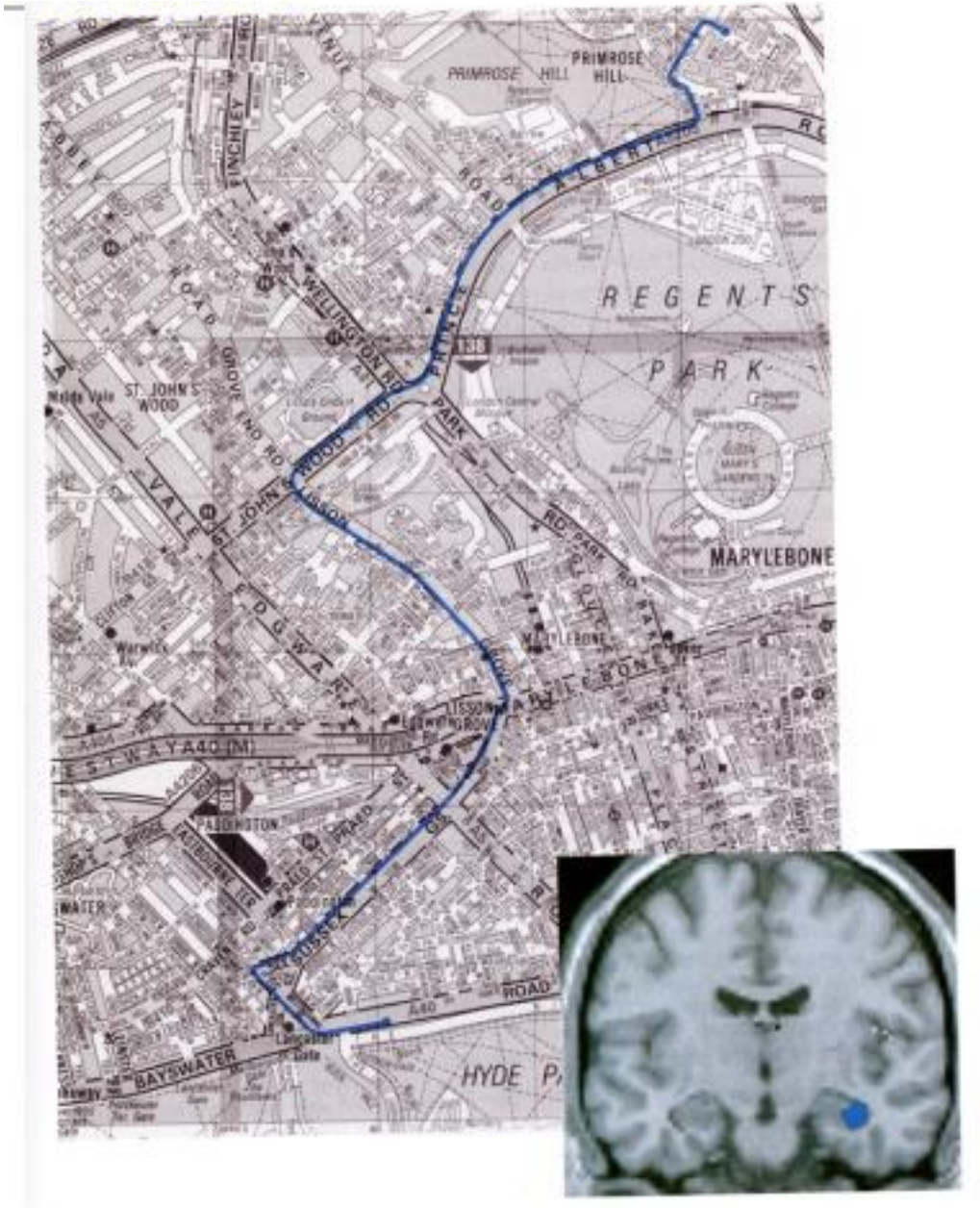
Molecular mechanisms of synaptic plasticity

WHY STUDYING HIPPOCAMPUS?

1. **DATA ON NORMAL AND LESIONATE HUMAN SUBJECTS**
2. **DATA ON ANIMALS IN SPACE TASKS (RADIAL MAZE , OPEN WATER)**
3. **HIPPOCAMPAL PLACE CELLS**
4. **LONG-TERM POTENTIATION**

1. IN HUMAN HIPPOCAMPUS IS ACTIVATED IN SPATIAL MEMORY TESTS (SEE IMAGE OBTAINED WITH THE PET OF THE BRAIN OF A LONDINIAN TAXIS WHILE IT IS IMAGINING TO TRAVEL A CERTAIN ITINERARY)



Navigation-related structural change in the hippocampi of taxi drivers

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Communicated by Brenda Milner, McGill University, Montreal, Canada, January 28, 2000 (received for review November 10, 1999)

Structural MRIs of the brains of humans with extensive navigation experience, licensed London taxi drivers, were analyzed and compared with those of control subjects who did not drive taxis. The posterior hippocampi of taxi drivers were significantly larger relative to those of control subjects. A more anterior hippocampal region was larger in control subjects than in taxi drivers. Hippocampal volume correlated with the amount of time spent as a taxi driver (positively in the posterior and negatively in the anterior hippocampus). These data are in accordance with the idea that the posterior hippocampus stores a spatial representation of the environment and can expand regionally to accommodate elaboration of this representation in people with a high dependence on navigational skills. It seems that there is a capacity for local plastic change in the structure of the healthy adult human brain in response to environmental demands.

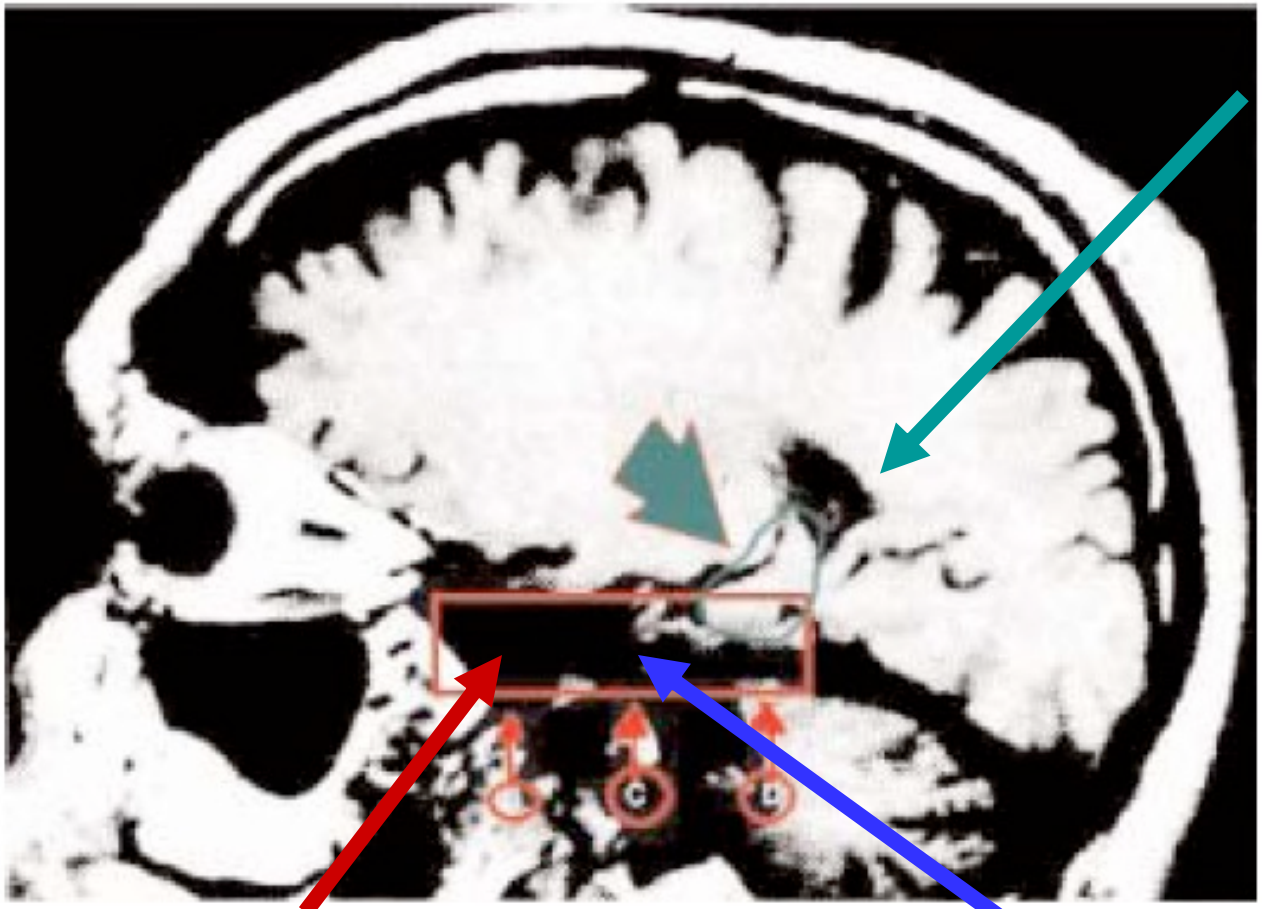
UNA PARTE DELL'IPPOCAMPO DI TASSISTI ESPERTI (LA PARTE POSTERIORE) RISULTA ESSERE PIU' ESTESA DI QUELLA DI UN GRUPPO DI CONTROLLO DI NON-TASSISTI = IL VOLUME IPPOCAMPALE CORRELA CON L'AMMONTARE DI ESPERIENZA DI NAVIGAZIONE SPAZIALE.

A CLINICAL CASE STUDY: H.M.

- H. M. had always suffered from epileptic seizures.
- When he was 27, doctors decided that the only way to intervene on his drug-resistant epilepsy was through a surgical operation:
- the amygdala, the uncus, the hippocampal gyrus and the two anterior parts of the hippocampus were removed from his brain.

CLINICAL CASE: H.M.

MNR: H.M.



caudal region of t
hippocampus,
Only remained
intact

amigdala

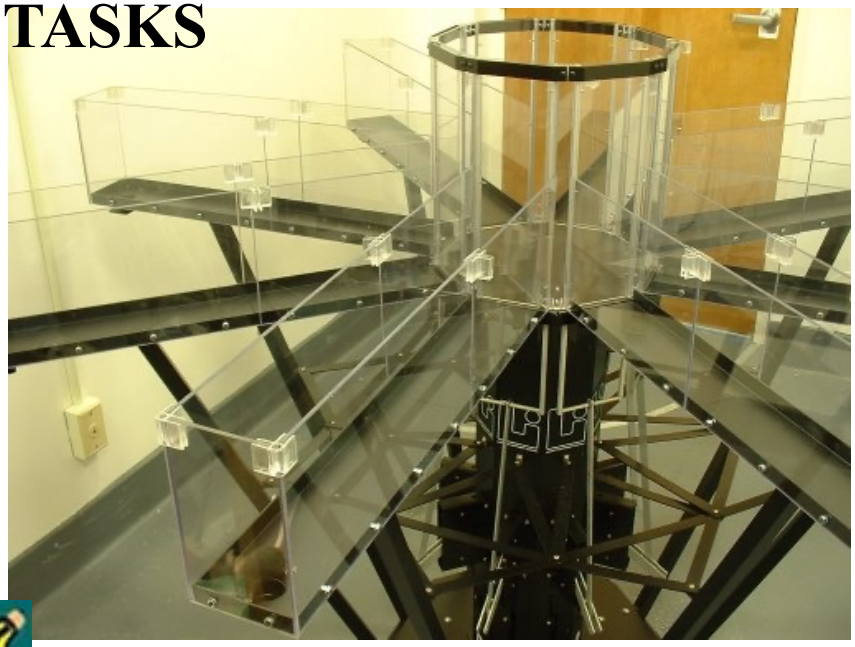
rostral part of the hippocampus

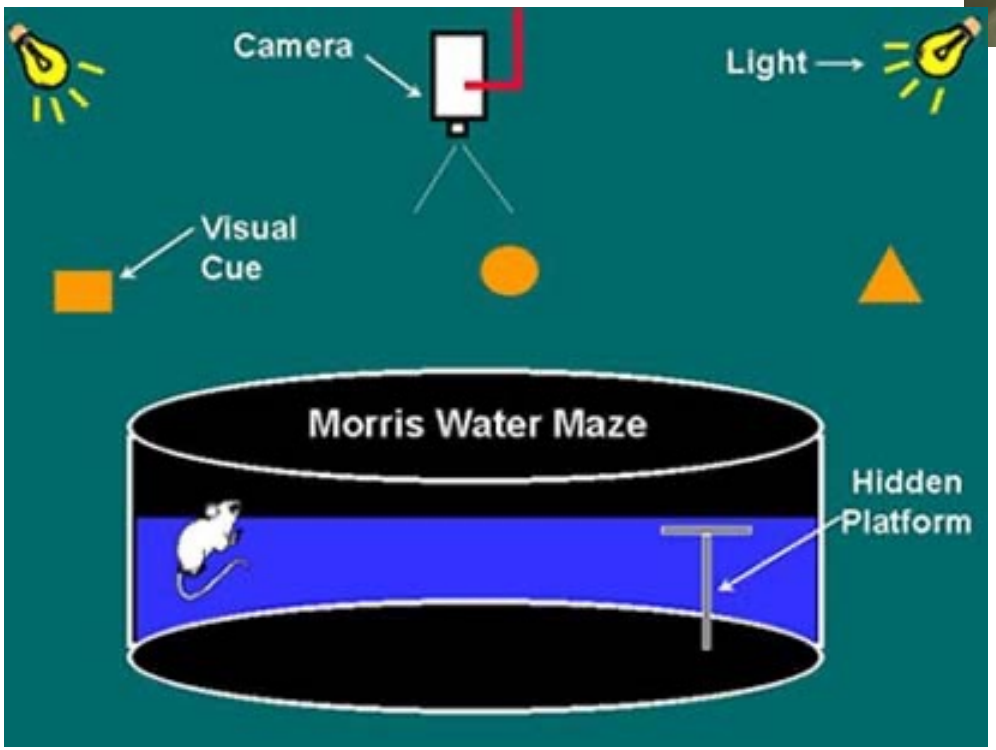
A CLINICAL CASE STUDY: H.M.

- Memory problems diagnosed systematically about two years after surgery
- When asked if he knew what day it was, he replied that it was a day in March 1953.
- His memories stopped at the day of the intervention that H. M. denies had ever taken place.
- His IQ was not low.
- It seemed that along with his medial temporal lobe the doctors had also removed his ability to form new memories.
- Serious loss of short-term declarative memory.
- Of his memory H.M. he had kept only the memories before the surgery.

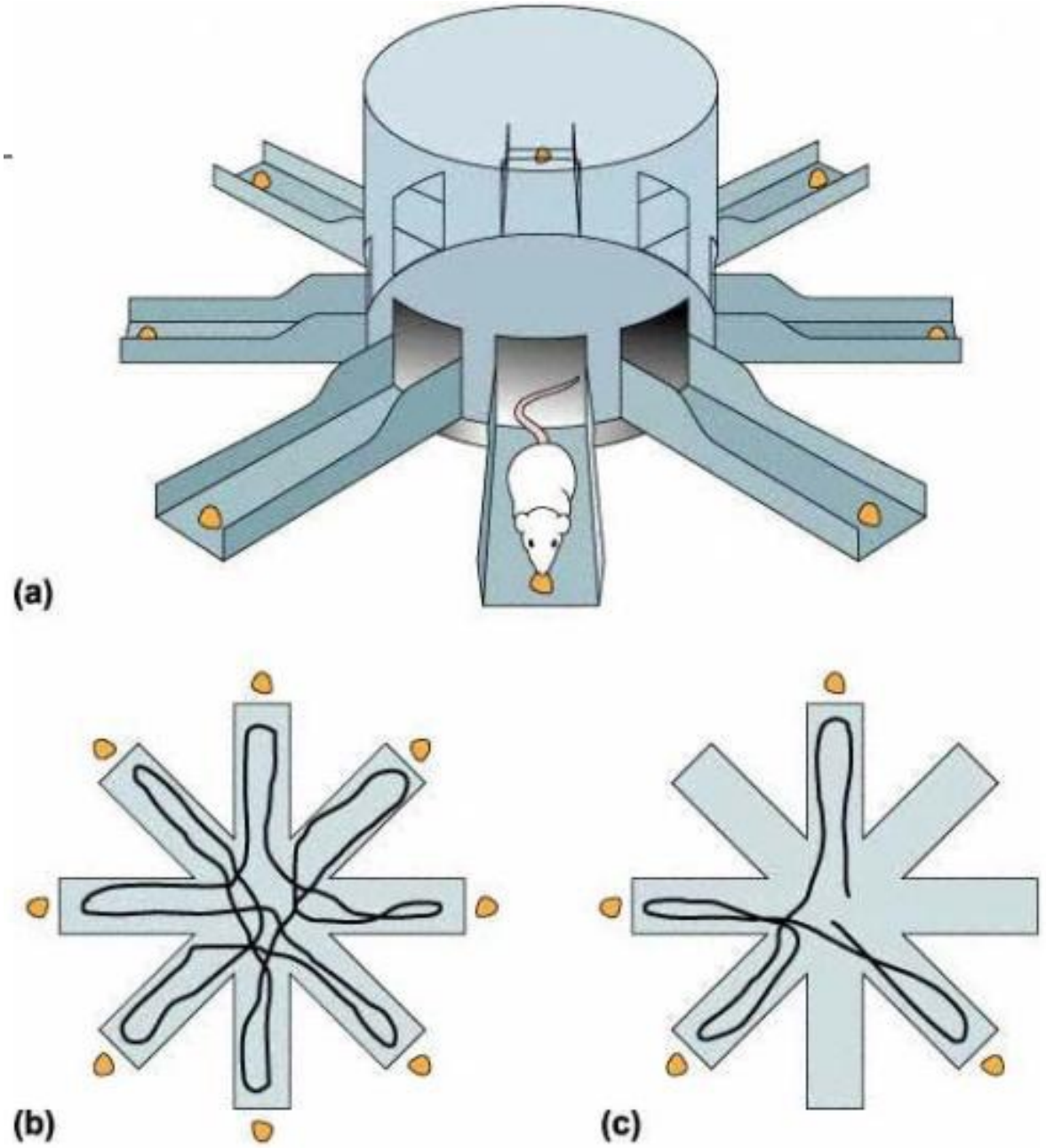
DATA ON ANIMALS IN SPACE TASKS

T-maze
Radial maze
Water maze





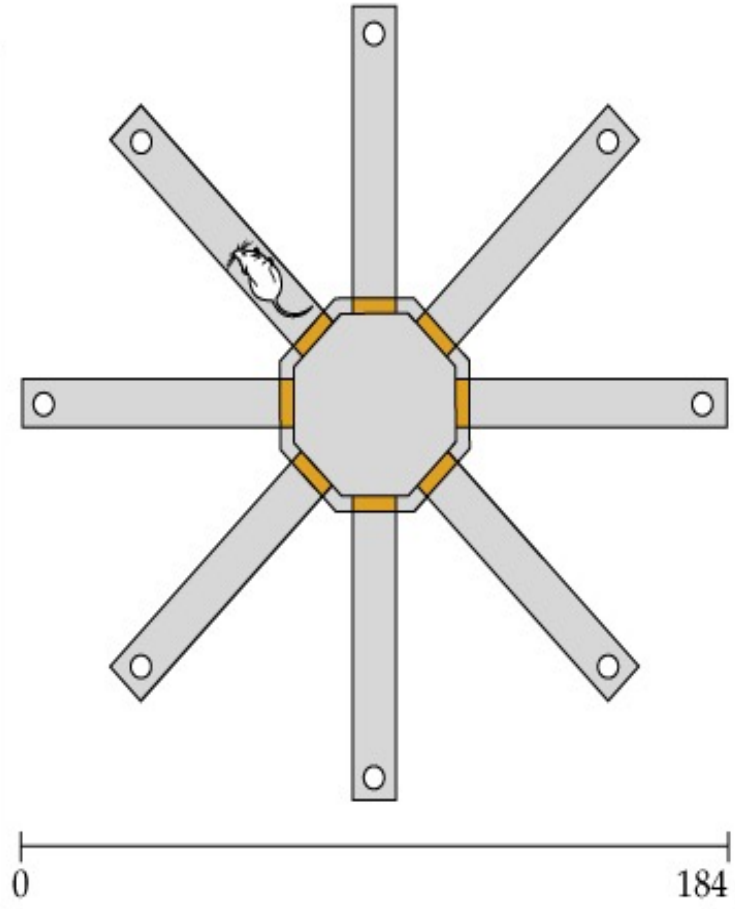
2. IPPOCAMPUS AND TASKS OF SPACE LEARNING IN ANIMAL MODELS (THE RADIAL MAZE)

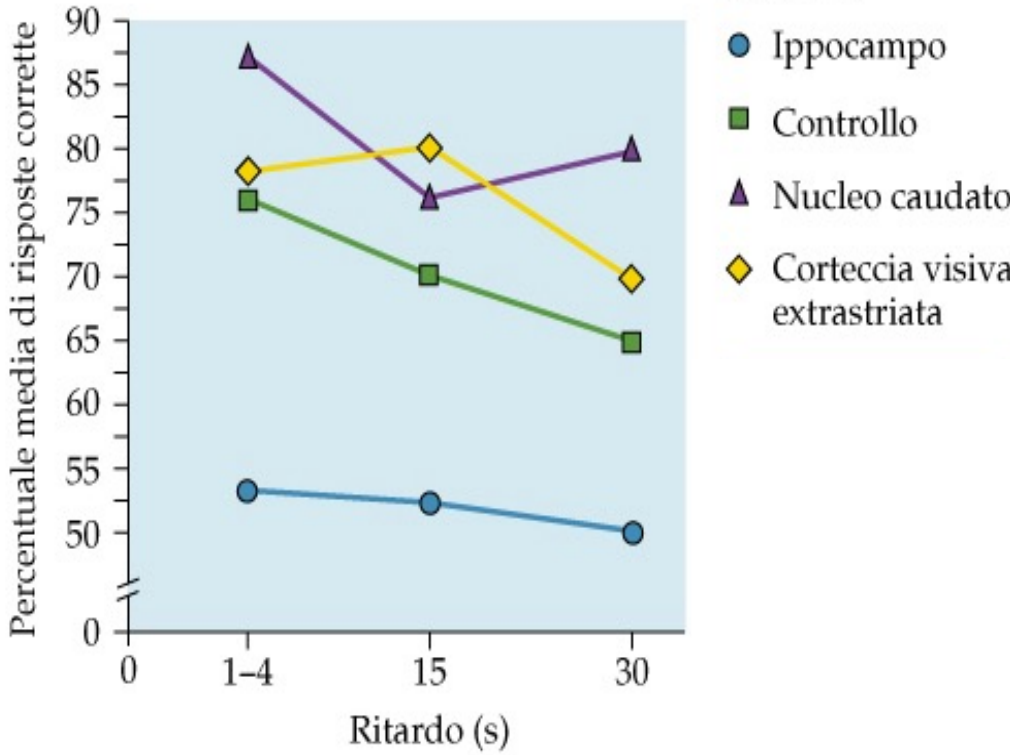


The performance of injured rats is inadequate in the recovery strategy, but performance in an implicit version of the task is not affected.

