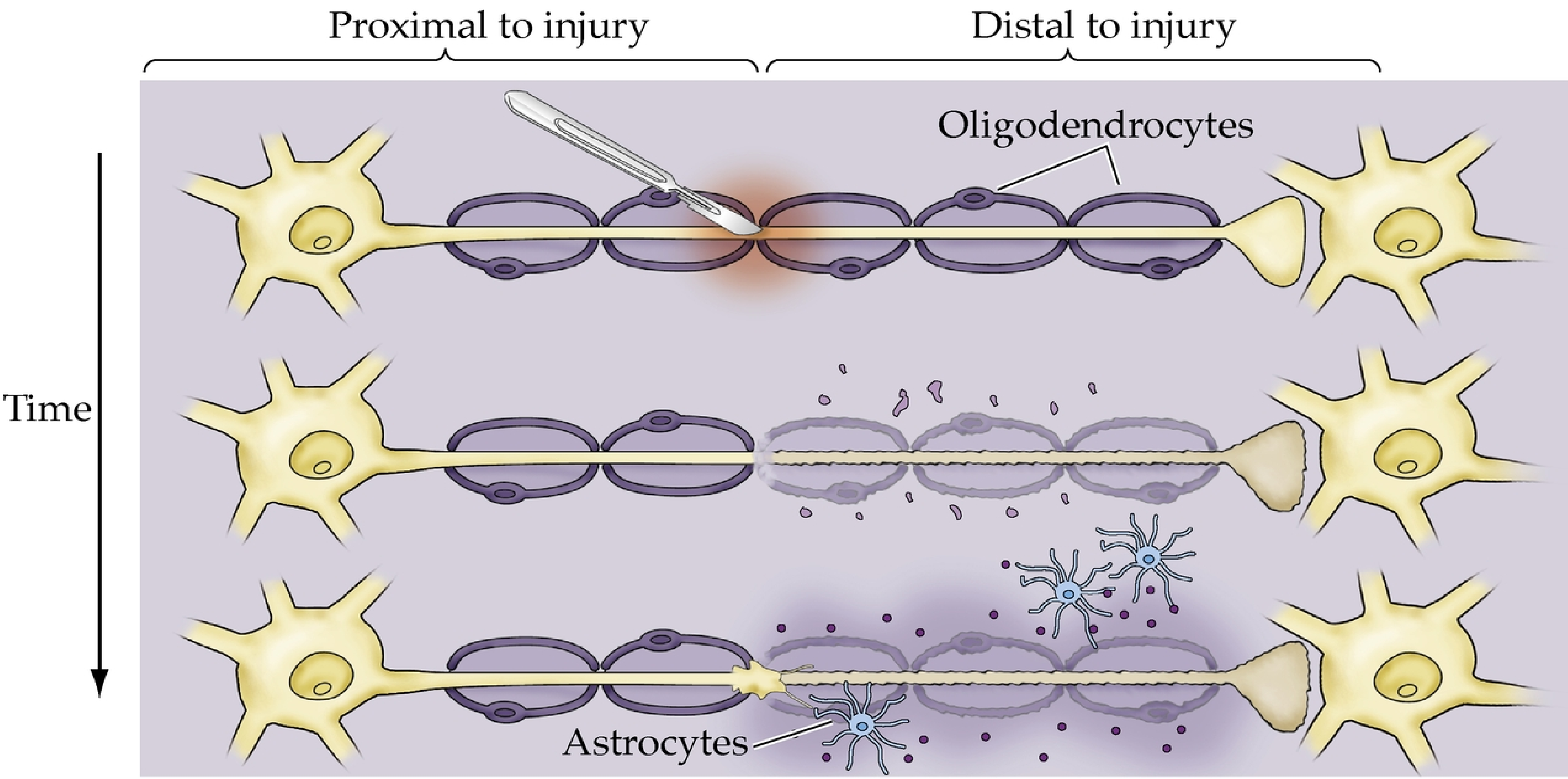
(C) Hand representation two months after digit 3 amputation