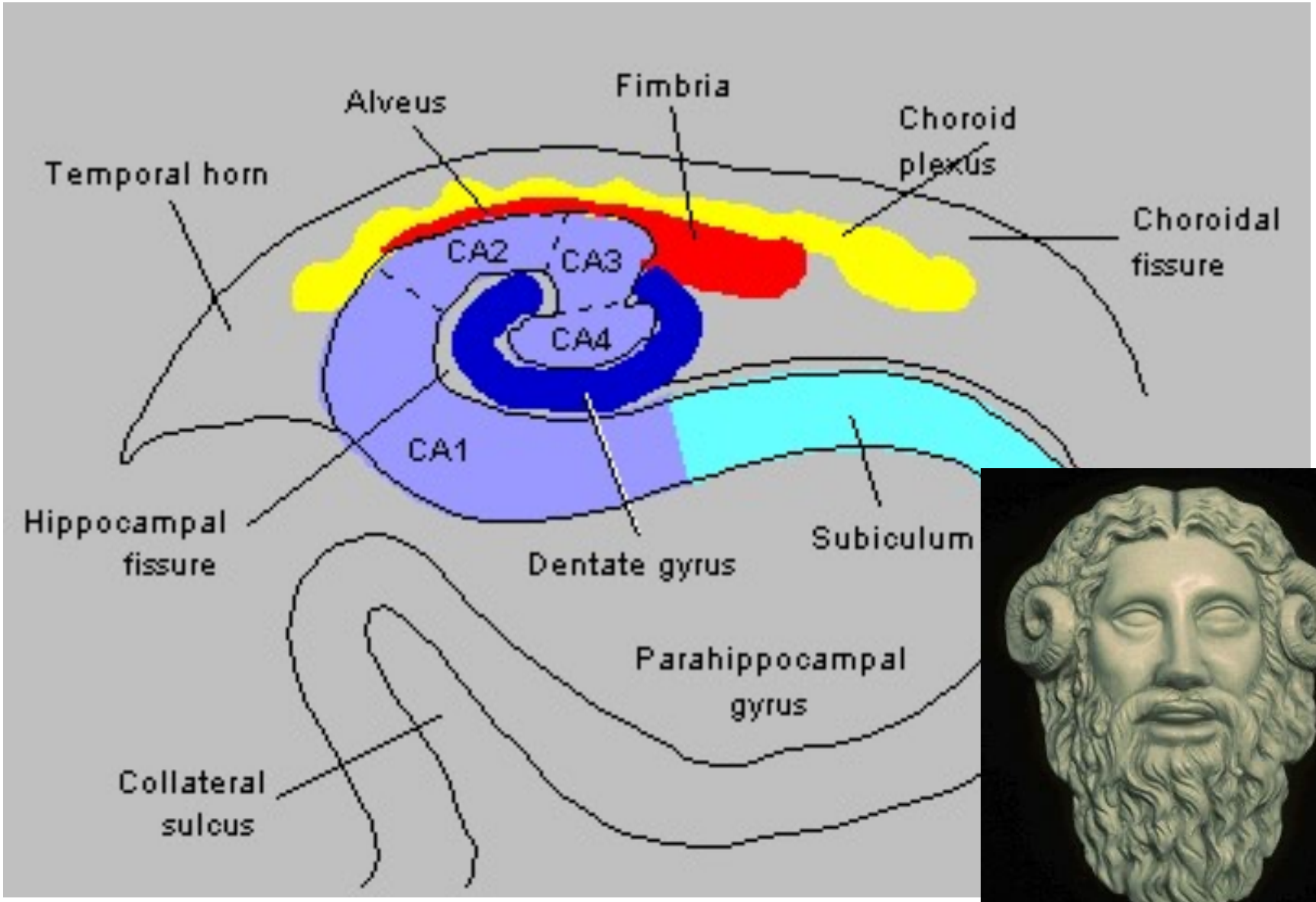
d. HIPPOCAMPAL LESIONS CORRELATE WITH DEFICIT OF WORKING MEMORY IN SPATIAL TASKS

a) Memoria di riconoscimento di localizzazioni spaziali



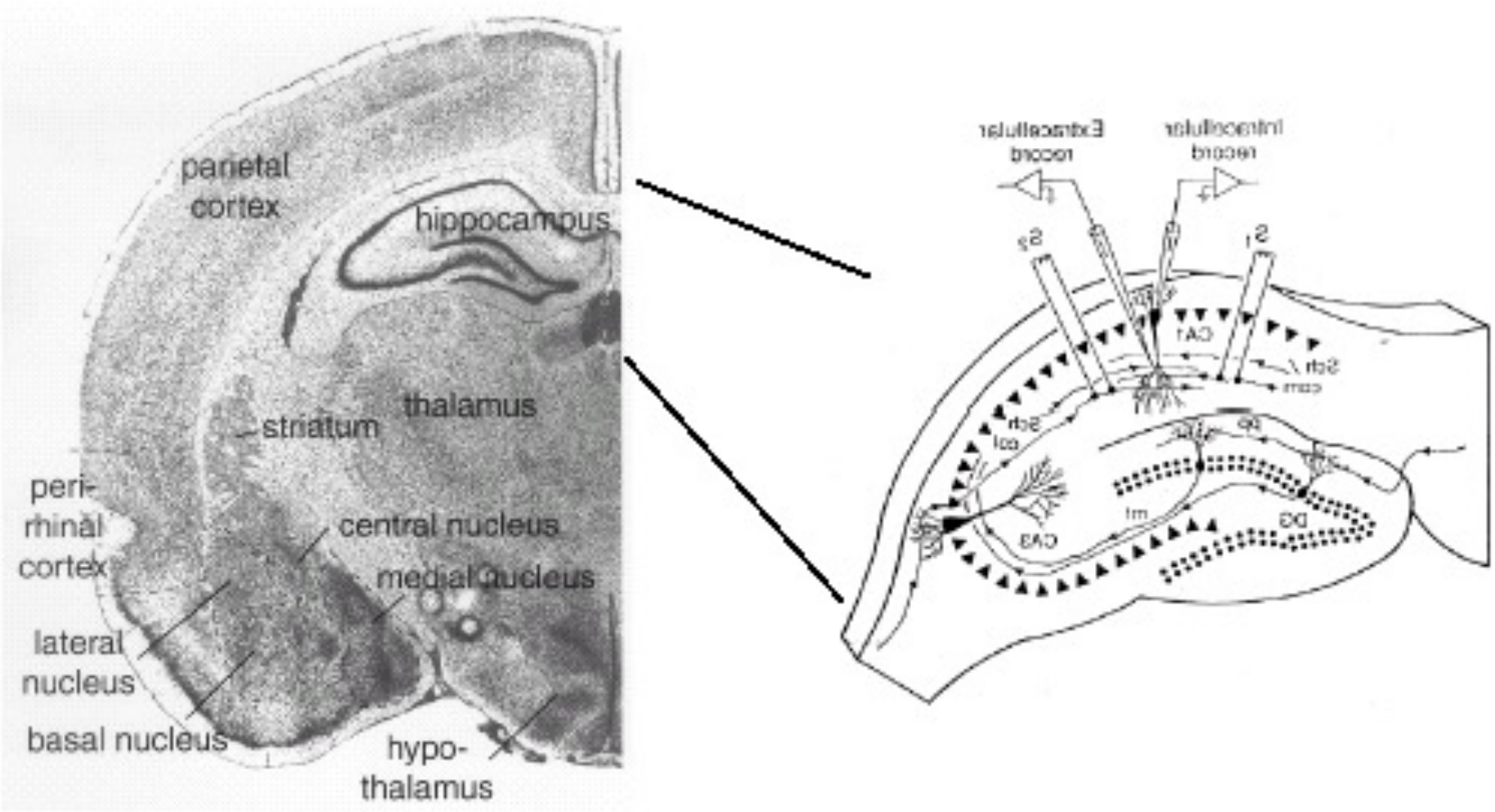


HIPPOCAMPAL ANATOMY



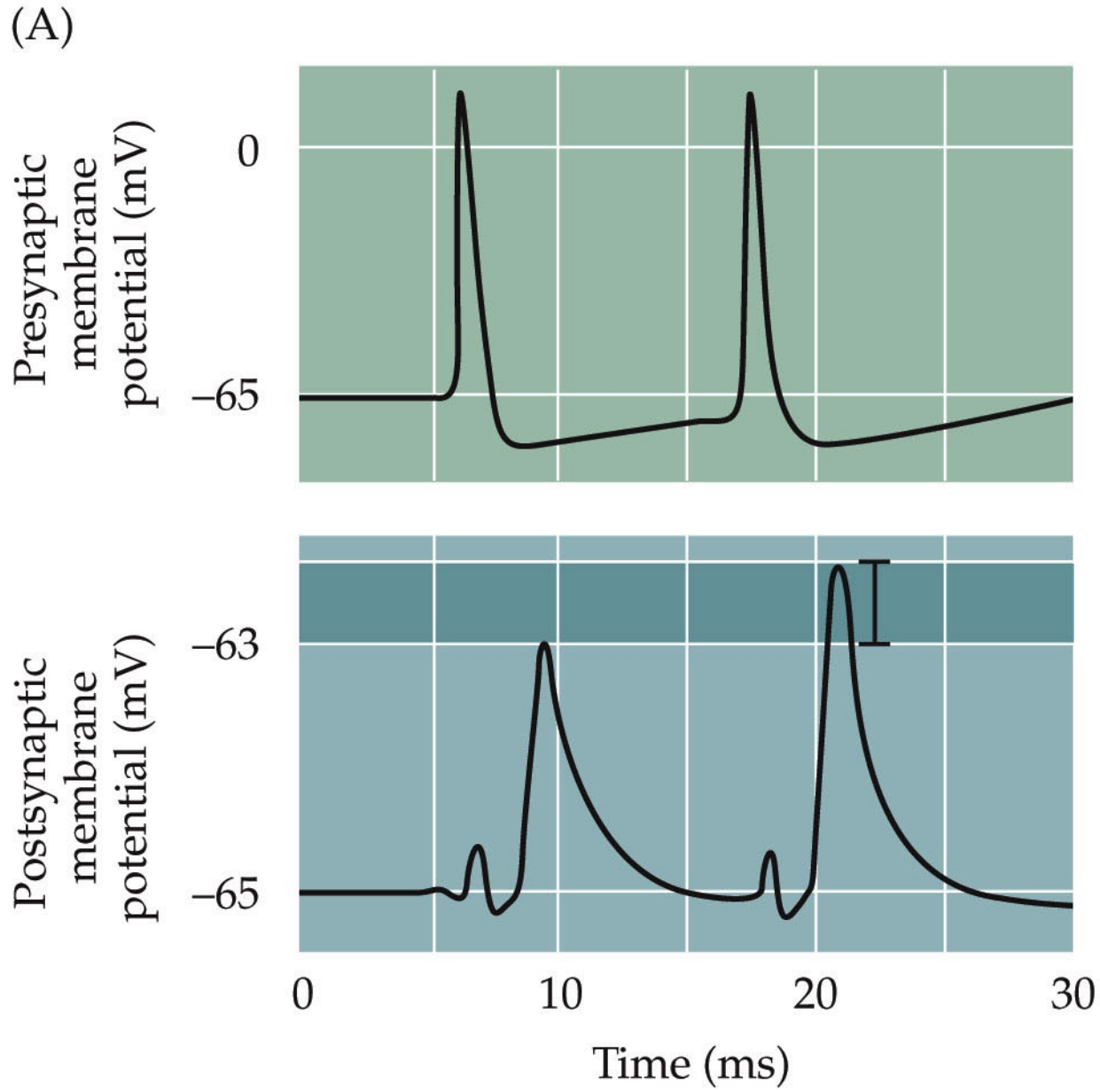
THE HIPPOCAMPUS

Learning in a dish: the hippocampus slice

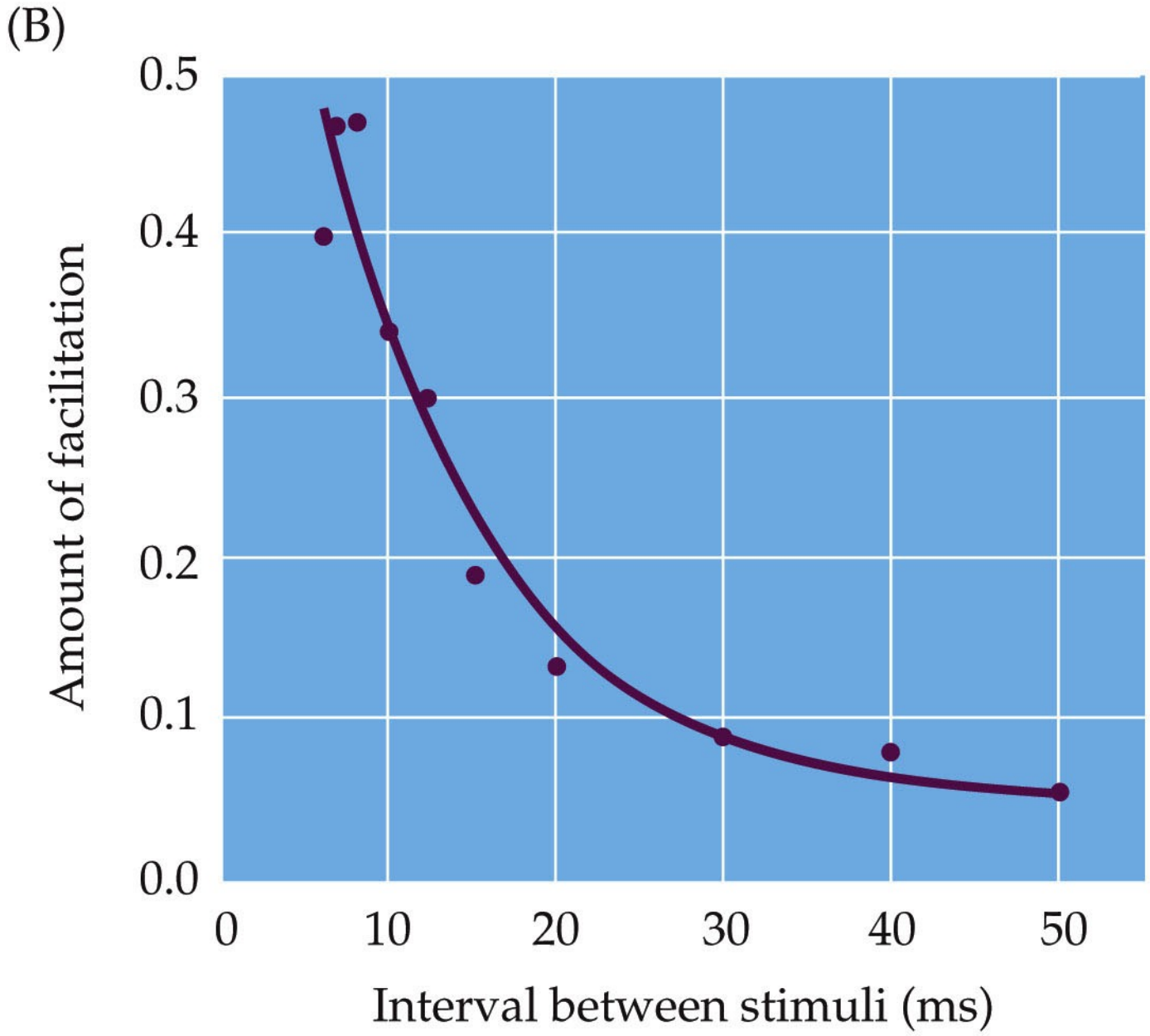


Bliss and Lomo (1973)

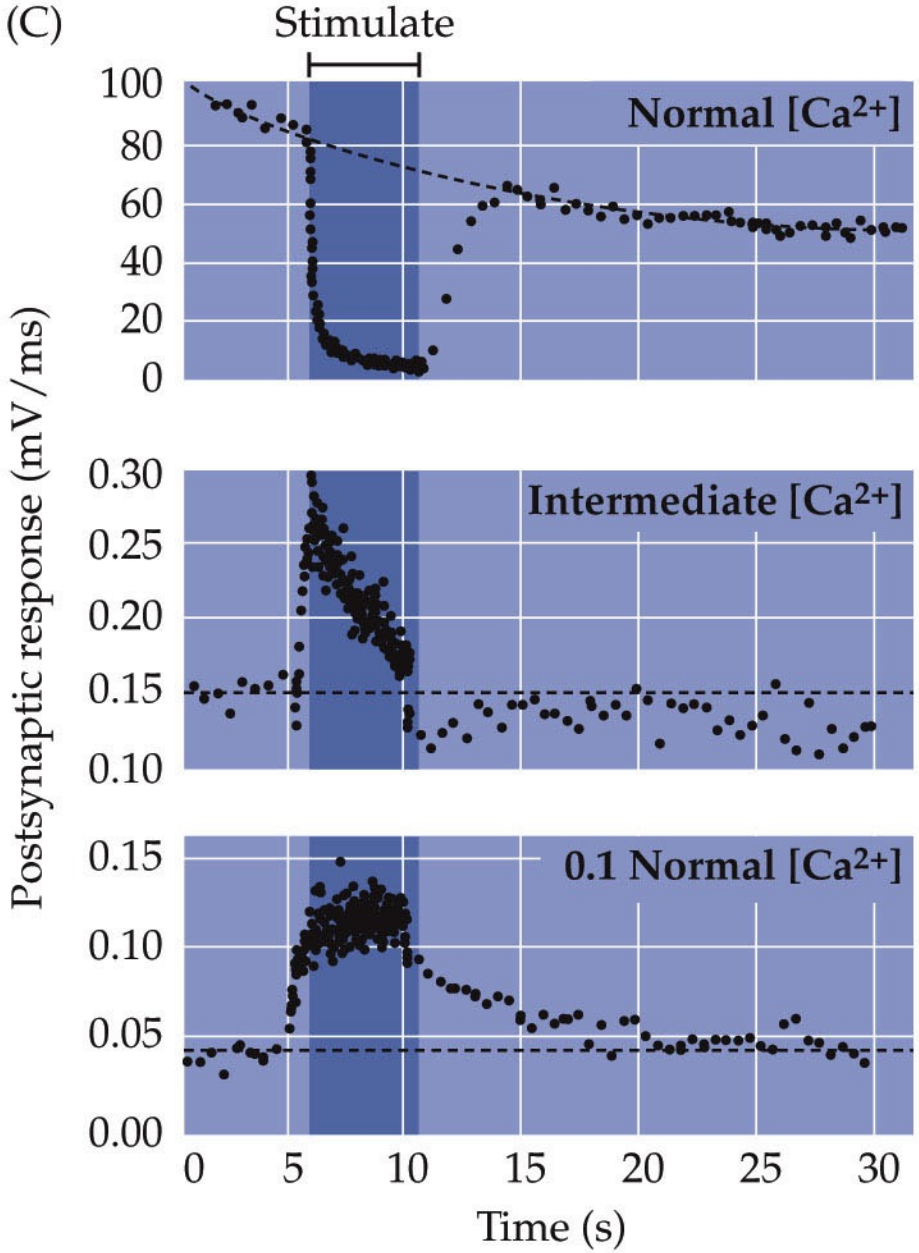
Forms of short-term synaptic plasticity: synaptic facilitation



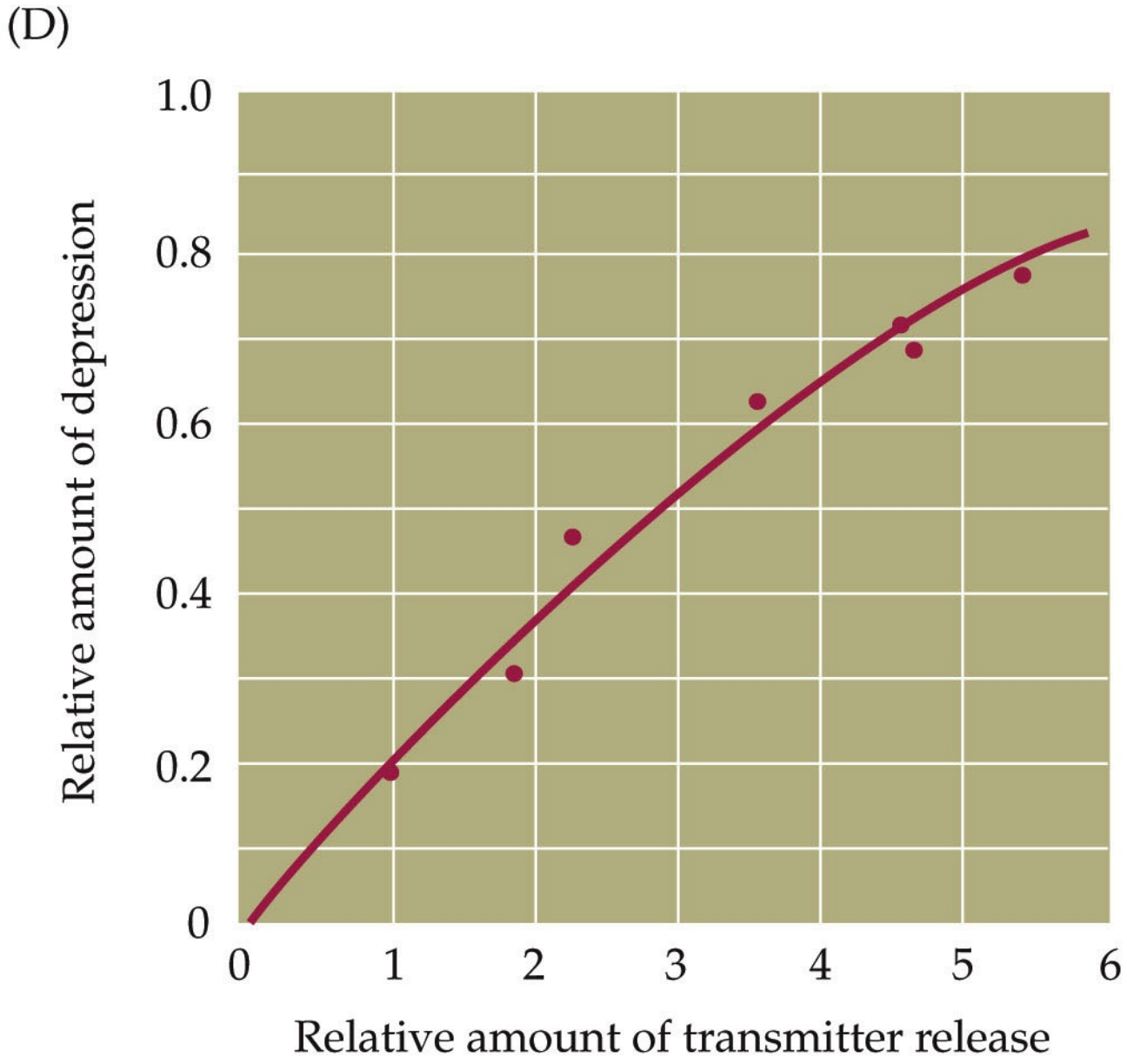
Dependence of facilitation on spike interval



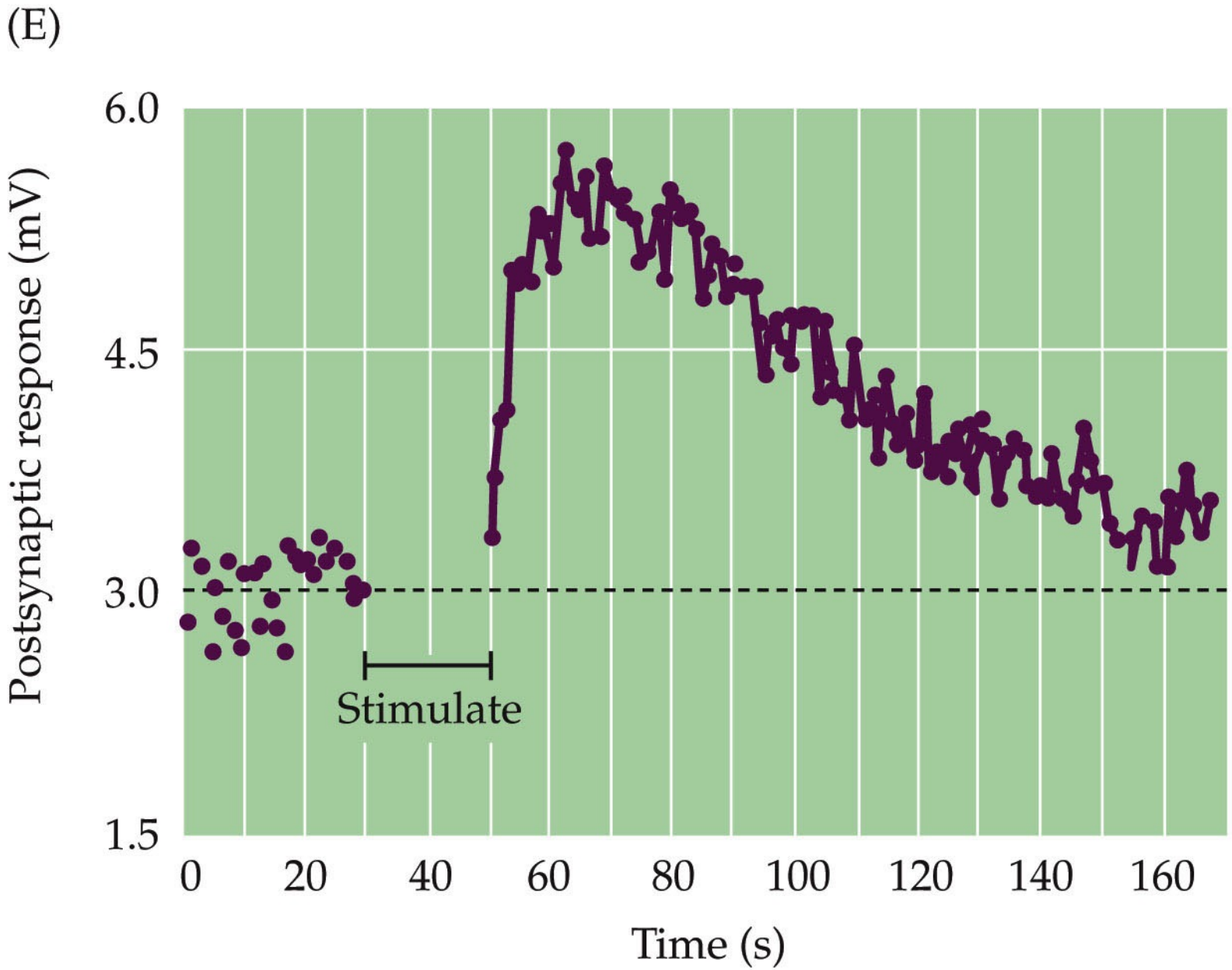
Synaptic depression & augmentation



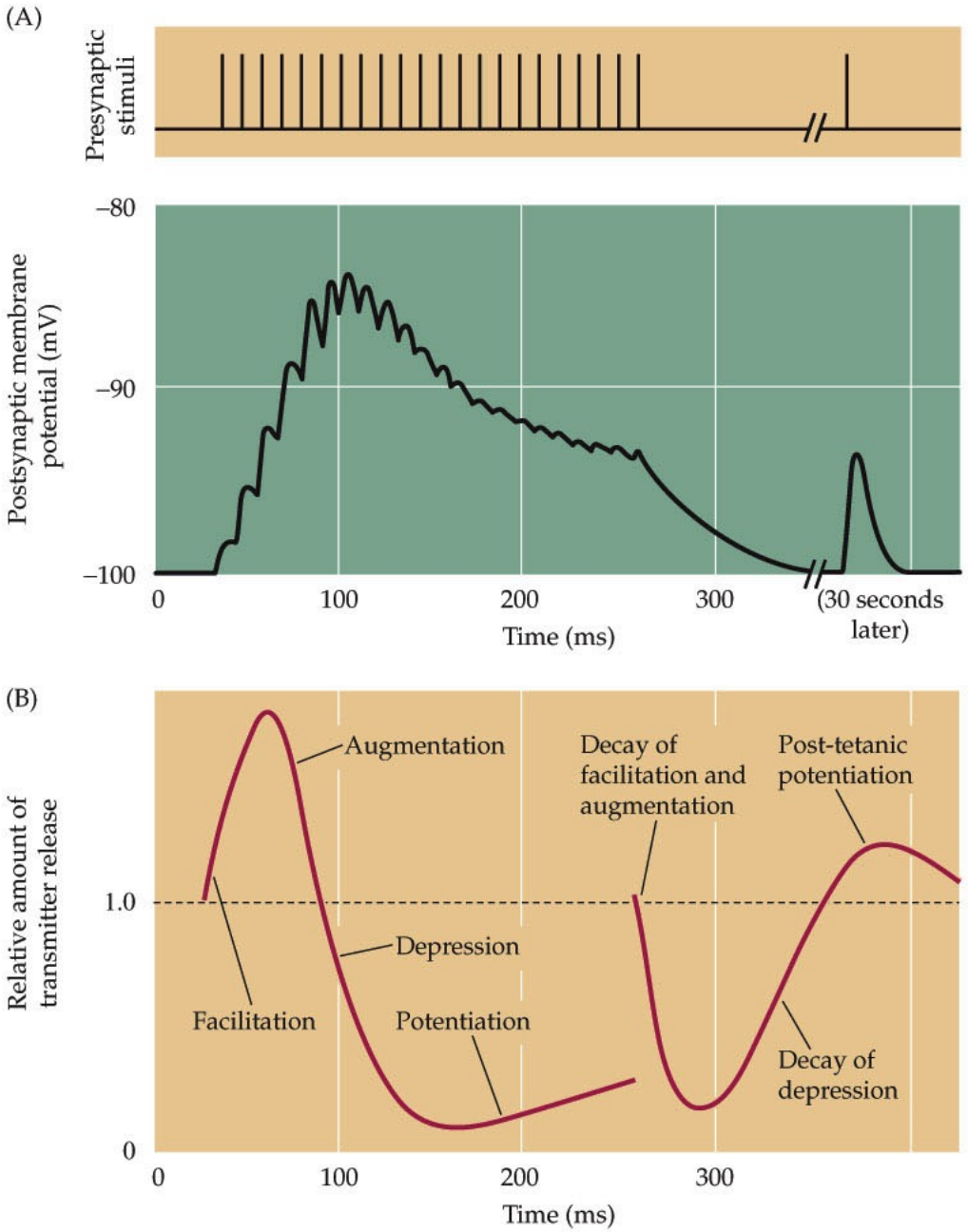
Dependence of synaptic depression on prior transmitter release