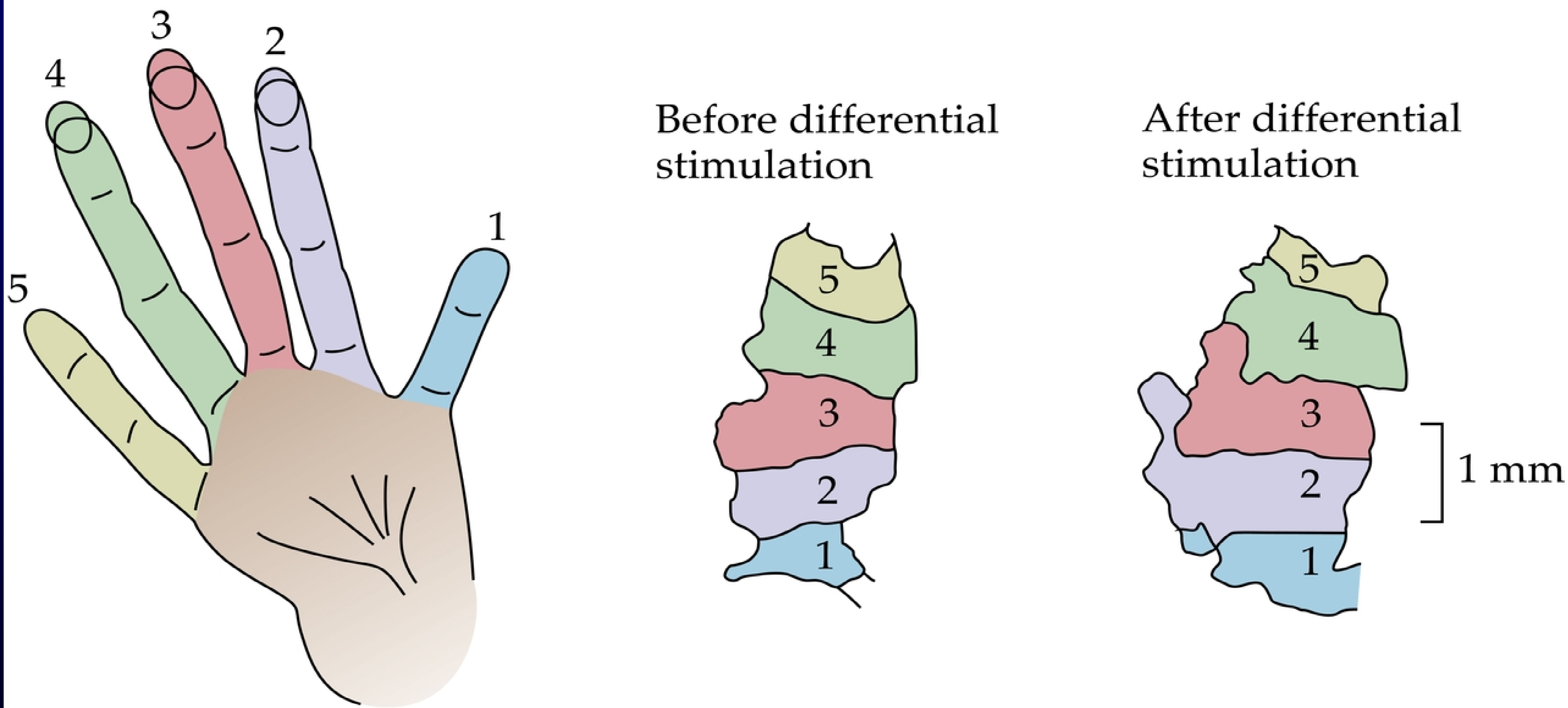
(A) Peripheral nervous system



(B) Central nervous system



Use-dependent alterations



4
3
2
1
5
Before differential stimulation
After differential stimulation
5
4
3
2
1
5
4
3
2
1
1 mm