Postsynaptic Potentiation (PTP)



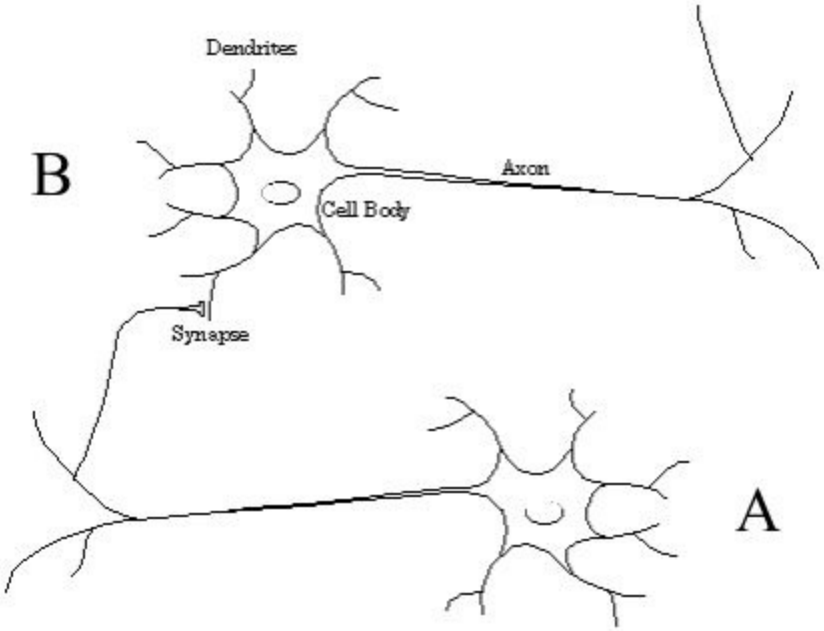
Short-term plasticity at the NMJ



Hebb's Postulate

"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."

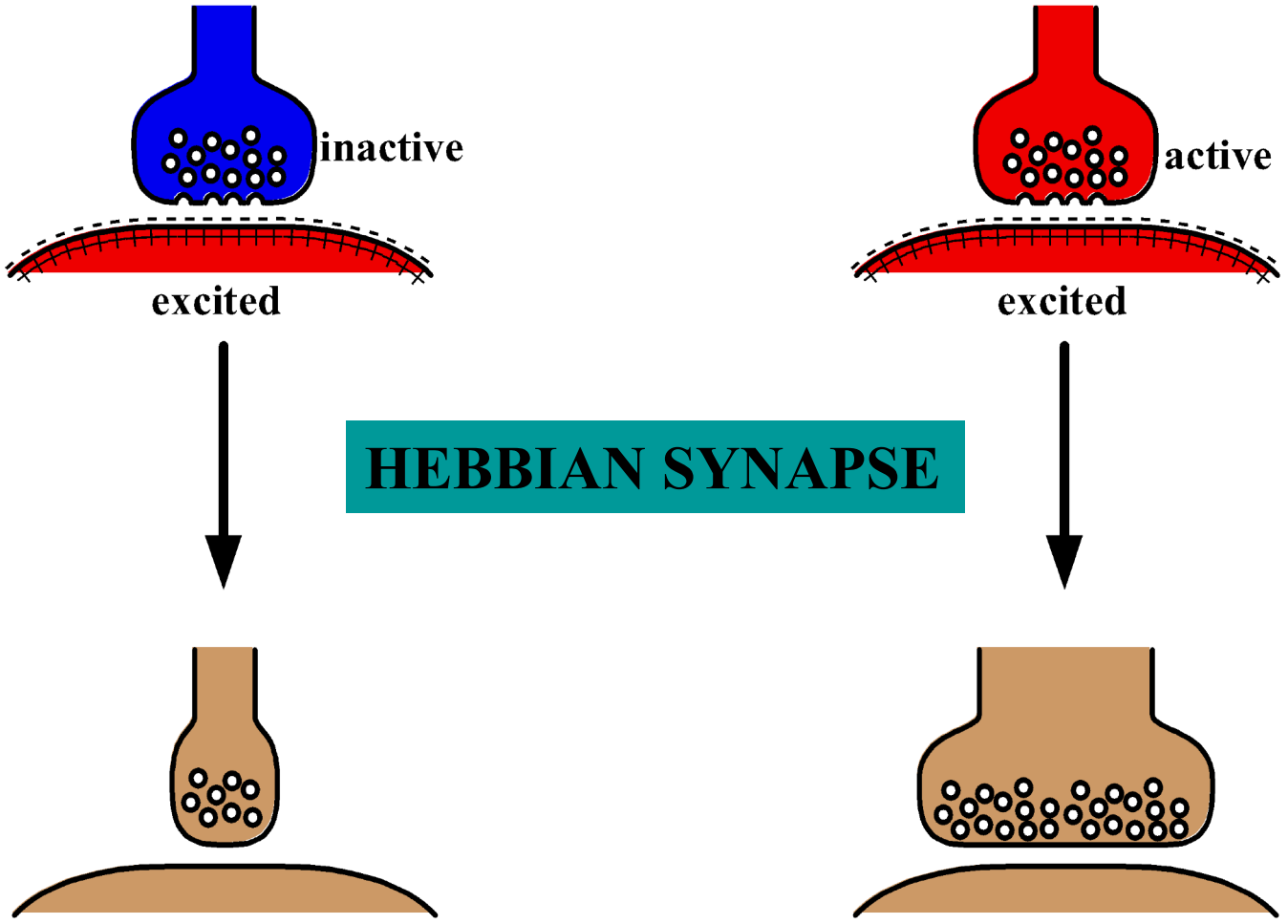
D. O. Hebb, 1949



Hebbian Learning Rule (1949)

"Cells that fire together wire together."

The Hebbian Learning Rule is a learning rule that specifies how much the weight of the connection between two units should be increased or decreased in proportion to the product of their activation. The rule builds on Hebbs's 1949 learning rule which states that the connections between two neurons might be strengthened if the neurons fire simultaneously.


inactive
excited
active
excited
HEBBIAN SYNAPSE
Synapse
Weakened
Synapse
Strengthened

SYNAPTIC PLASTICITY: LONG TERM POTENTIATION AND LONG-TERM INHIBITION (LTP & LTD)

 LTP and LTD are phenomena induced by the activation of NMDA receptors and by appropriate modifications of calcium concentrations within the postsynaptic neuron

 LTP is a form of prolonged facilitation, in which the response of the postsynaptic cell to a constant stimulus is increased over a period of time ranging from hours to weeks

 When the NMDA channels are opened and Ca ++ enters the cells postsynaptic cascade of seconds messengers takes place

 Following the activation of these pathways, the postsynaptic cellreleases a paracrine substance that acts on the presynaptic cell to increase the release of glutammmate

 In addition there is an increase in the number of AMPA receptors for glutamate on the postsynaptic membrane

Activity-dependent changes in synaptic strength -Hebb

Experience activates sensory pathways to convey information to the CNS

Short-term increases in neuronal activity in distributed reverberating loops

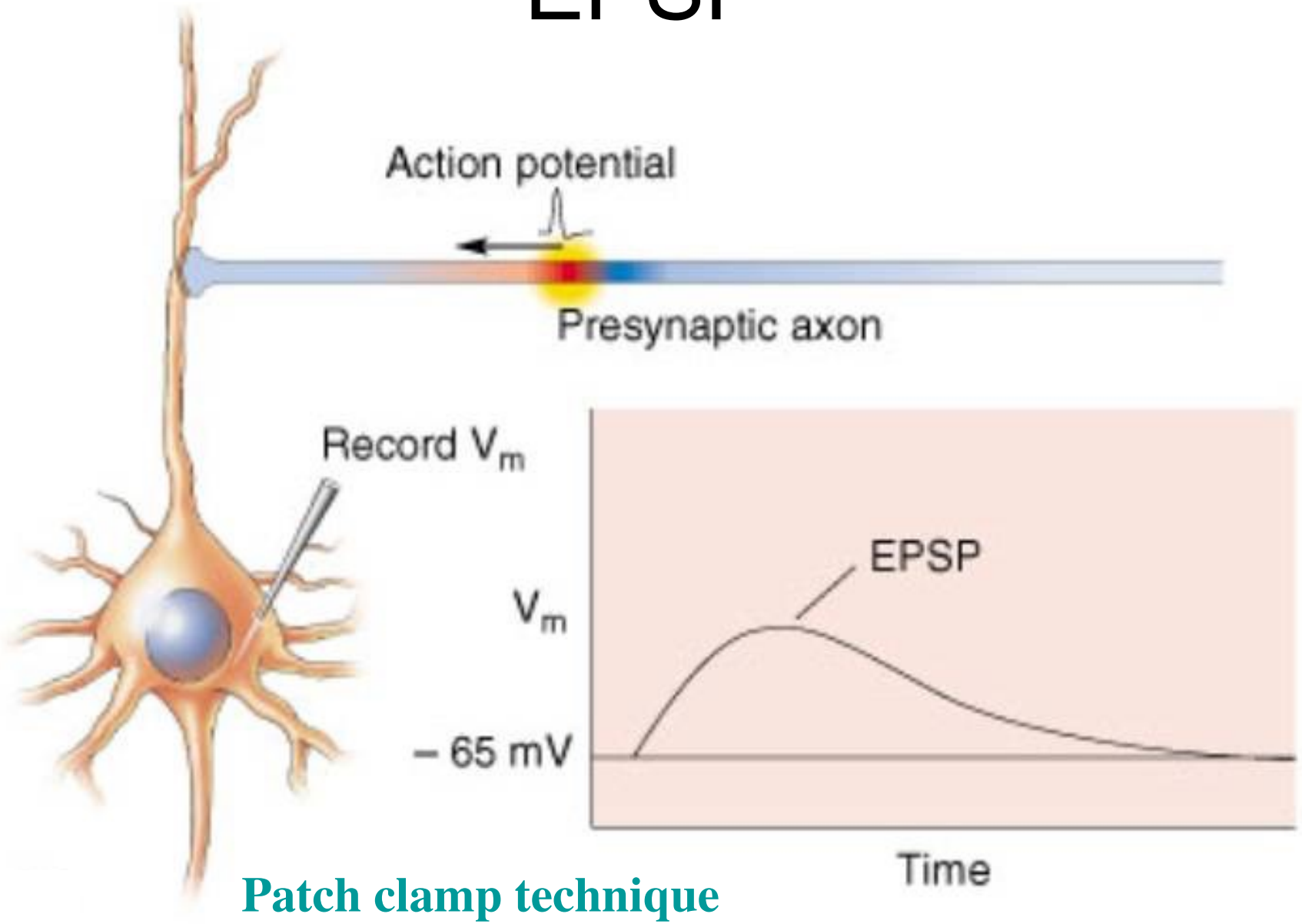
If reverberating activity is maintained, it induces structural changes in synapses, resulting in alterations in the strength of synaptic connections

Changes in synaptic strength facilitate the transmission of specific information

Alterations in information transmission through distributed networks affect subsequent behavioral expression

Long-Term Potentiation

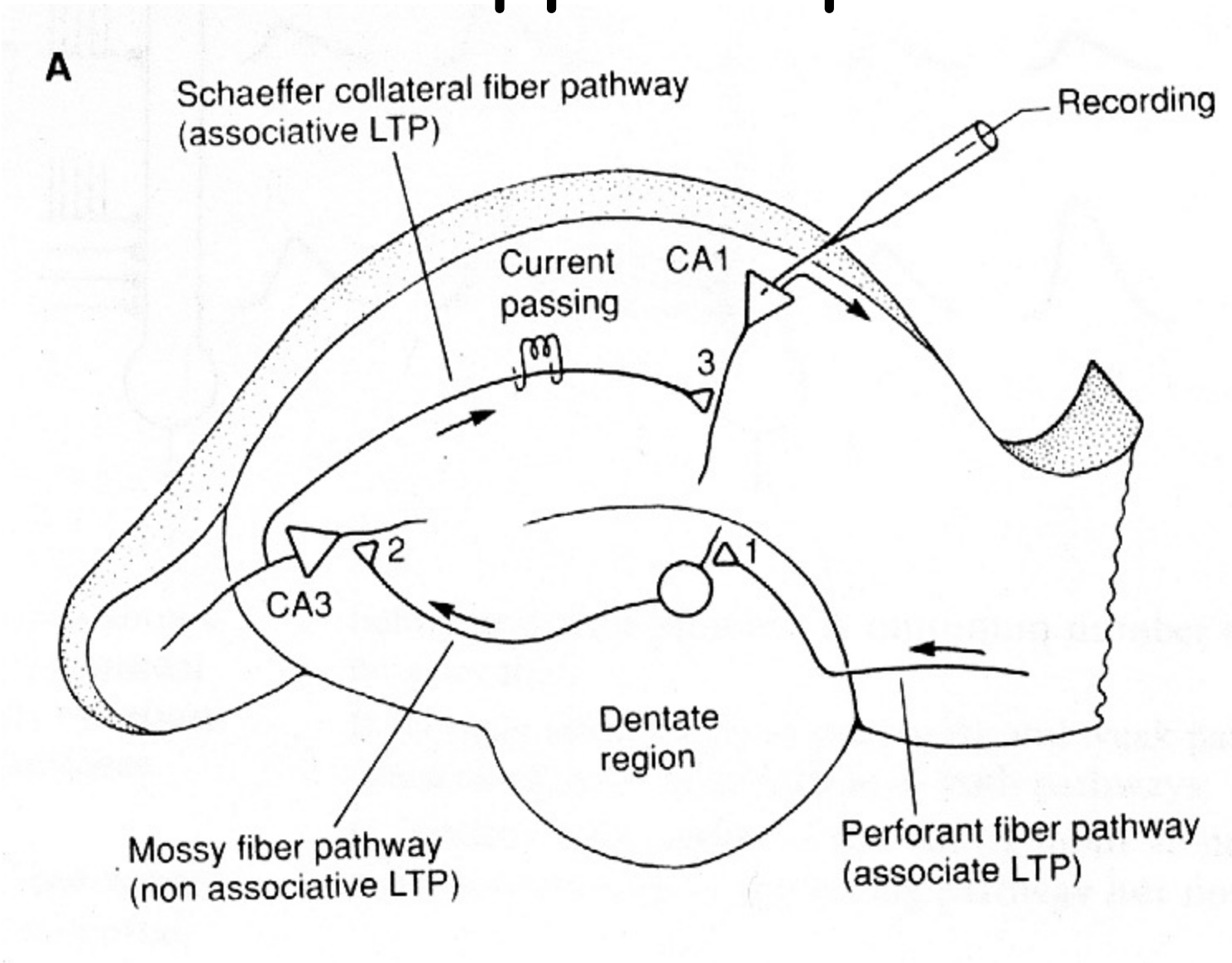
EPSP



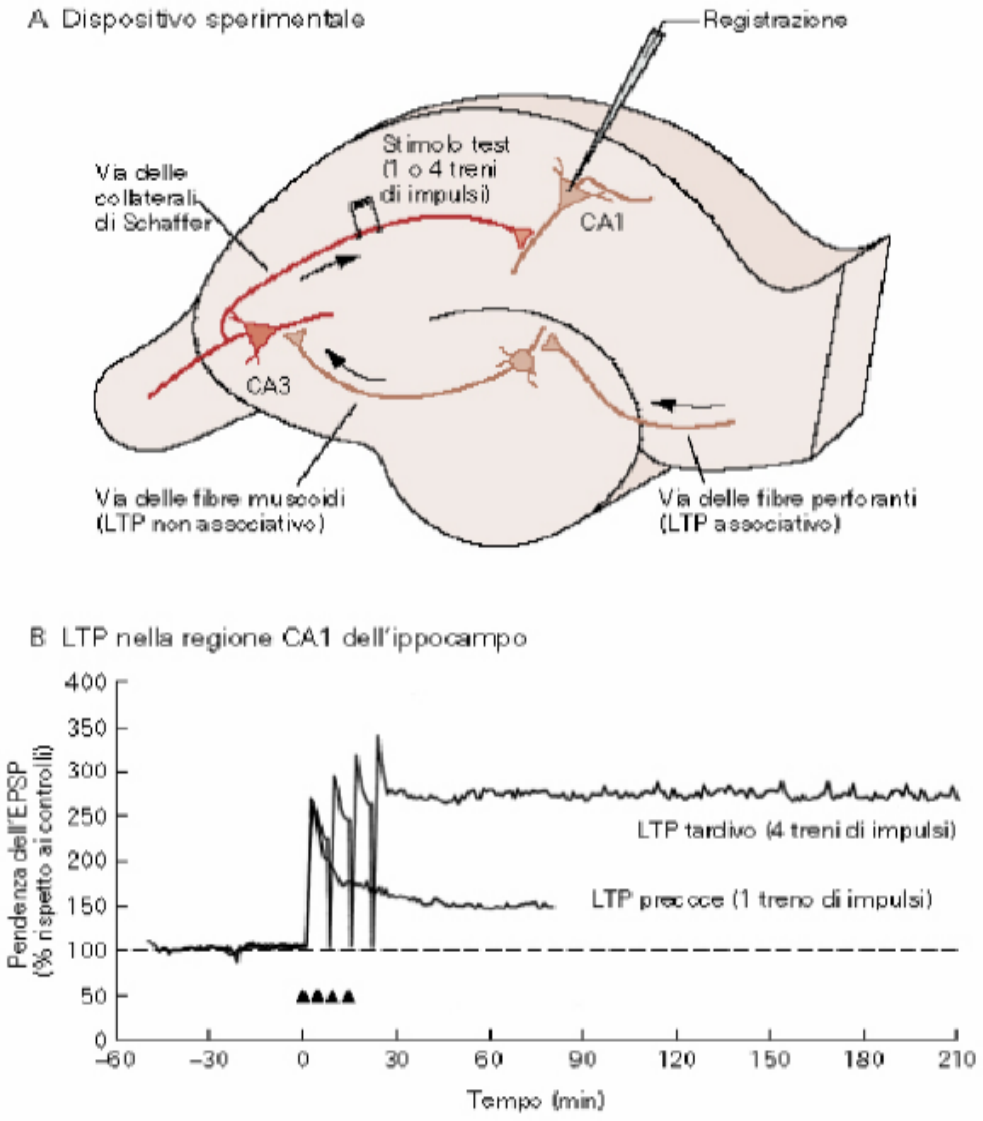
Patch clamp technique

AMPA AND NMDA RECEPTORS

Hippocampus

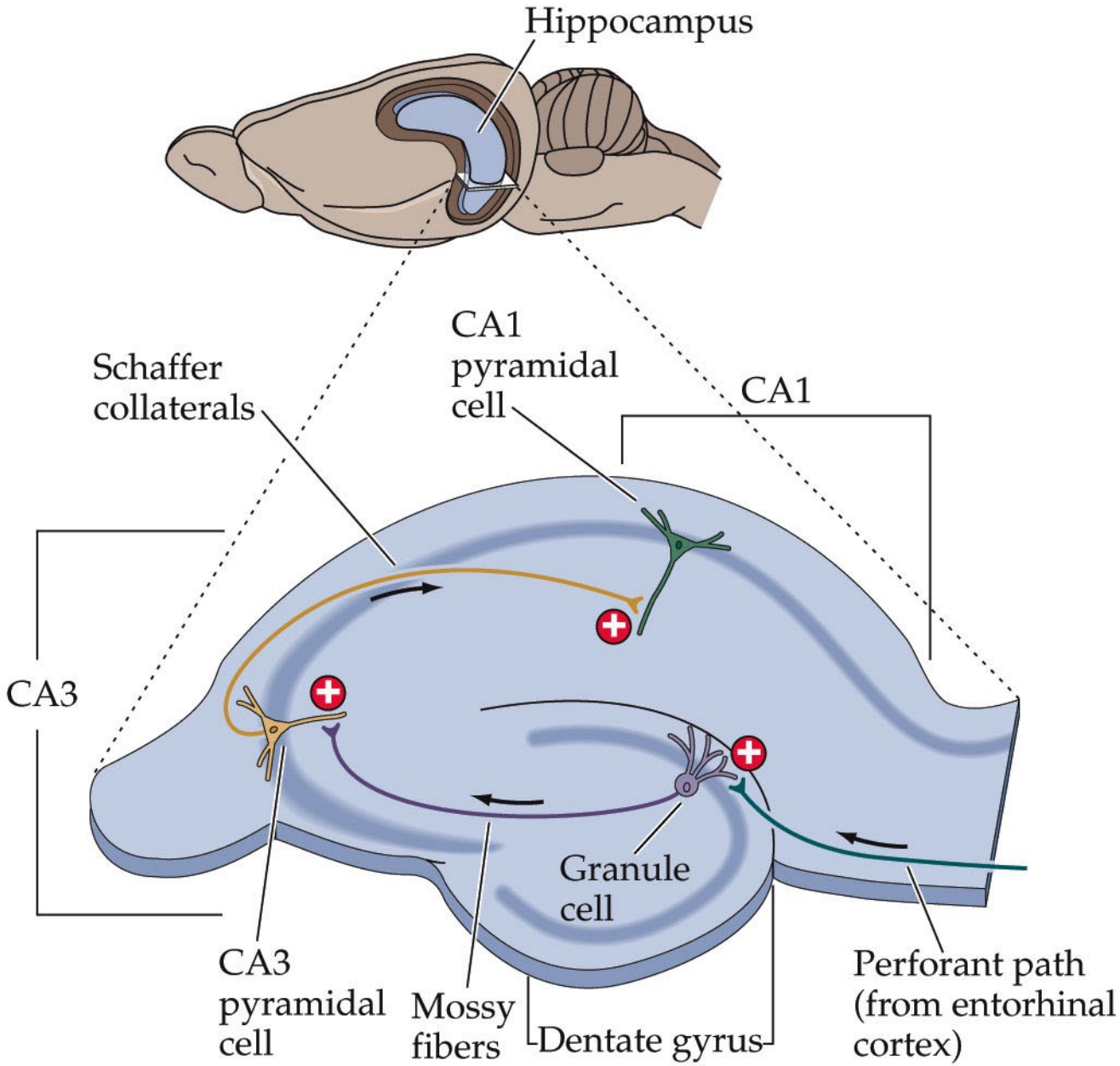


The hippocampus consists of a trisinaptic circuit. Hippocampal synapses are extremely plastic.

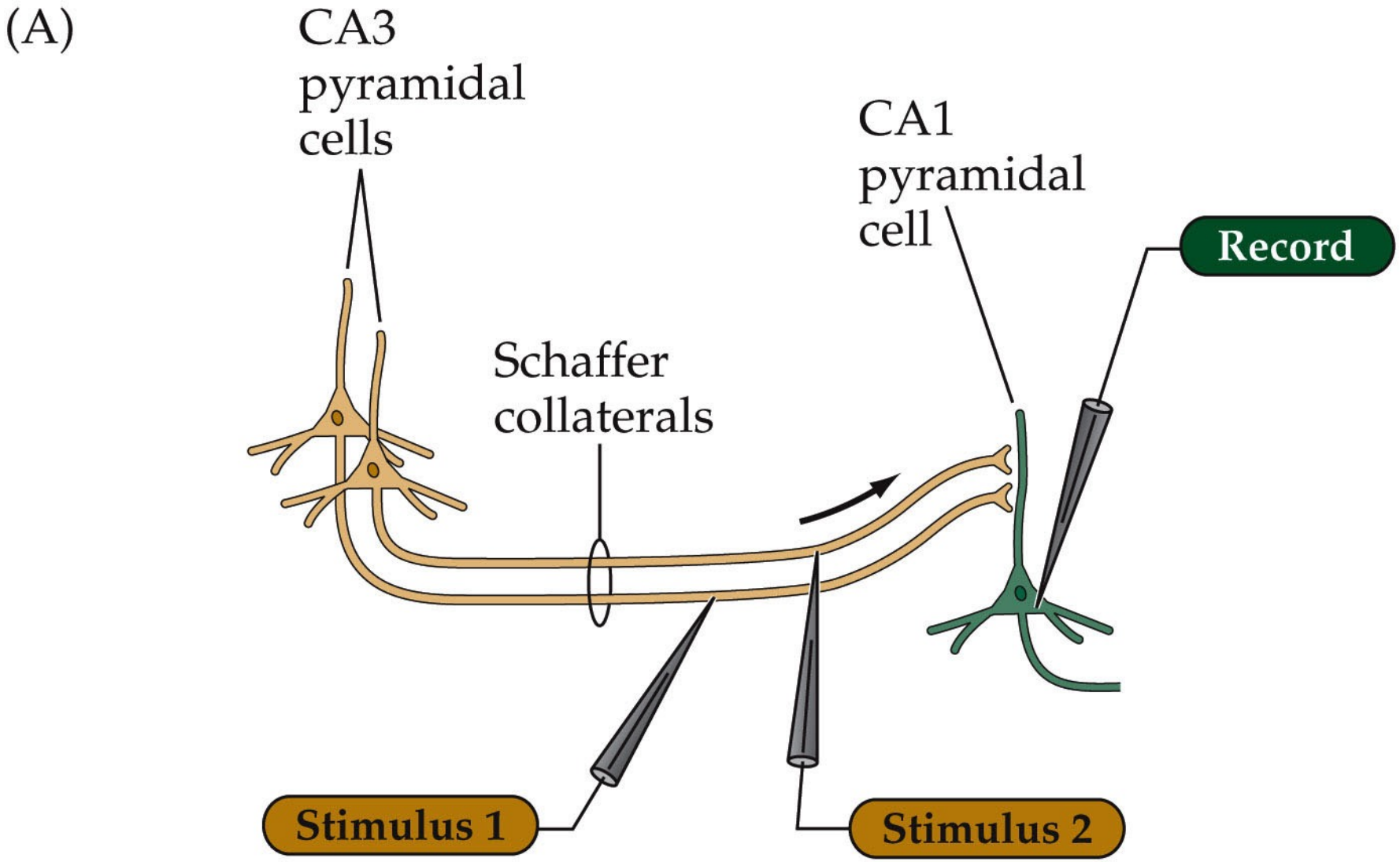


In 1973 Bliss and Lomo discovered that a high-frequency stimulus in any of the three pathways gave rise to long-term potentiation (LTP) observable both in vitro and in vivo.

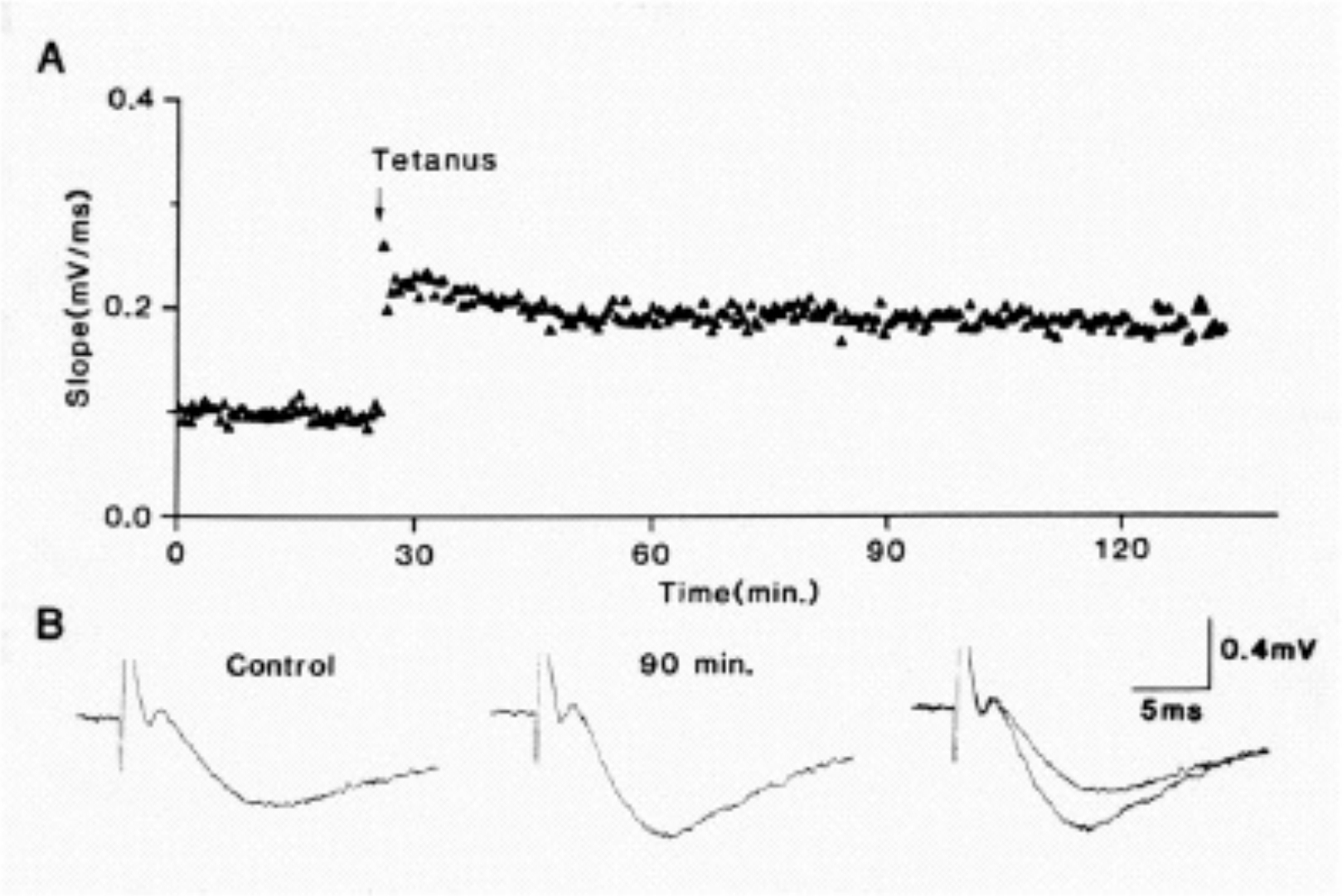
The rodent hippocampus



Long-term potentiation of Schaffer collateral-CA1 synapses



Long-term potentiation (LTP)



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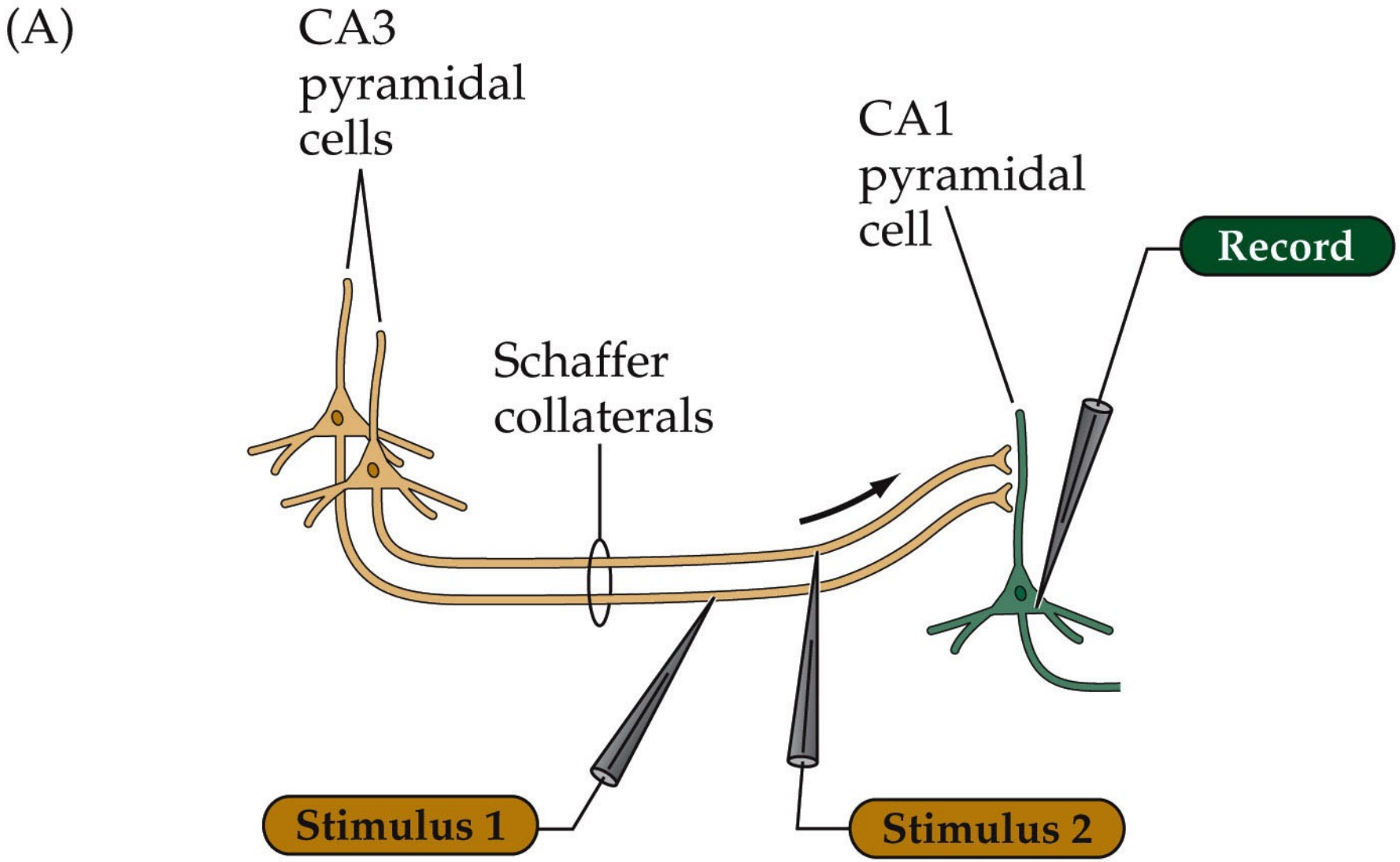
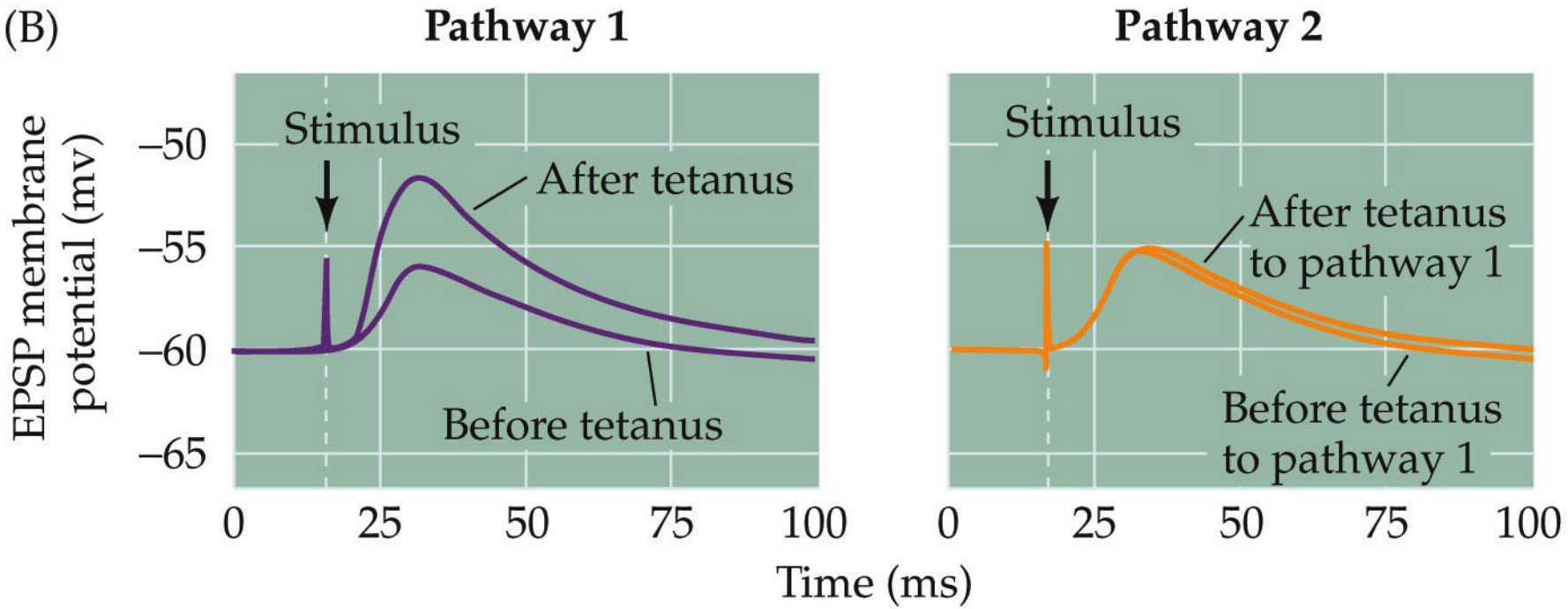


LTP of Schaffer collateral-CA1 synapses



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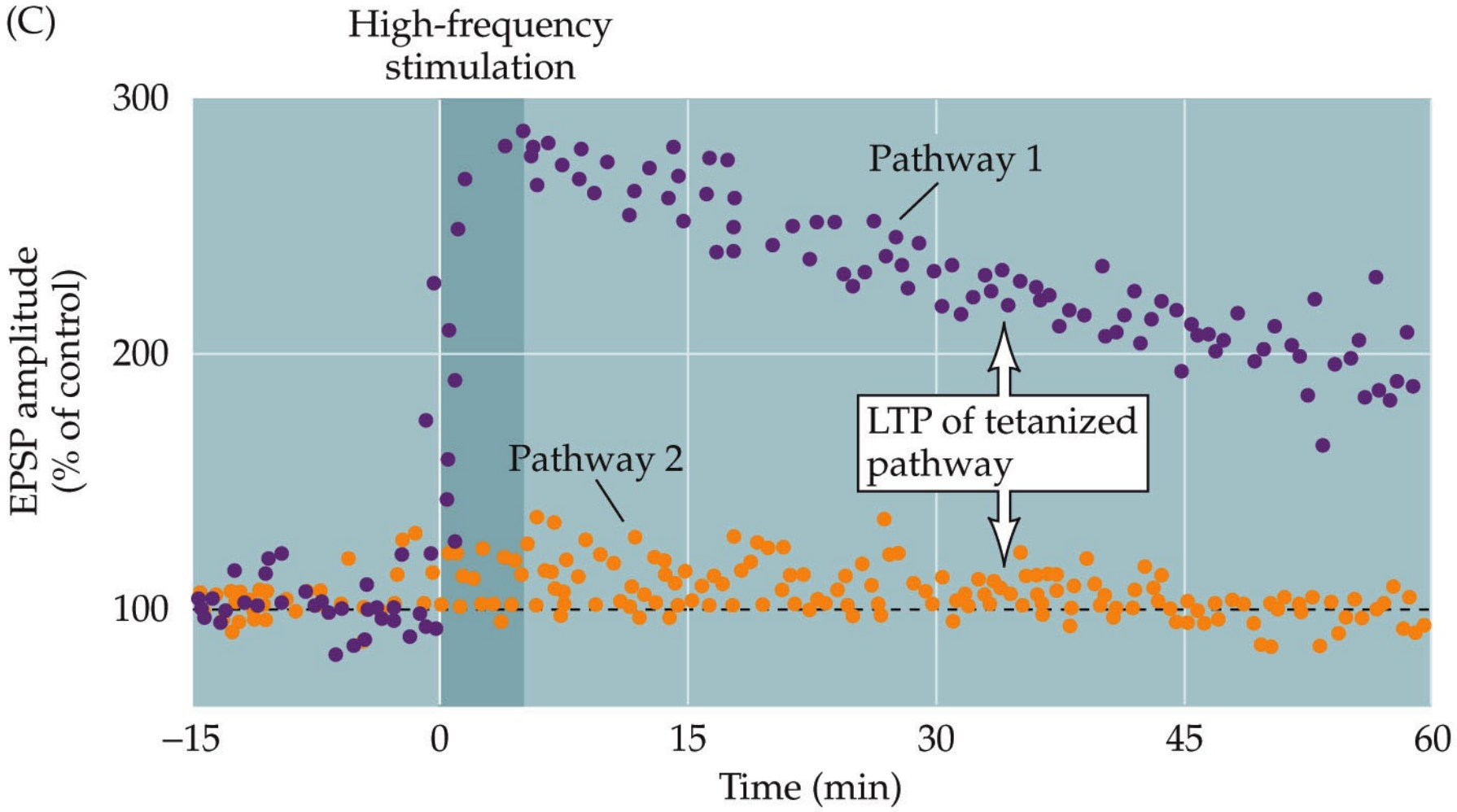

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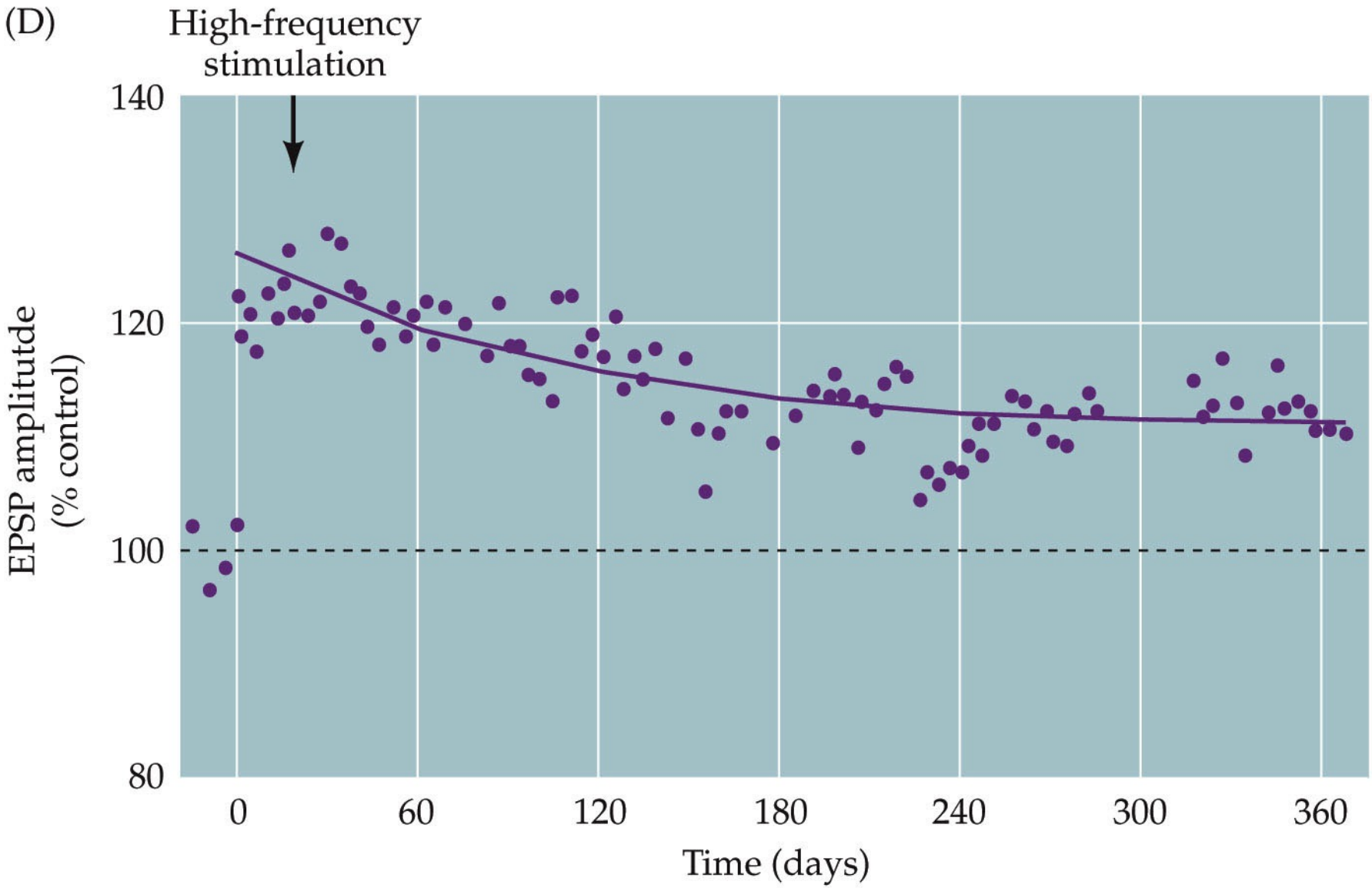
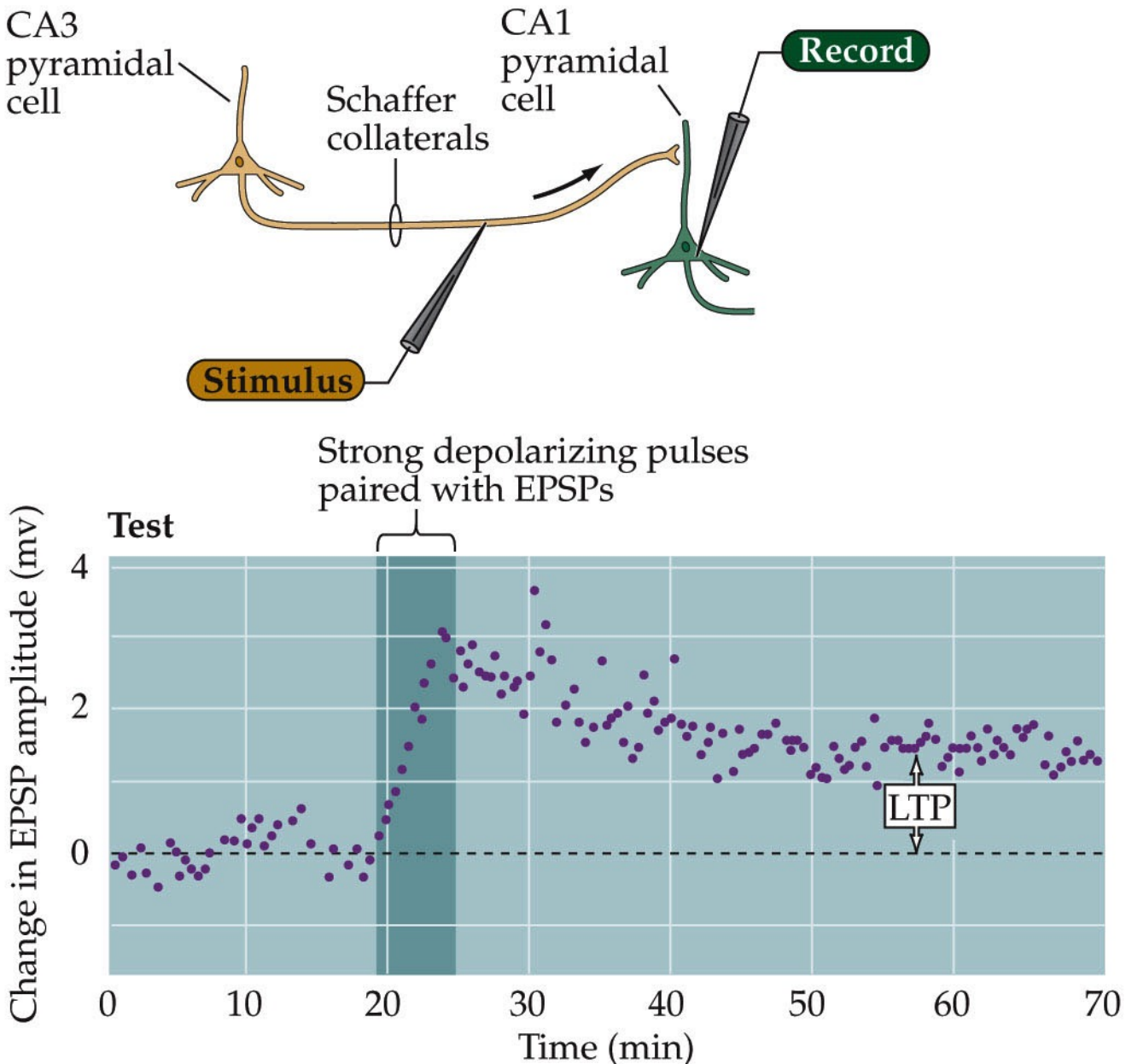


Pairing presynaptic and postsynaptic activity causes LTP



Some properties of the LTP:

Induction:

High frequency stimulation (theta burst or tetanus)

Pairing of presynaptic activity with postsynaptic (associative) depolarization

Specificity:For each neuron only the stimulated inputs are enhanced

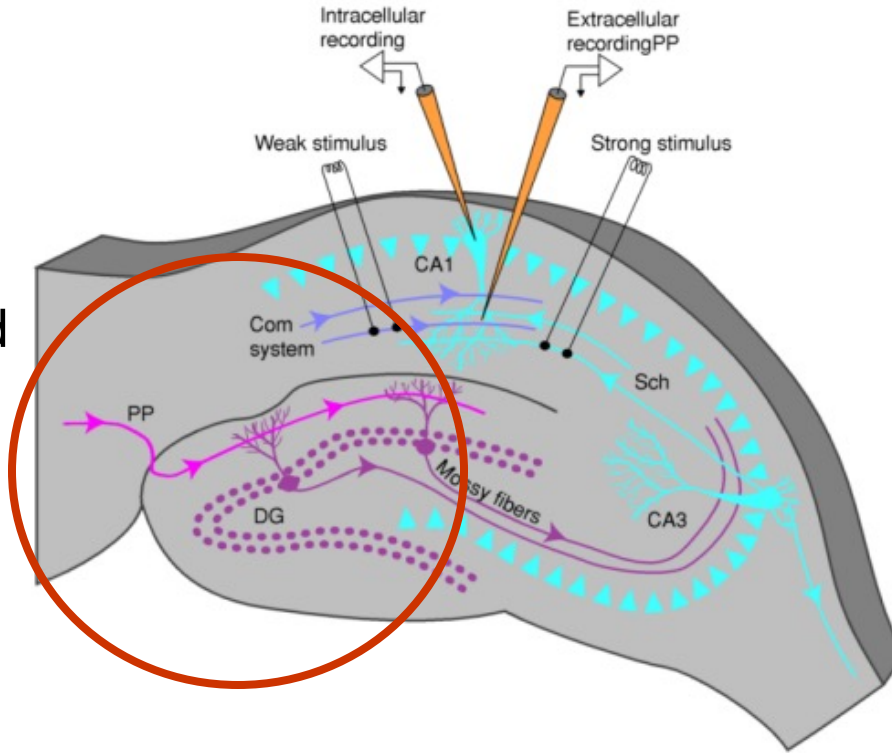
Long-Term Potentiation Activity-dependent changes in synaptic strength

A candidate mechanism for activity-dependent changes in the strength of synaptic connections between neurons.

LTP is usually measured as an increase in the magnitude of the excitatory postsynaptic potential (EPSP).

Bliss and Lomo (1973) demonstrated LTP in the anaesthetized rabbit: high-frequency stimulation of the perforant path (inputs to the dentate gyrus) produced a long-lasting enhancement of the extracellular field potential.

LTP can last for several weeks or even months.

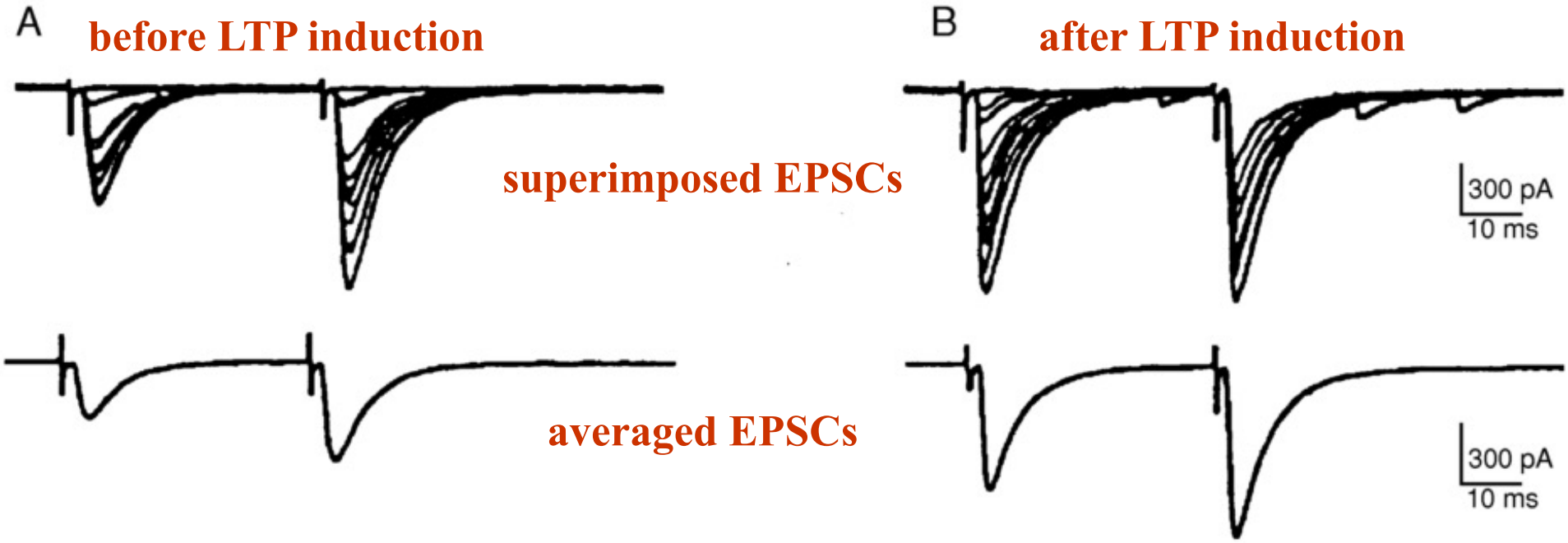


Long-Term Potentiation

Brain sections studied *in vitro*

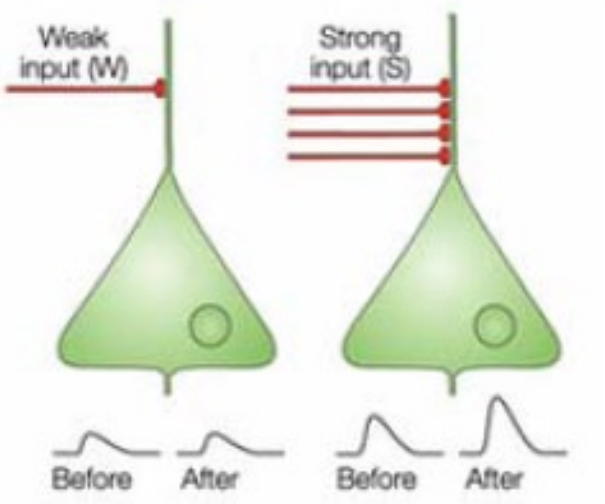
Mossy fiber excitatory postsynaptic currents are greater after LTP induction

LTP is induced by stimulating mossy fibers with 5-10 electrical stimuli @ 100Hz



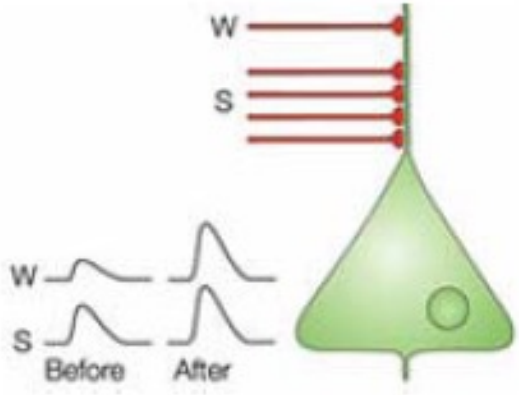
LTP properties

A. cooperativity

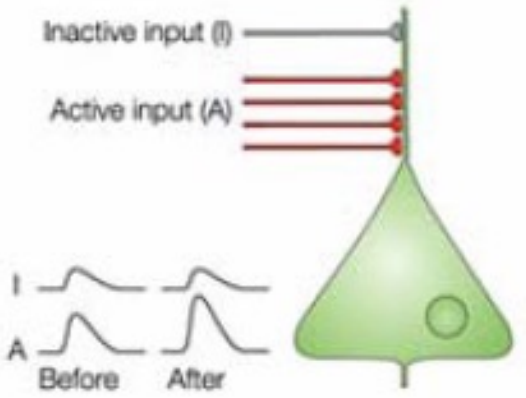


Voltage-dependence of NMDAR

B. associativity



C. Synapse specificity



Localization of glutamate and calcium

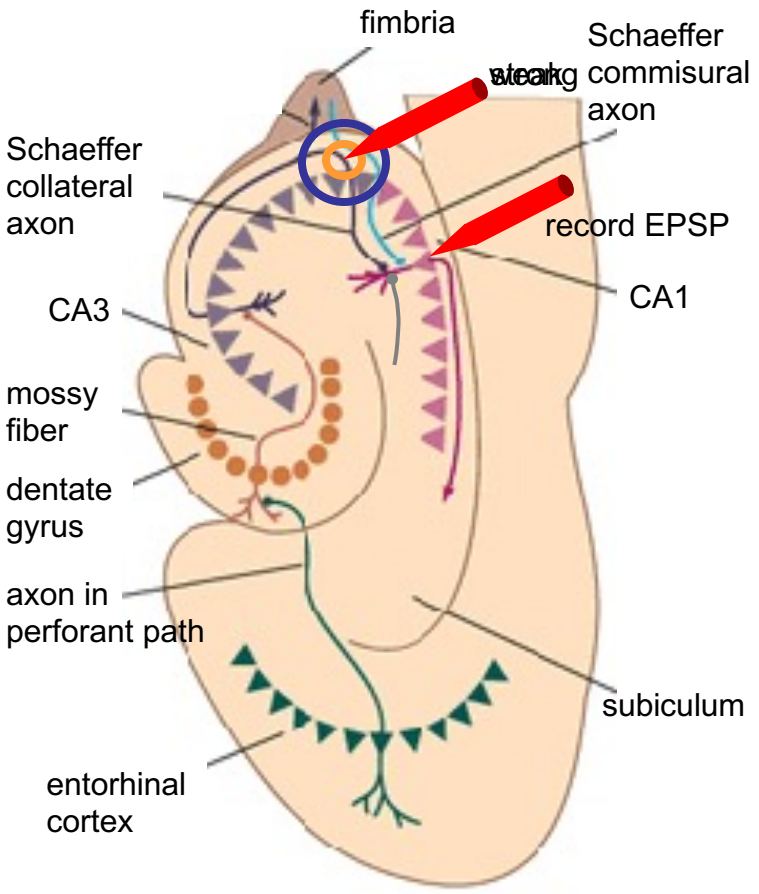
“Classical properties” of LTP

Cooperativity, associativity, input specificity, and spatiotemporal specificity:

1) Cooperativity -

The probability of inducing LTP, or the magnitude of induced LTP increases if the number of stimulated afferents is increased. (by increasing the current intensity.)

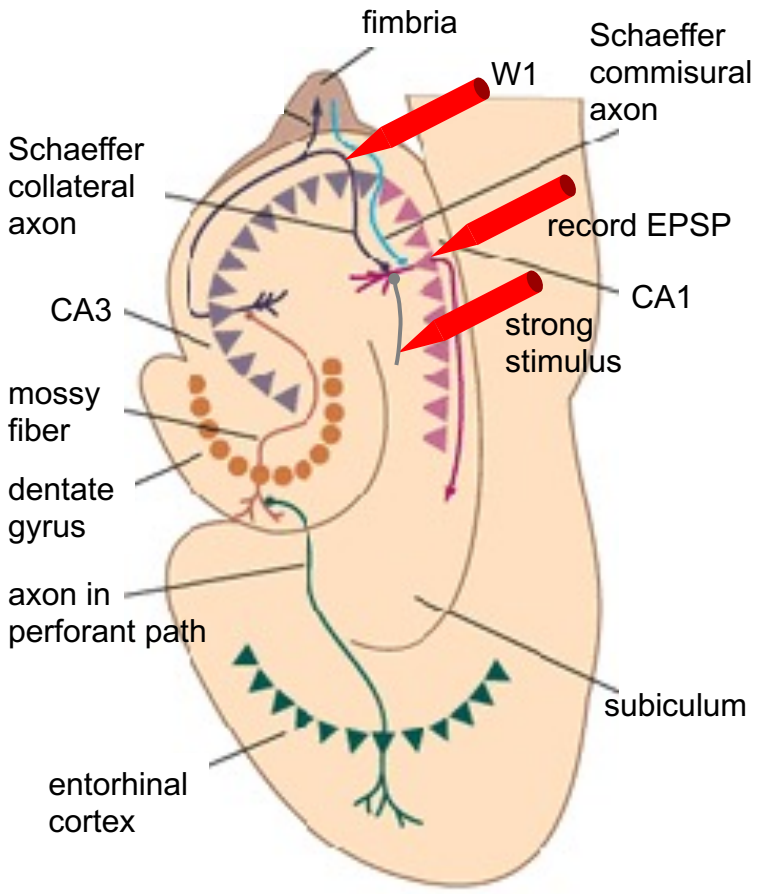
Weak, high frequency stimulation often will not induce LTP, while strong stimulation at the same frequency will reliably produce LTP



2) Associativity -

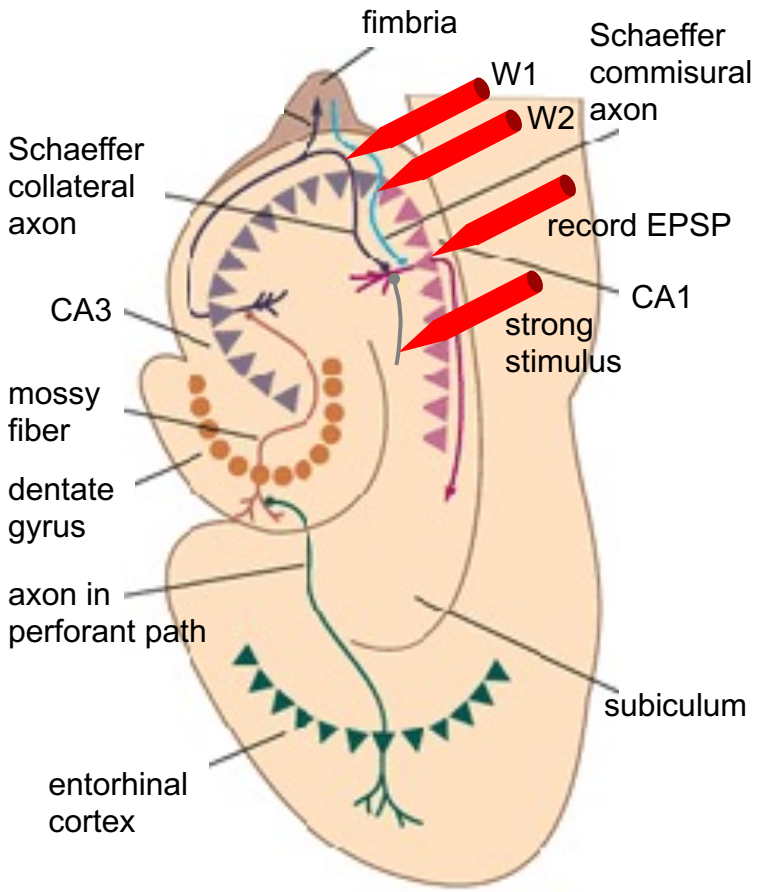
Stimulation of two distinct axonal inputs to a single postsynaptic target, one weak stimulus and one strong stimulus,

will produce LTP for further stimulation of the weak input, even thoughrepeated stimulation of the weak inputs alone would not.



3) Input Specificity -

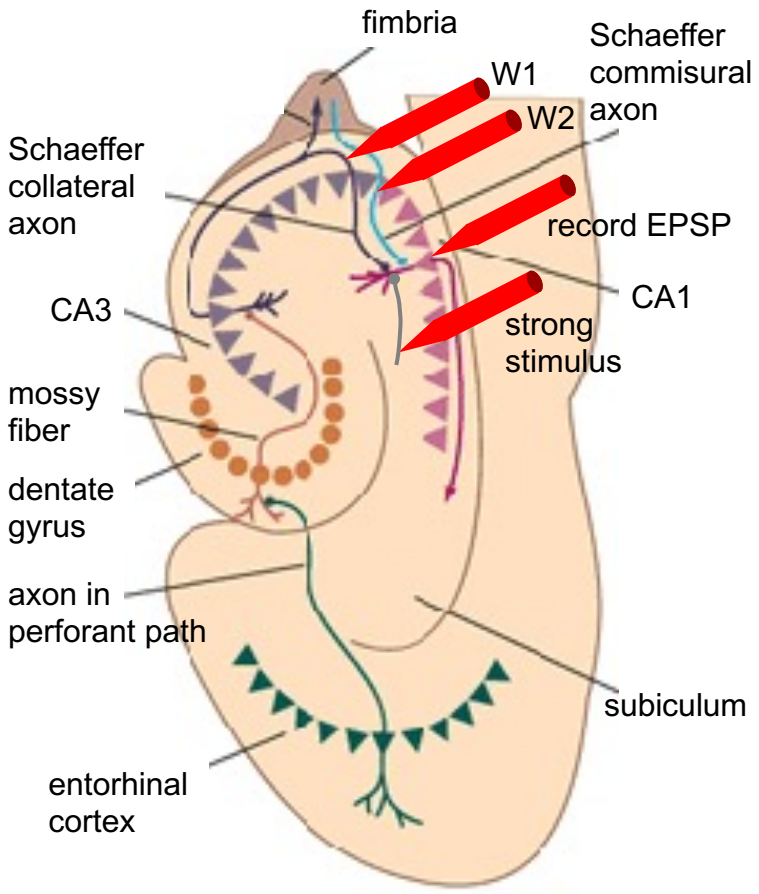
LTP is restricted to the inputs that received the high frequency stimulation.



4) Spatiotemporal Specificity -

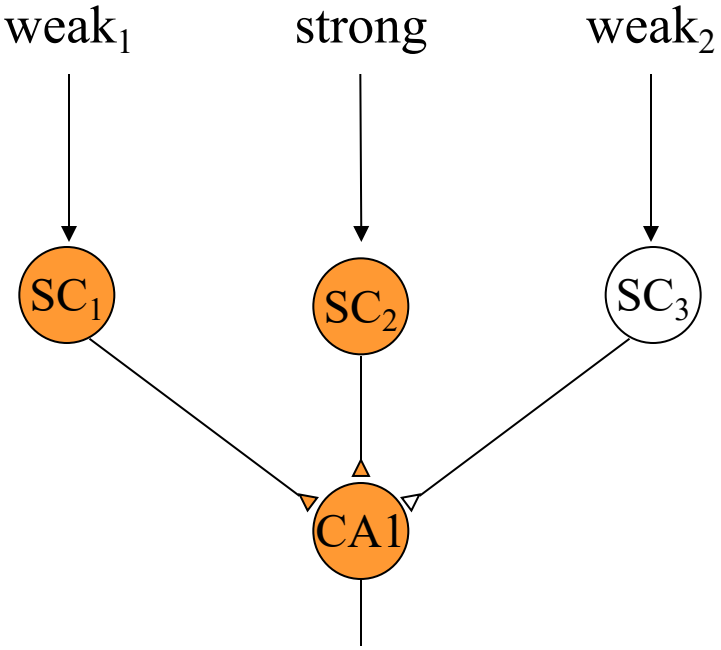
LTP is restricted to the inputs that received the high frequency weak stimulation that was paired specifically with the strong stimulation.

Note that this is true even when the inputs from W1 and W2 are both Schaeffer collaterals that synapse on the same apical dendrites of CA1 pyramidal neurons.



LTP can be explained in Hebbian terms - *When an axon of cell A is near enough to excite 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 (Hebb, 1949).*

Cooperativity occurs when the stimulus is *strong enough to induce sufficient depolarization* of the postsynaptic membrane during presynaptic activity of the weak input.

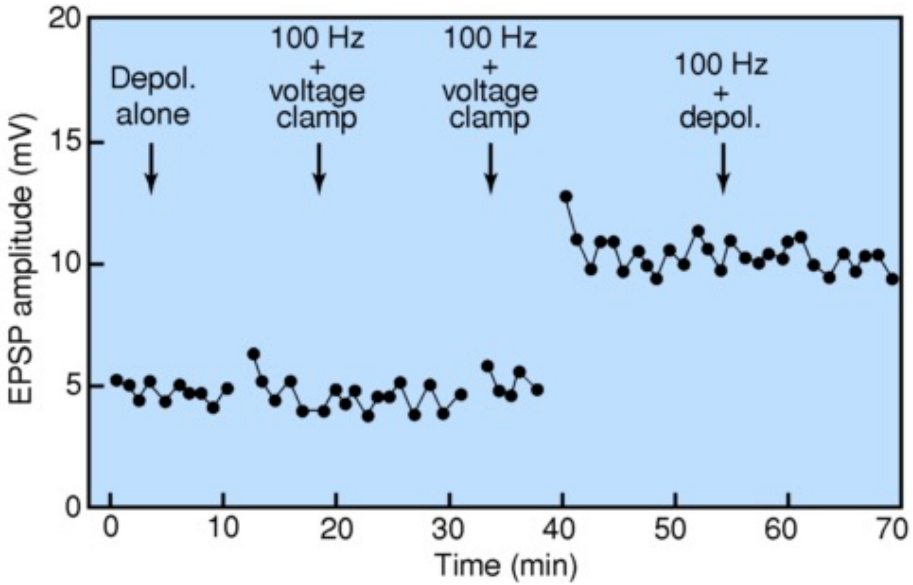


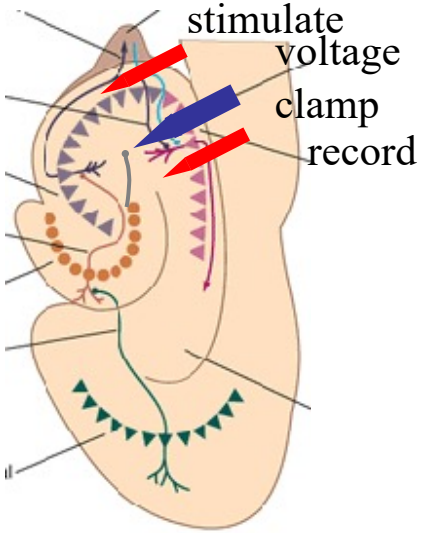
Associativity, input specificity, and spatiotemporal specificity occur because the strong input occurs at the same time as the weak input only the *imultaneously active* synapses are strengthened.

LTP can be explained in Hebbian terms -

Does LTP of Schaeffer collateral inputs to CA1 pyramidal neurons function in a Hebbian fashion? –

Can LTP be achieved by concurrent electrical stimulation of the Schaeffer collateral and the postsynaptic neuron?





1. Pyramidal EPSPs assessed every 12 sec to establish stable baseline: **no LTP induction**
2. Tetanic weak stimulation (100 Hz) to a Schaeffer collateral while the pyramidal cell was voltage clamped at -80 mV: **no LTP induction**
3. Tetanic weak stimulation (100 Hz) while the pyramidal cell was depolarized under voltage clamp: **LTP**

Long-Term Potentiation

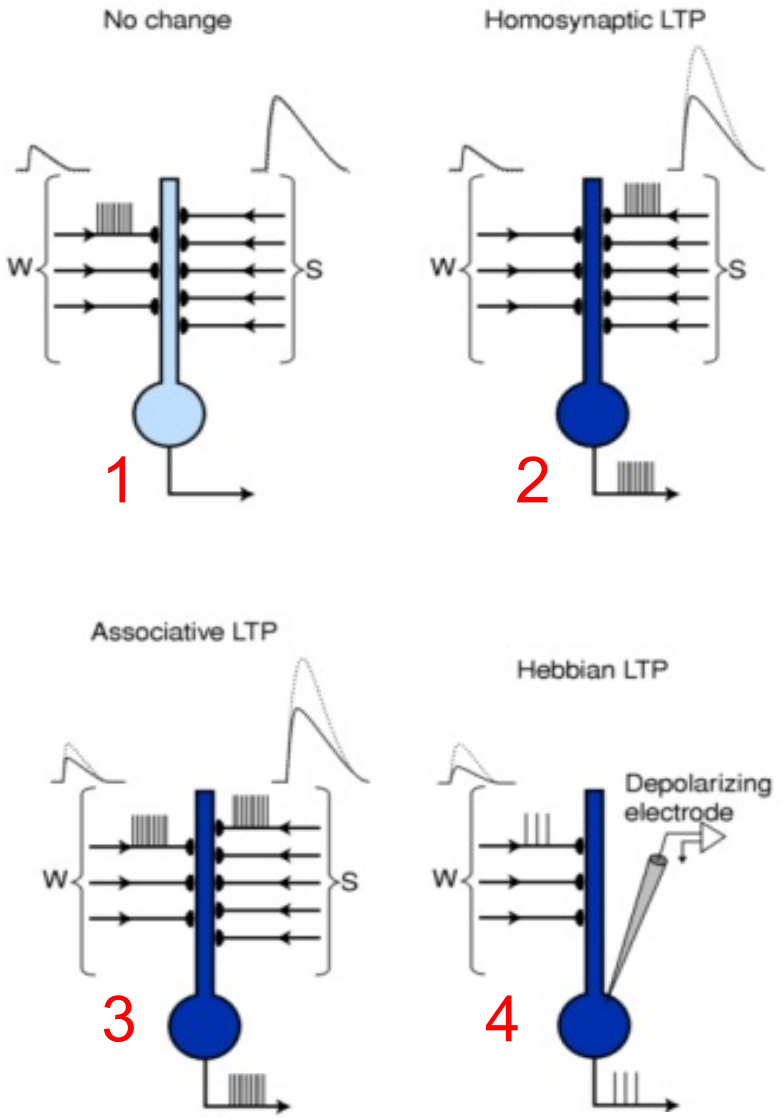
LTP induction can take many forms -

1. High frequency stimulation of a weak input does not produce LTP.

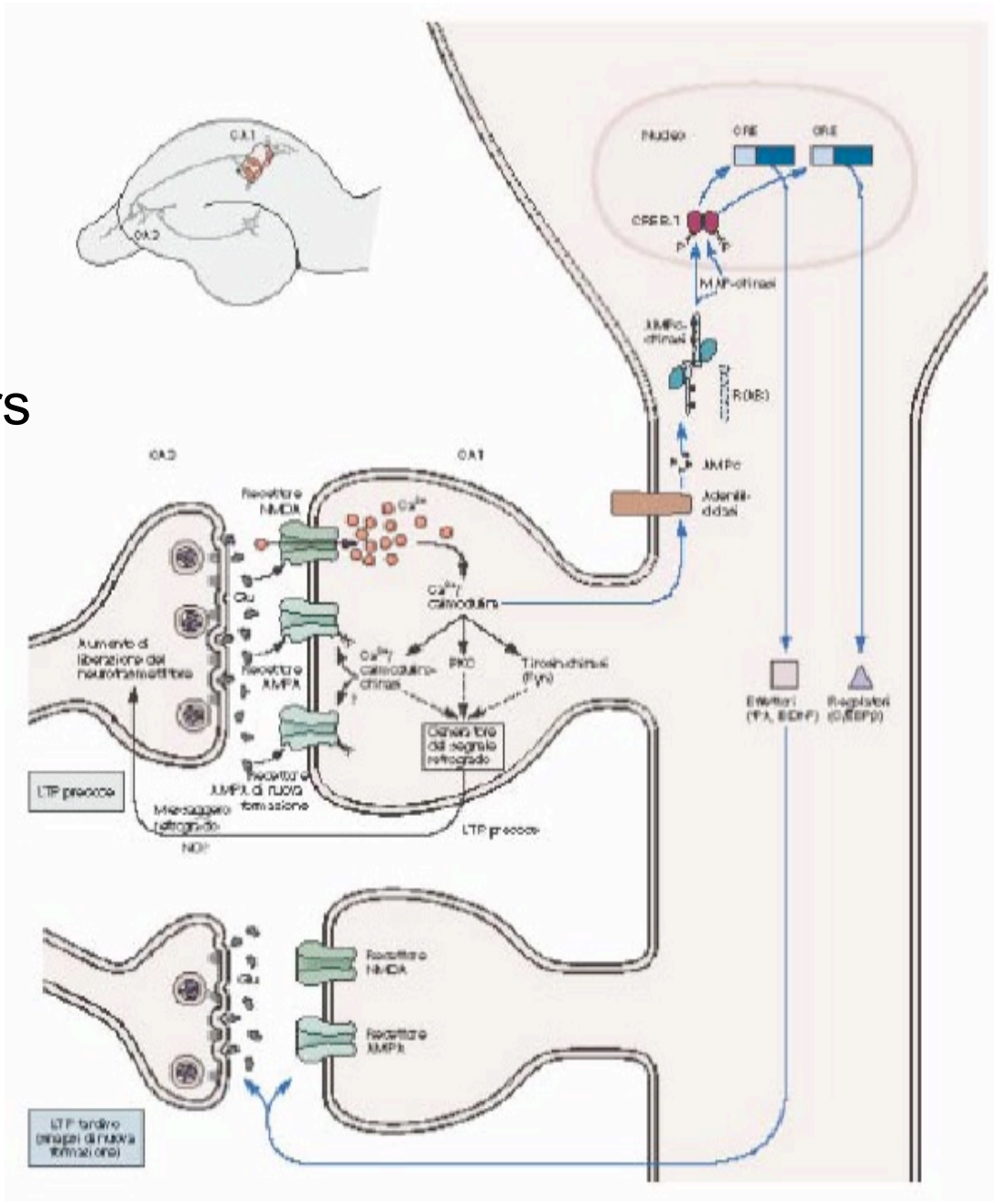
2. High frequency stimulation of a strong input produces LTP in that specific synapse.

3. Contiguous high frequency stimulation of weak and strong inputs produces LTP in both inputs.

4. Contiguous stimulation of a weak input and depolarization of the postsynaptic neuron produces LTP in the weak input.



- 4 groups of molecules:
- NT receptors
- Intracellular 2° messengers
- Protein sysntesis an gene regulators
- Retrograde factors



LTP phases

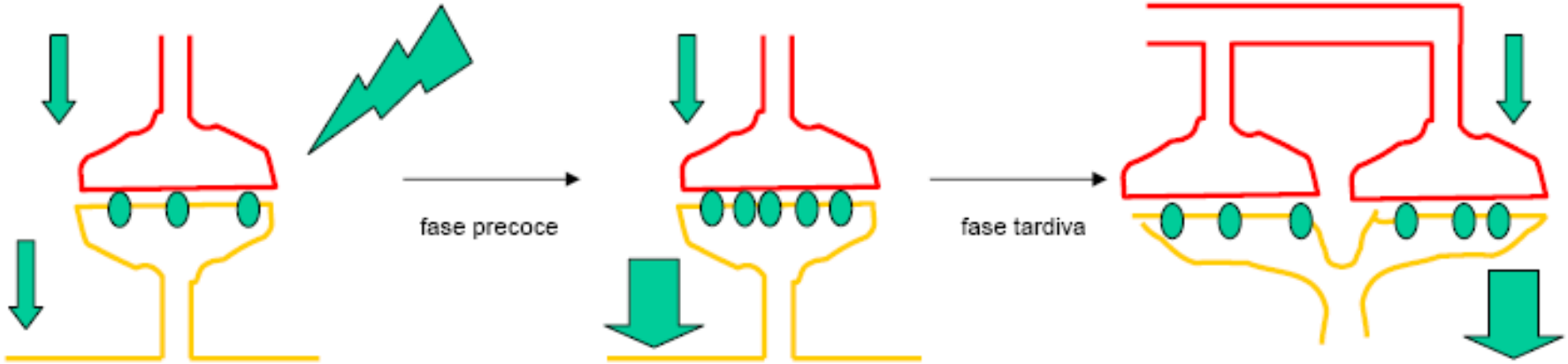


Fig. 1.10 Le frecce indicano, con la loro dimensione, l'ampiezza del potenziale pre e post sinaptico. Dopo un prolungato aumento dell'attività nel circuito (fulmine) la risposta postsinaptica aumenta (potenziamento post sinaptico). La fase precoce del potenziamento dell'efficacia sinaptica prevede alterazioni solamente funzionali della trasmissione sinaptica dovuti all'inserzione di nuovi recettori sinaptici. Nella fase tardiva potrebbero entrare in gioco cambiamenti strutturali.

Mechanisms of LTP induction

There are multiple mechanisms and pathways leading to persistent enhancement of synaptic strength.

Glutamate Most systems in which LTP has been studied are glutamatergic. Glutamate receptors (ionotropic and metabotropic)

Ionotropic glutamatergic receptors (GluRs) can be divided into two main types:

NMDA receptors - respond optimally to *N*-methyl-D-aspartate (NMDA).

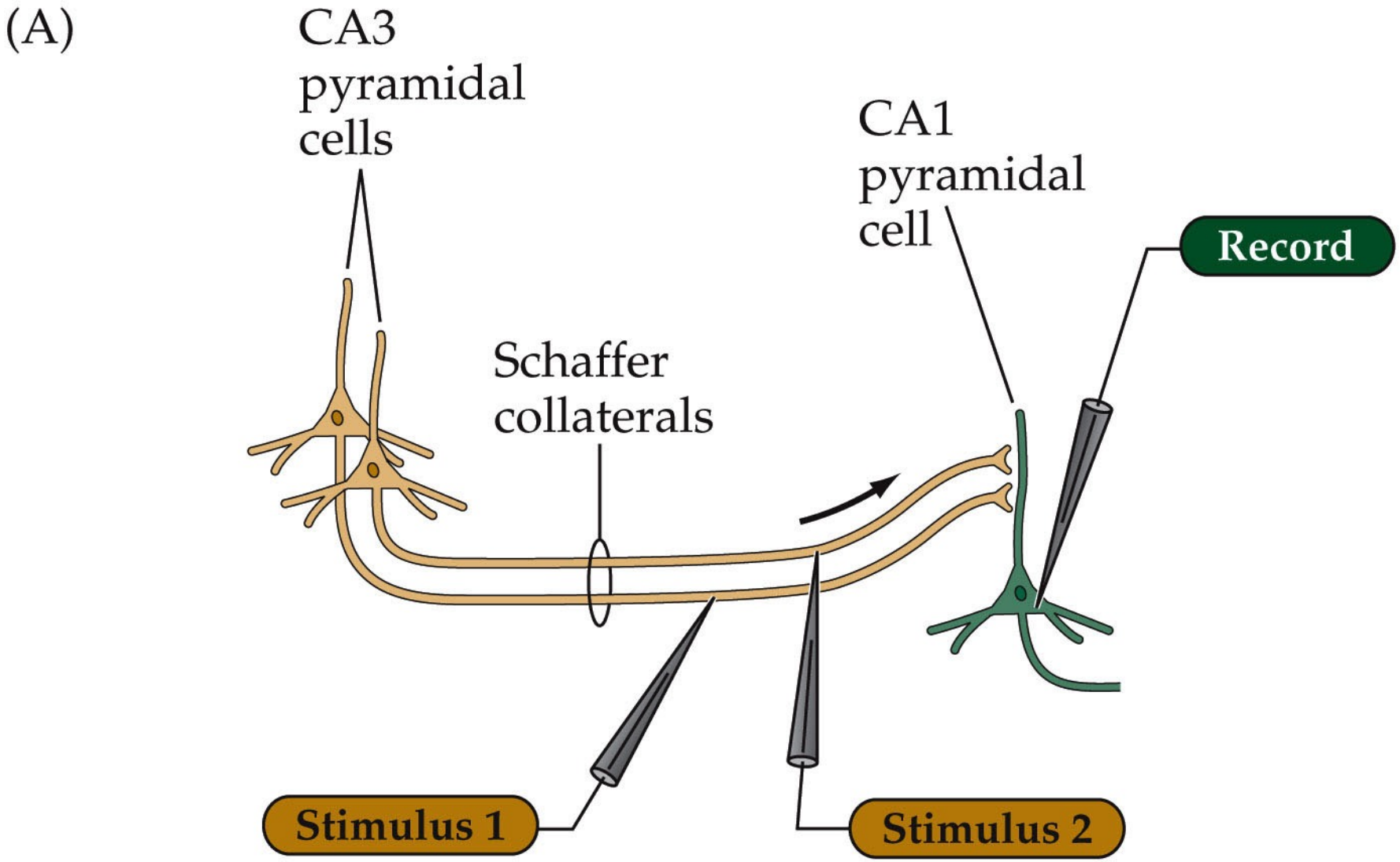
AMPA receptors - respond maximally to kainic acid (KA) or a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA).

Mechanisms of LTP induction

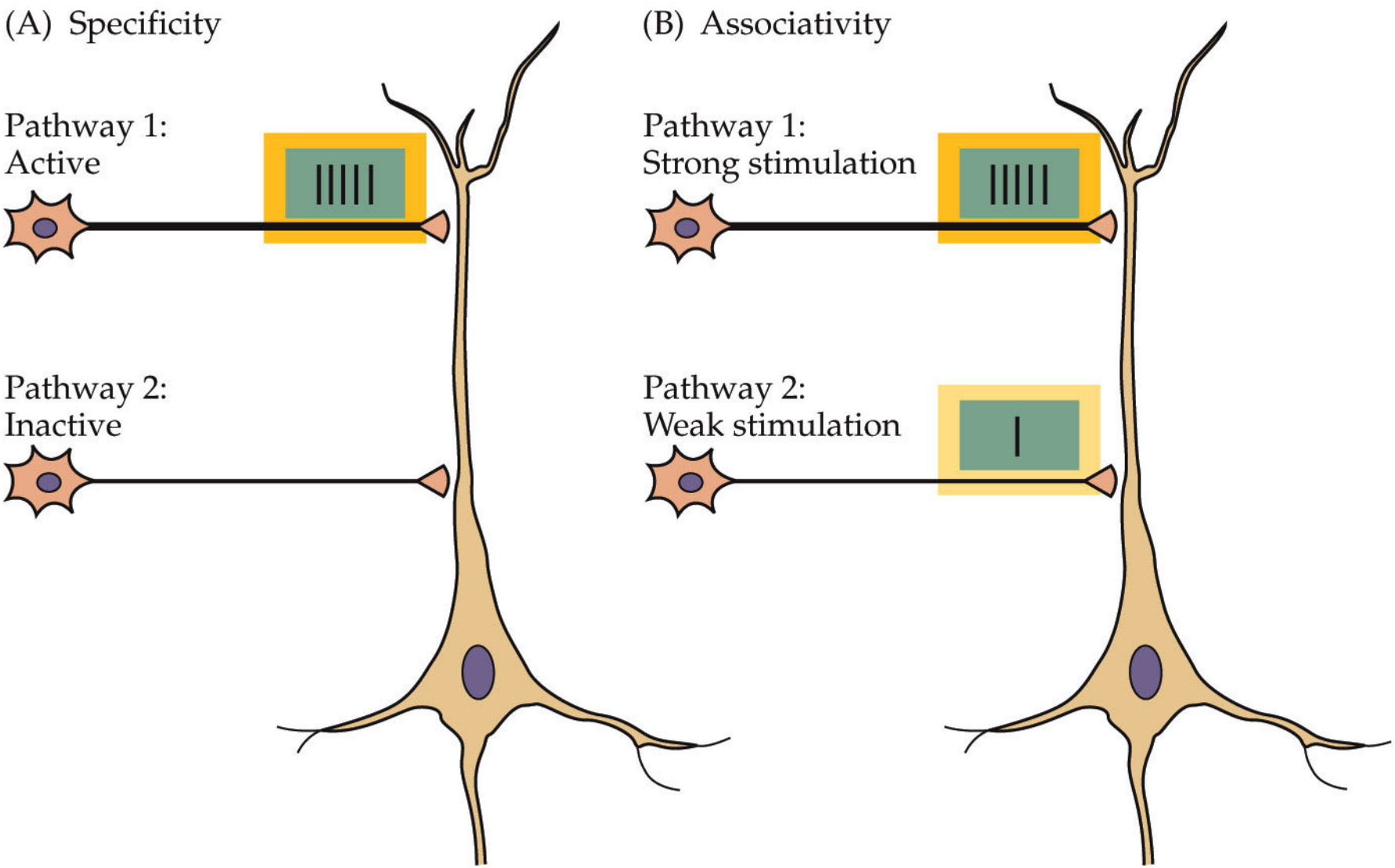
Calcium ions -
The exact role of Ca^{2+} in LTP induction depends upon the particular form of LTP, and the synaptic system.

Three routes of intracellular Ca^{2+} elevation have been studied:
Ionotropic GluRs, especially NMDA receptors
•voltage-gated Ca^{2+} channels (VGCCs)
•release from intracellular stores

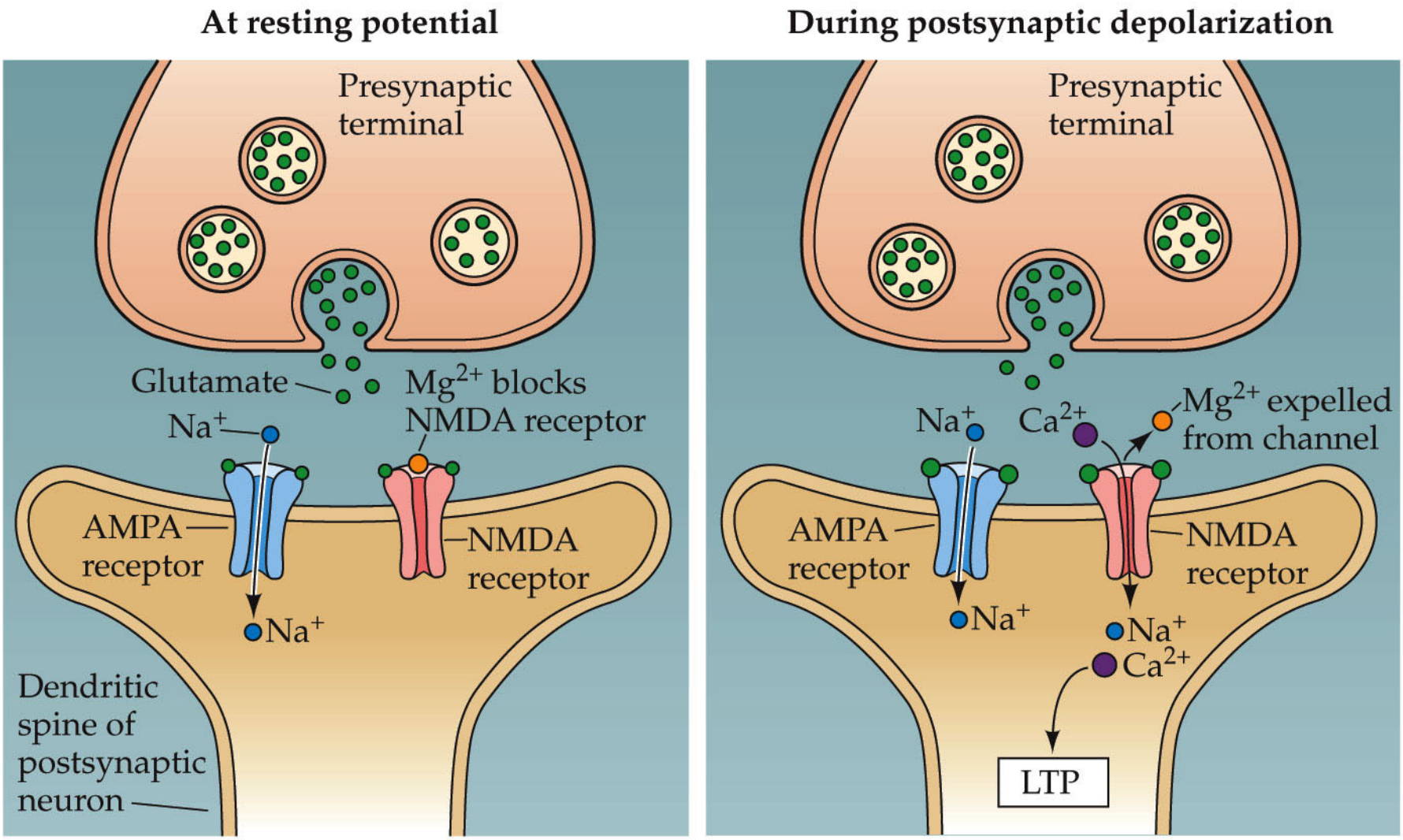
Long-term potentiation of Schaffer collateral-CA1 synapses



LTP at a CA1 pyramidal neuron receiving inputs from two independent pathways



The NMDA receptor channel can open only during depolarization



Signaling mechanisms underlying LTP

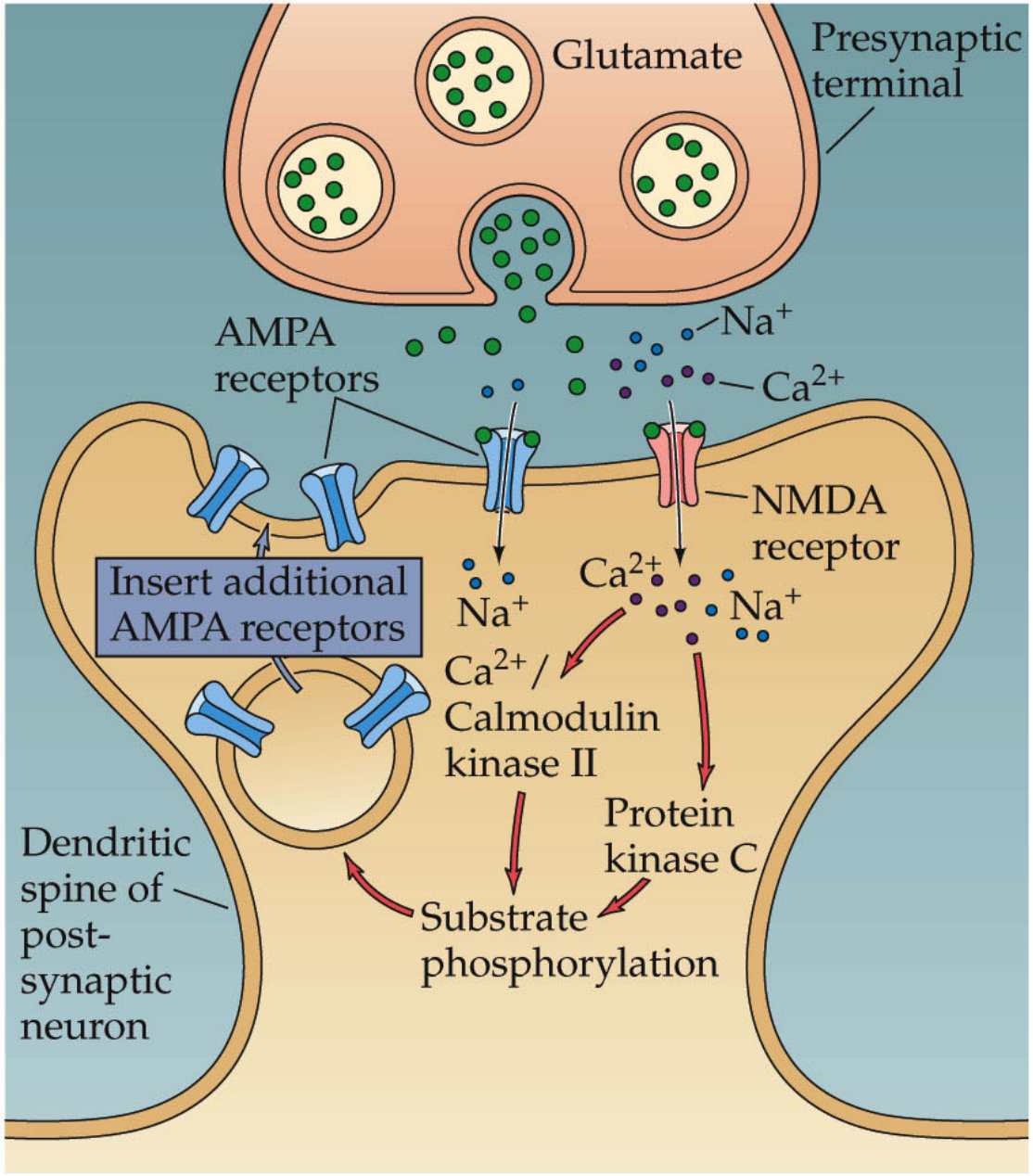
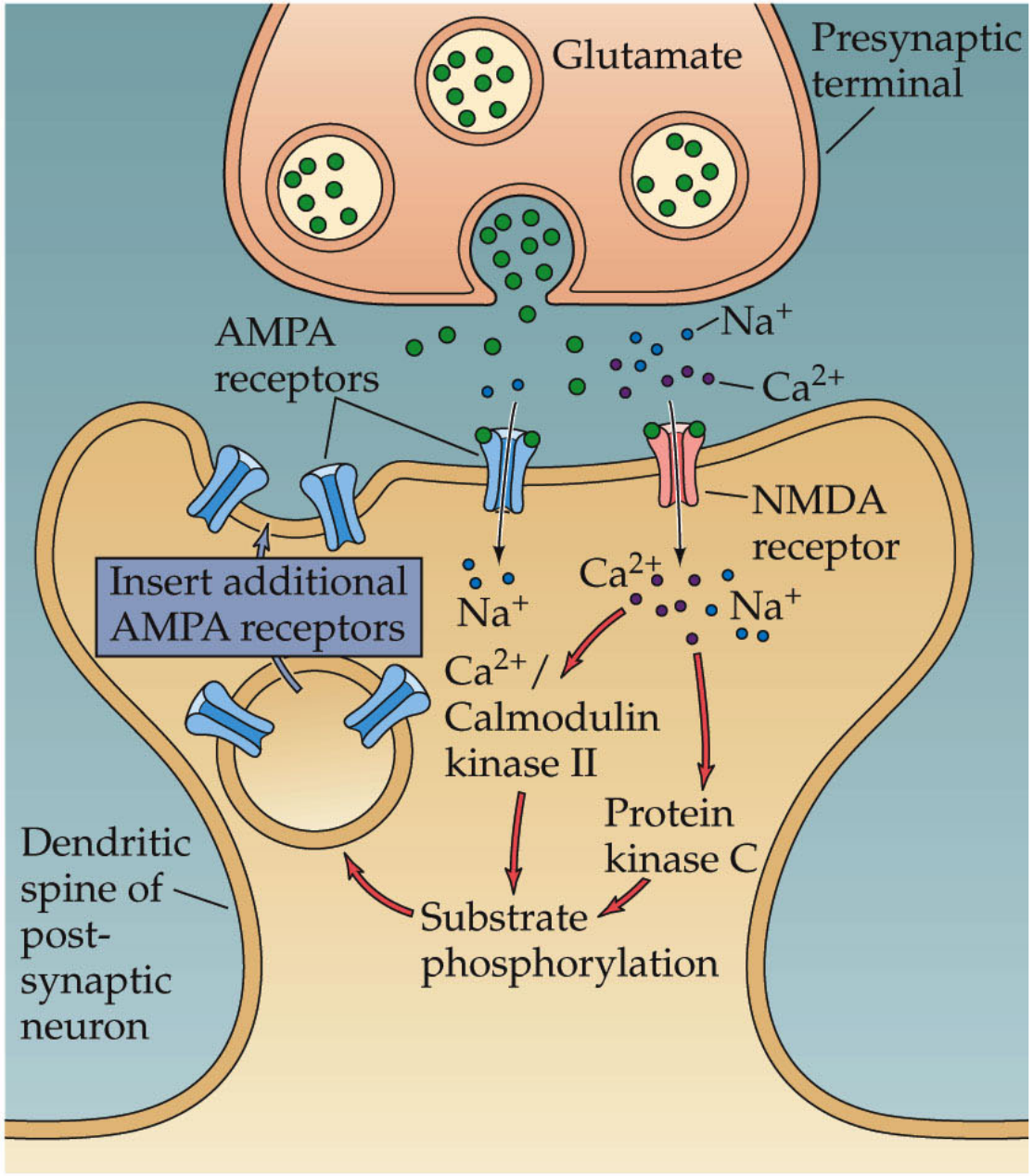
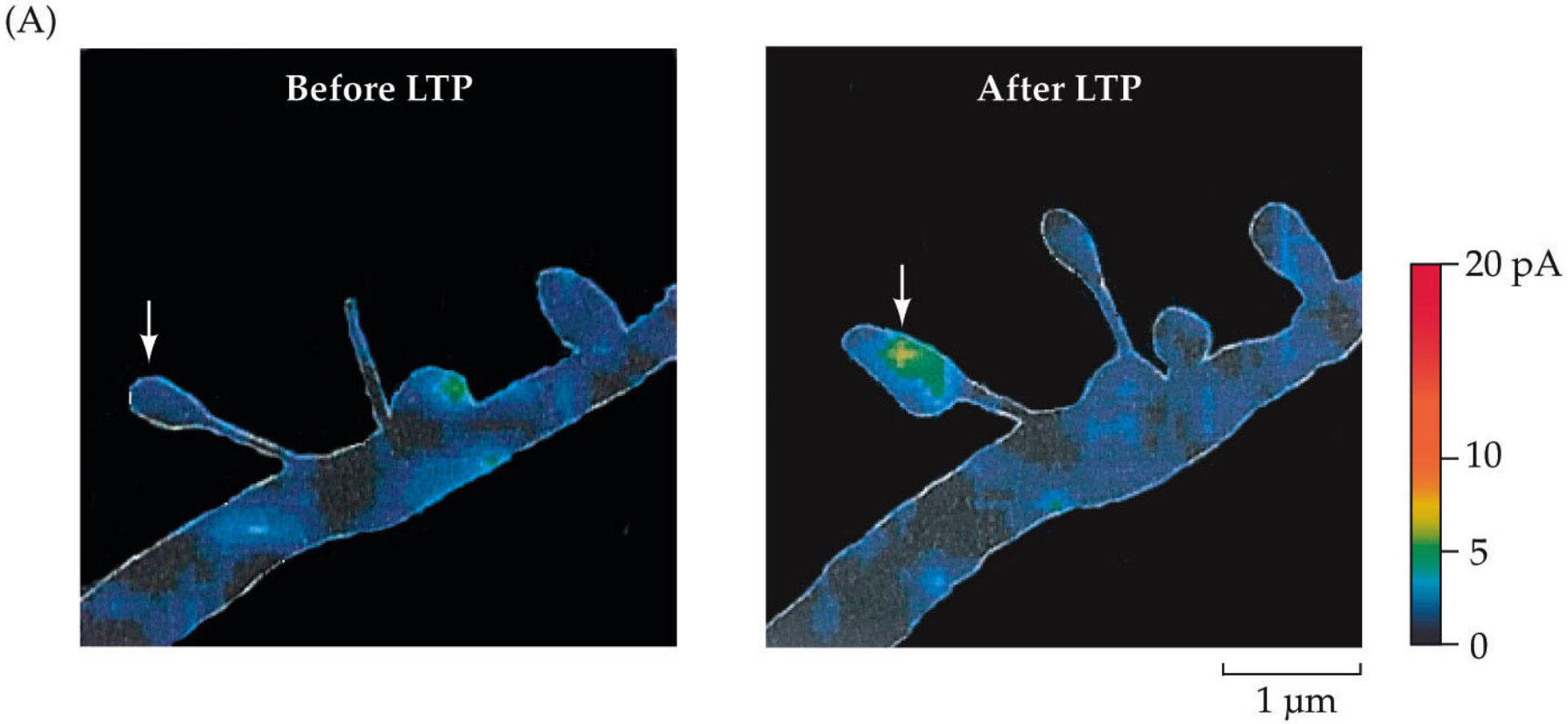


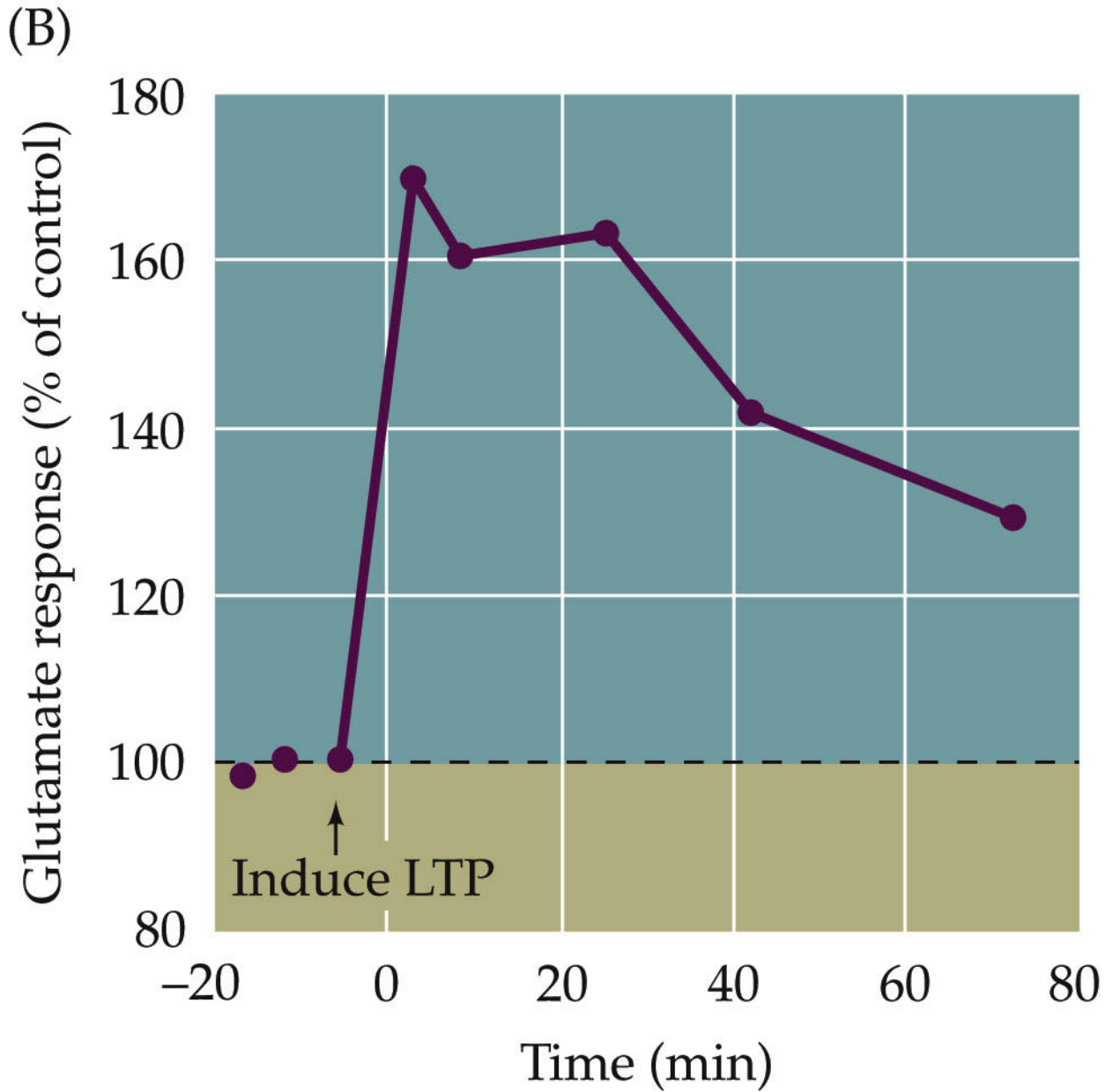
Fig 8.11 Signaling mechanisms underlying LTP



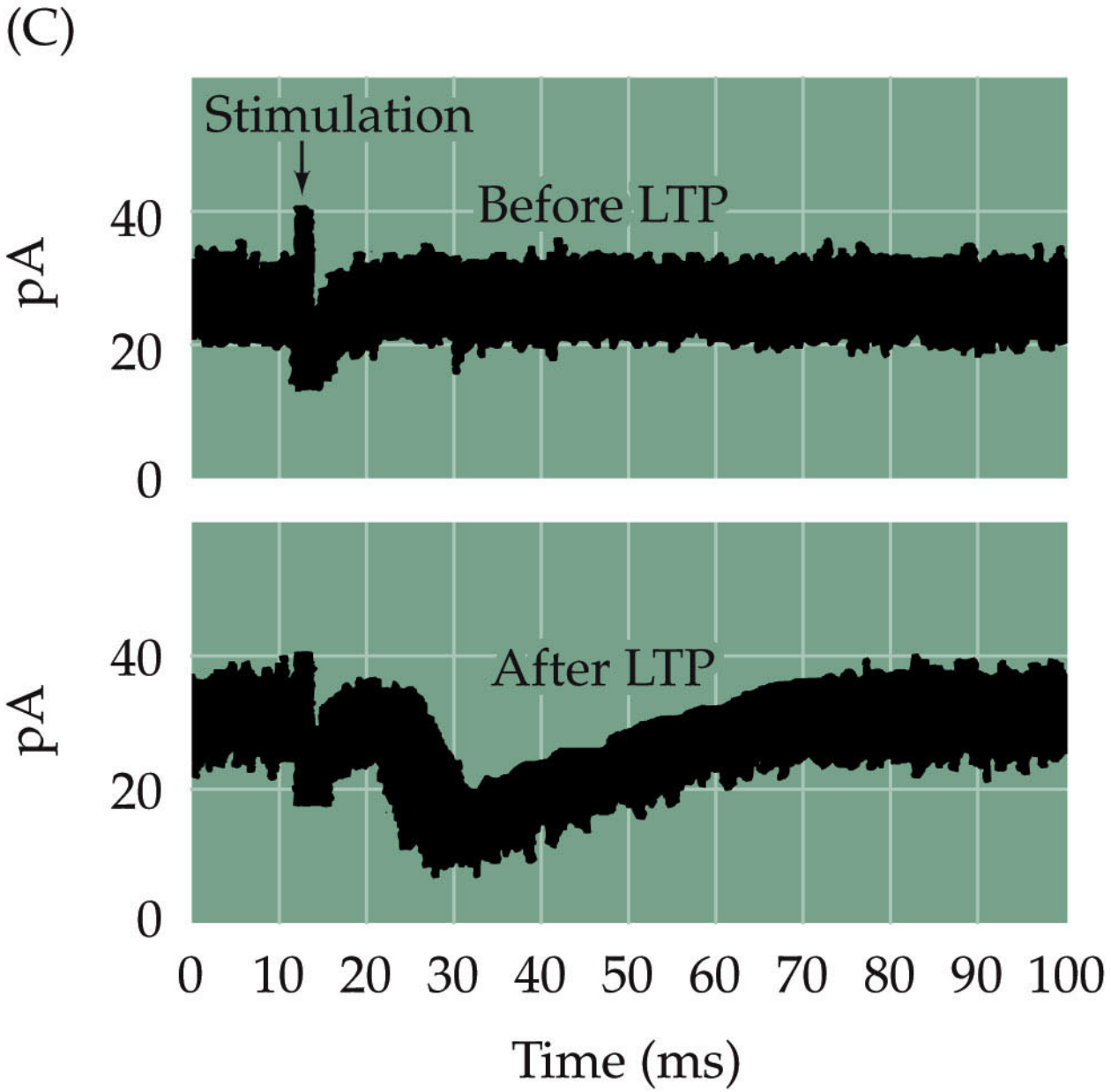
Addition of postsynaptic AMPA receptors during LTP



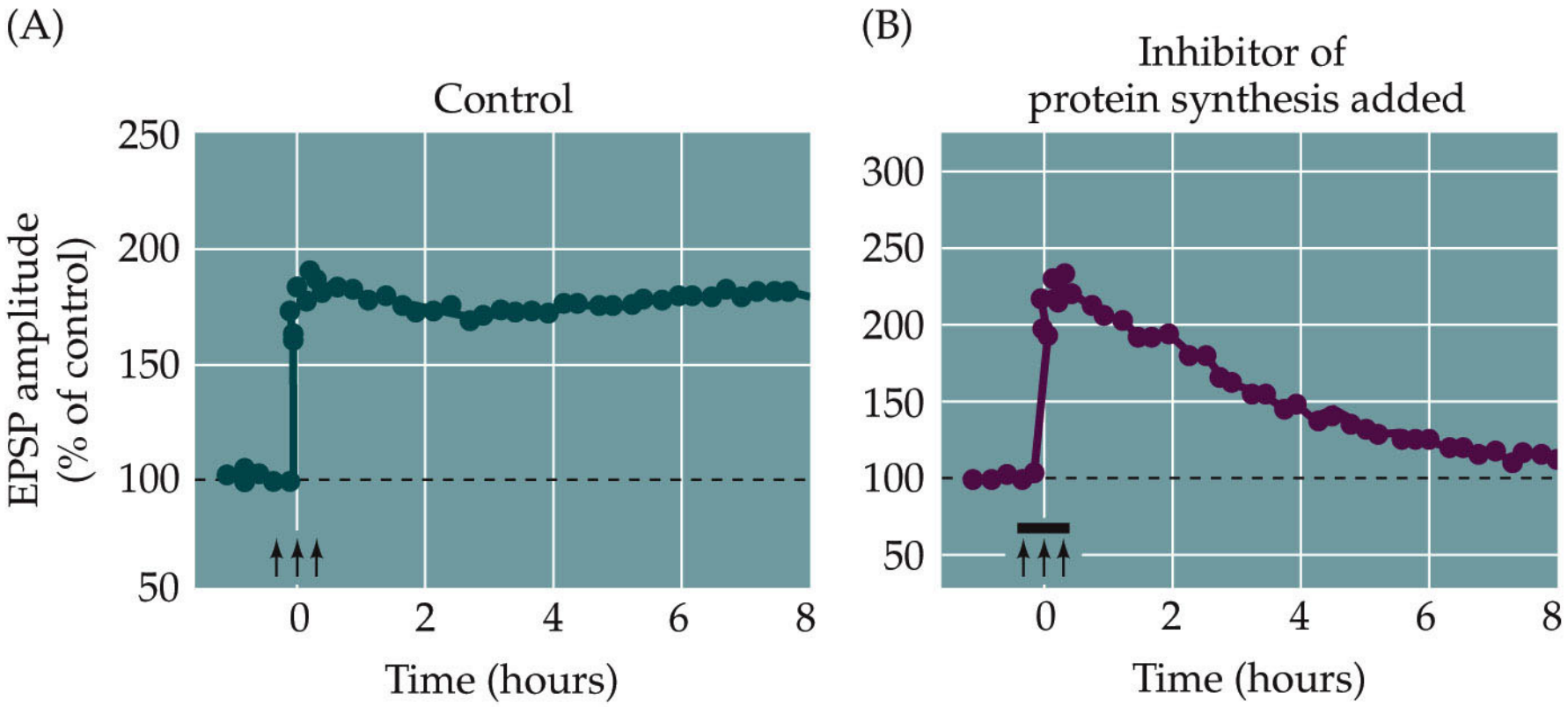
Addition of postsynaptic AMPA receptors during LTP



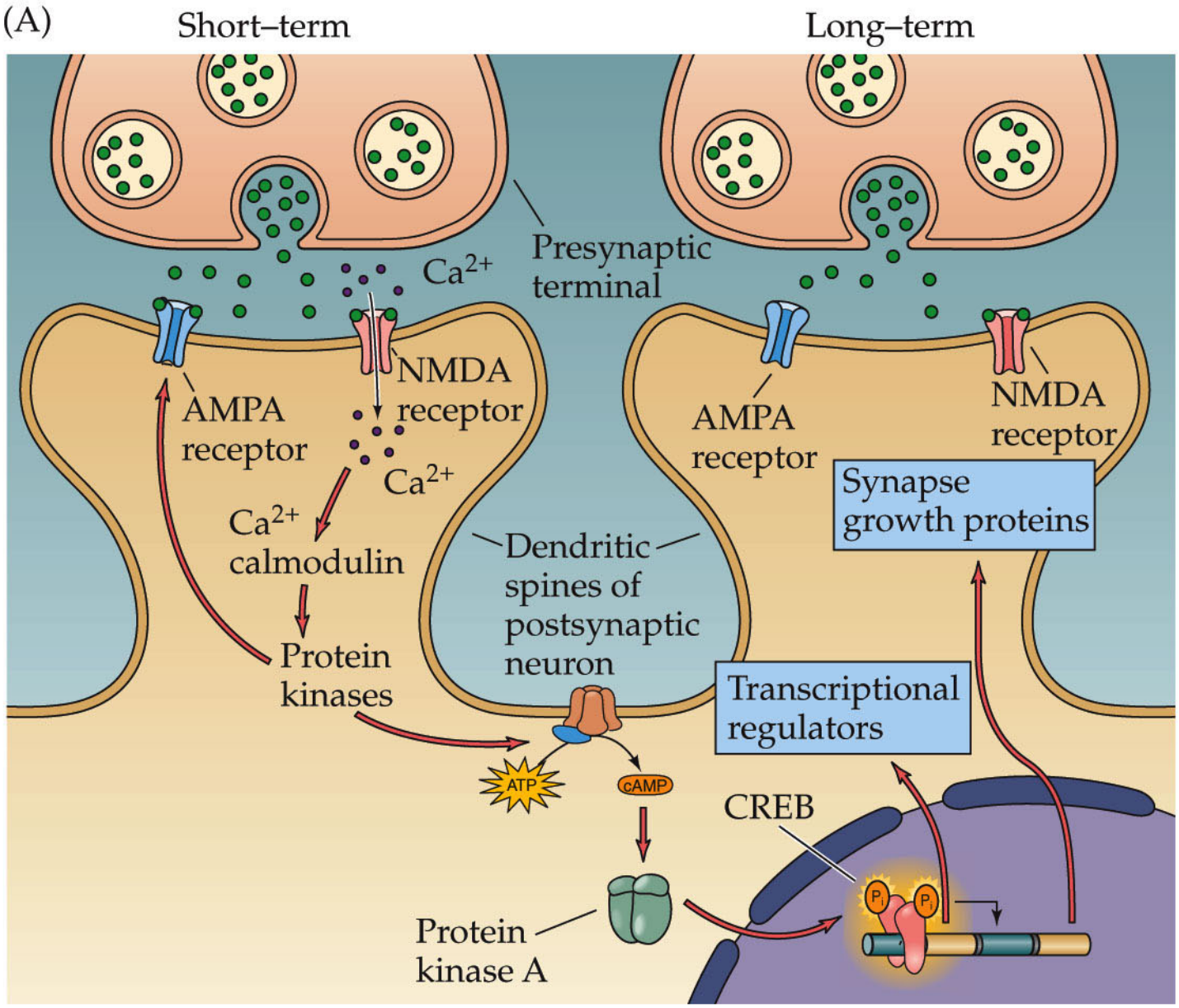
Addition of postsynaptic AMPA receptors during LTP



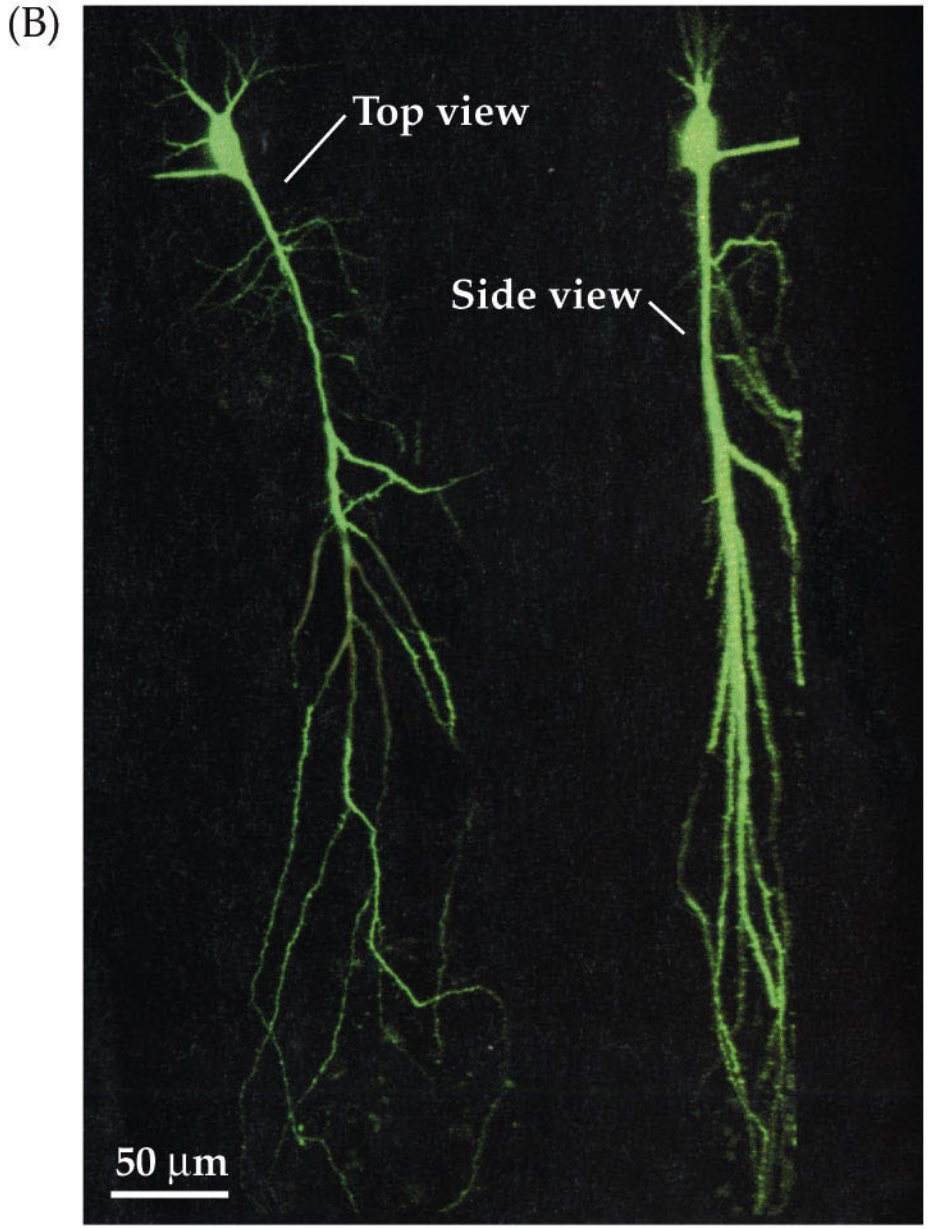
Role of protein synthesis in maintaining LTP

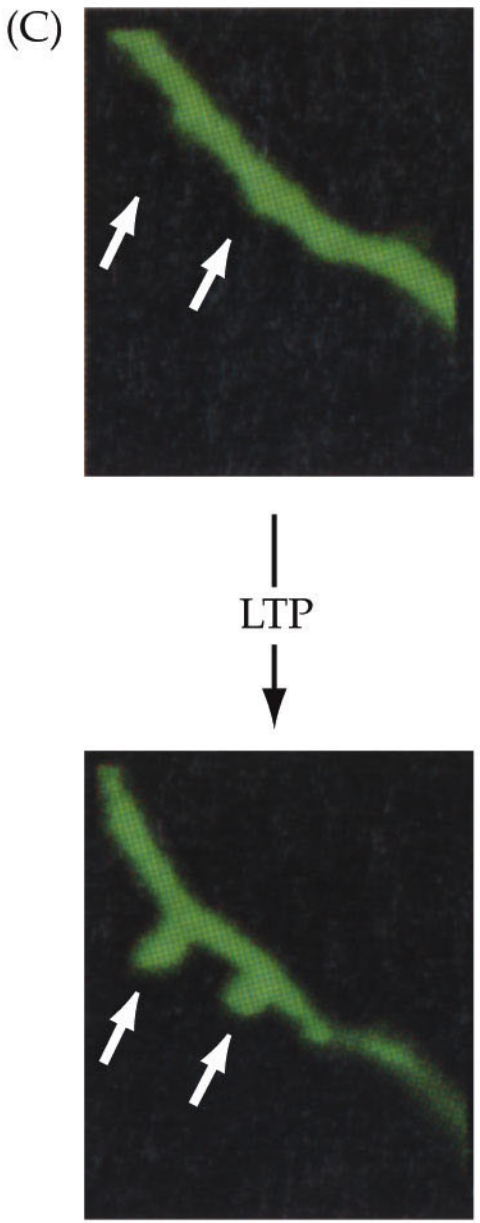


Mechanisms causing synaptic change in LTP

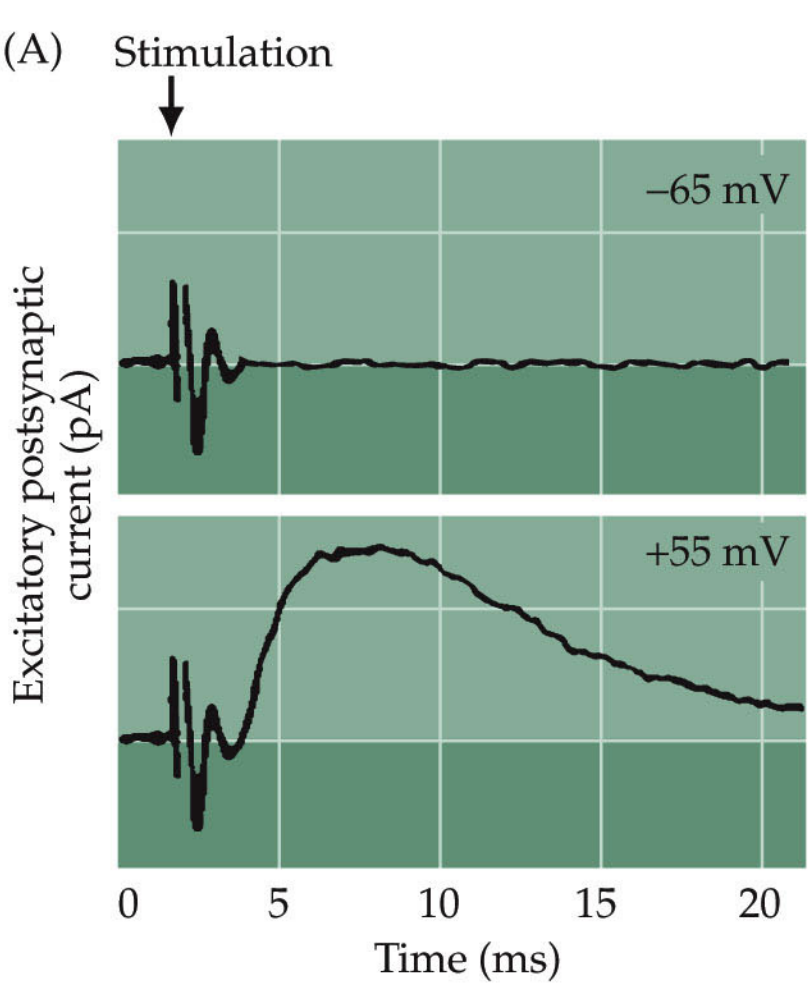


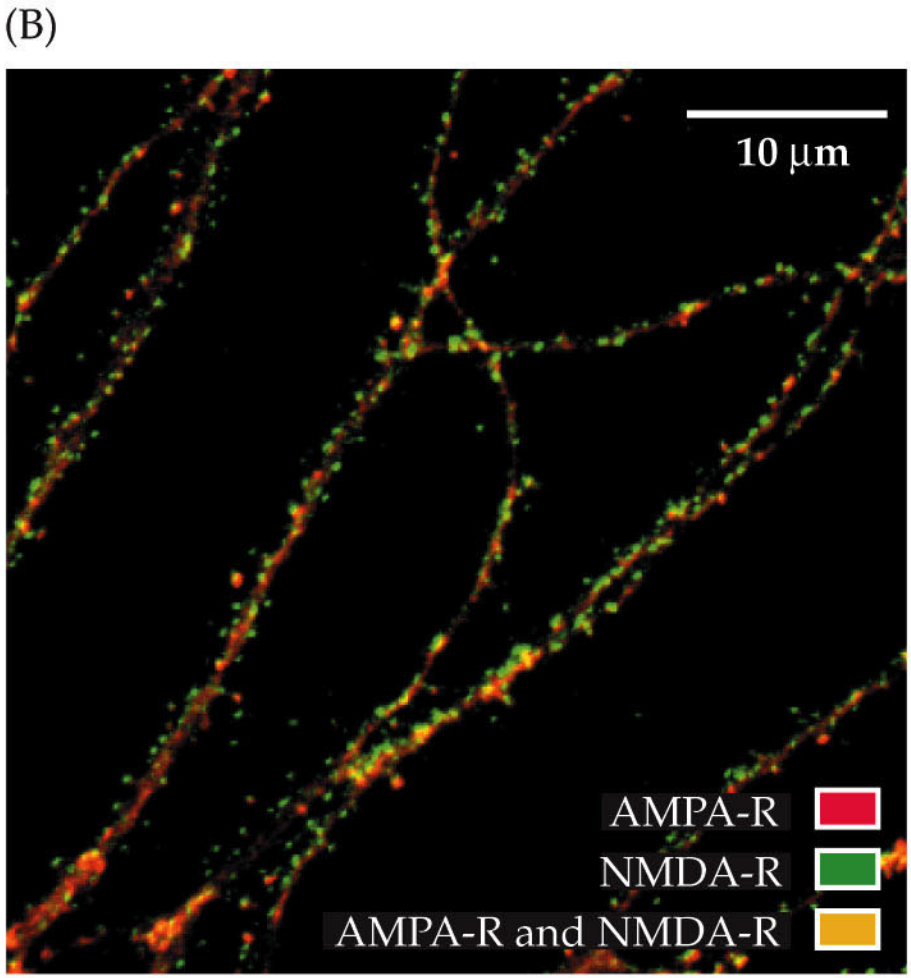
Mechanisms causing synaptic change in LTP



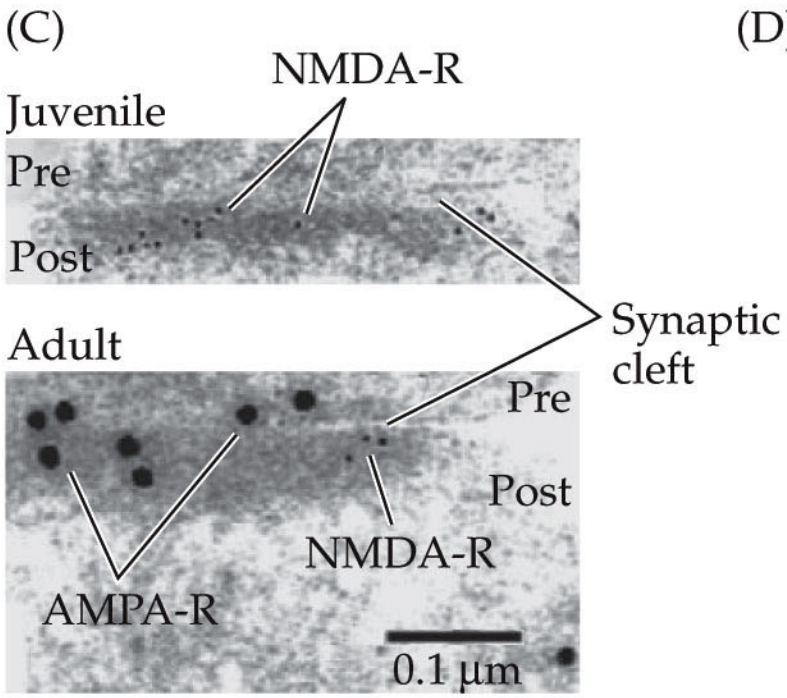


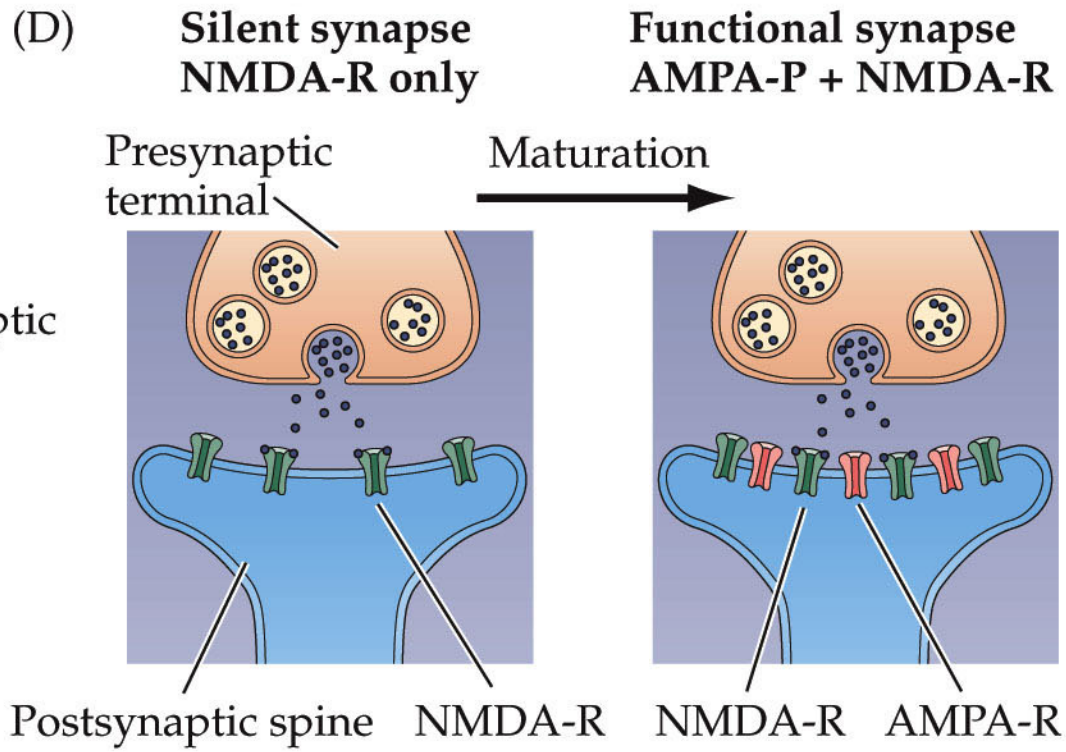
Silent Synapses



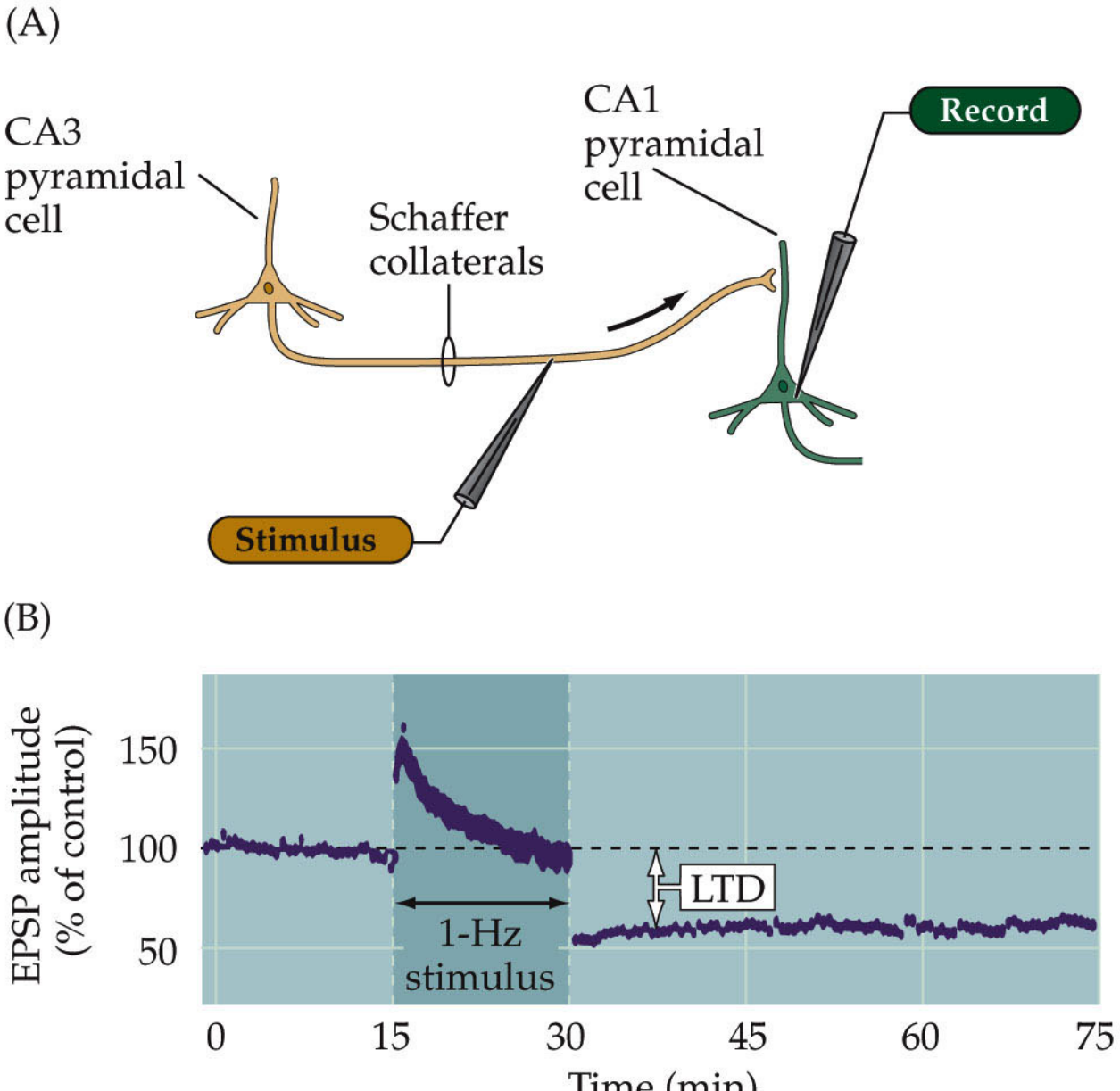


Silent Synapses

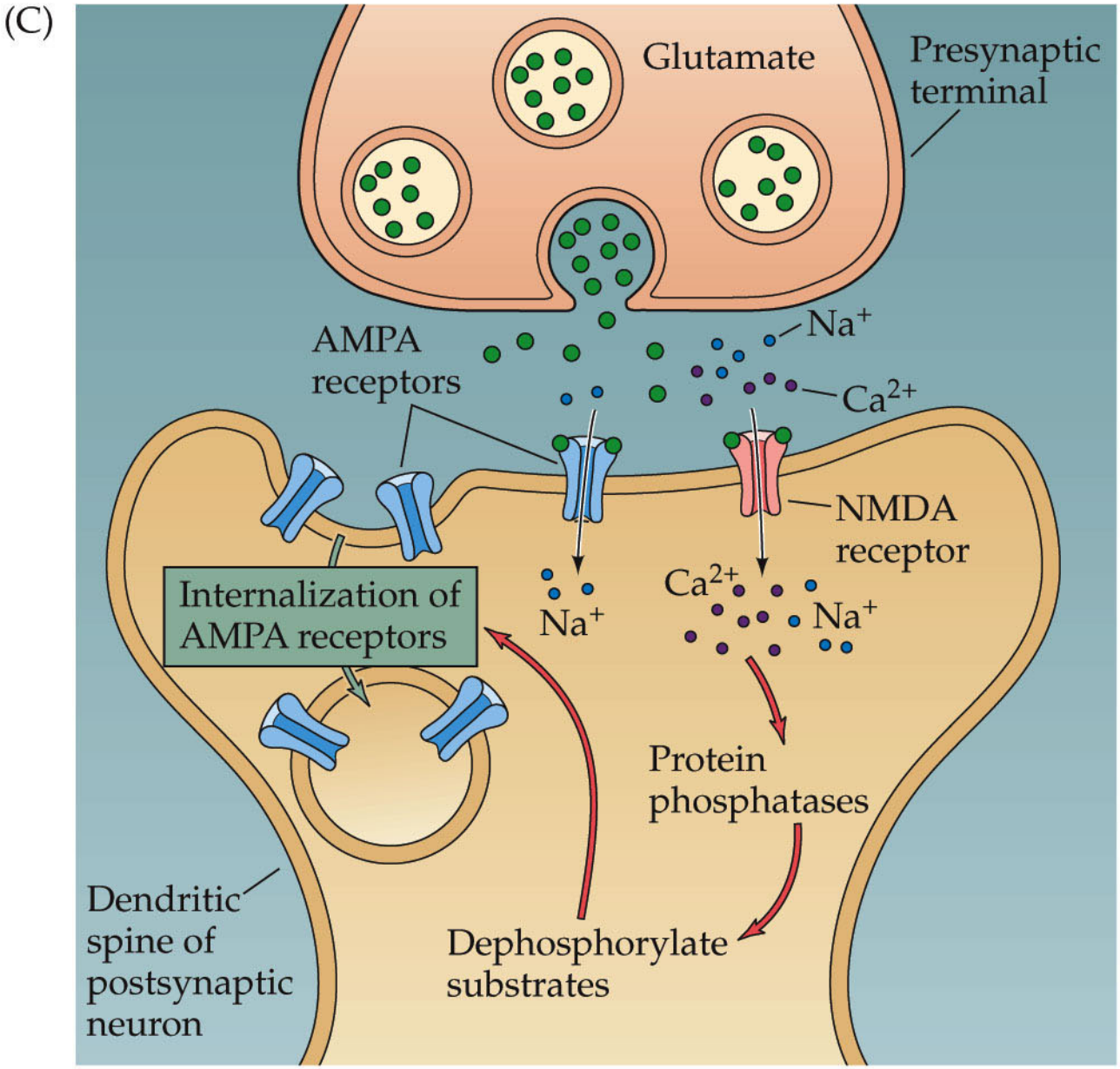


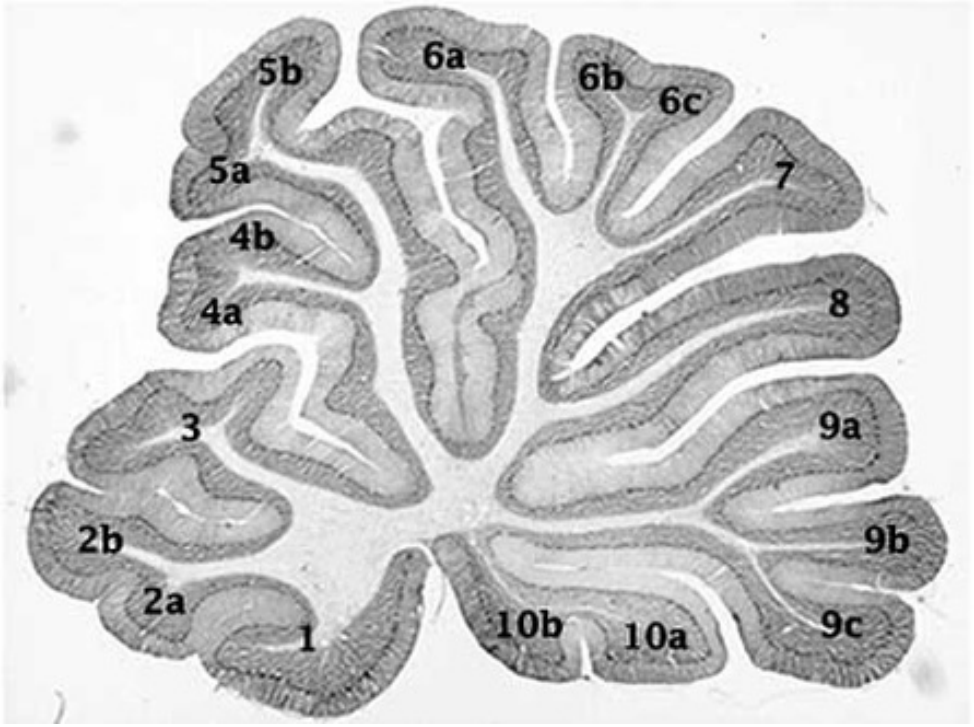


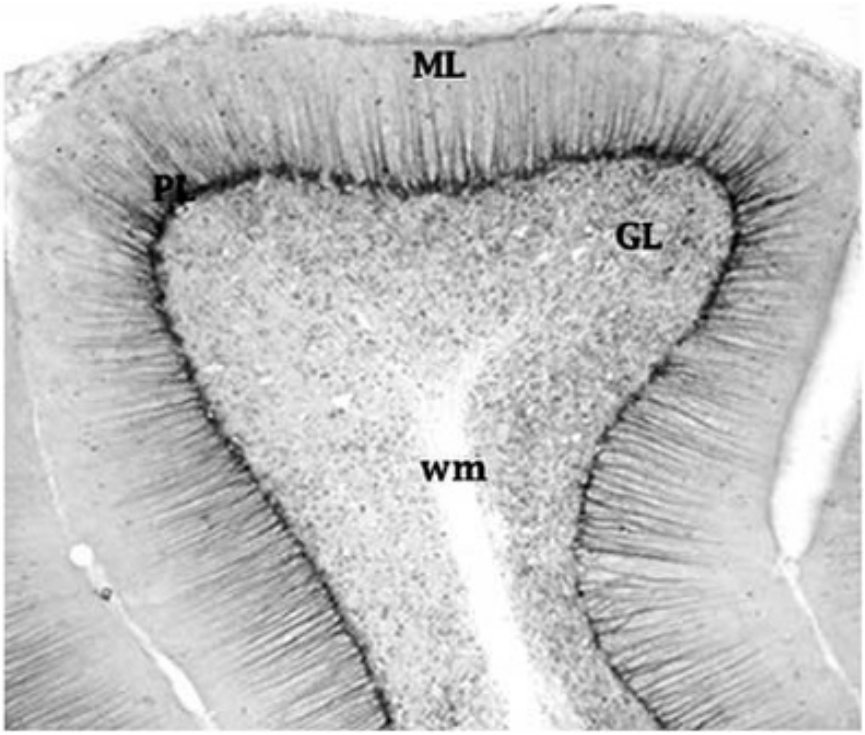
Long-term synaptic depression in the hippocampus



Long-term synaptic depression in the hippocampus




5b
6a
6b
6c
5a
7
4b
4a
8
3
9a
2b
9b
2a
1
10b
10a
9c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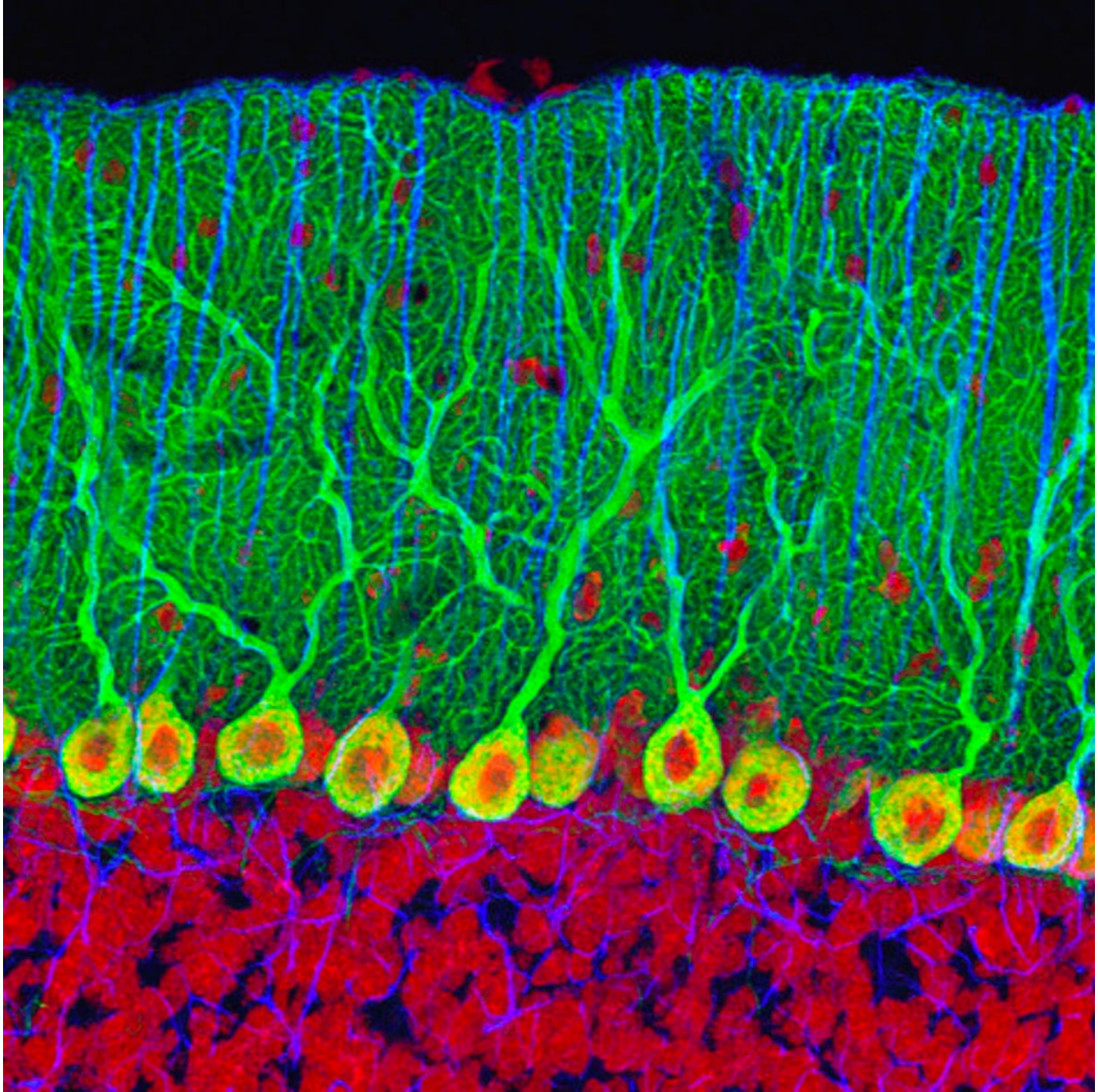
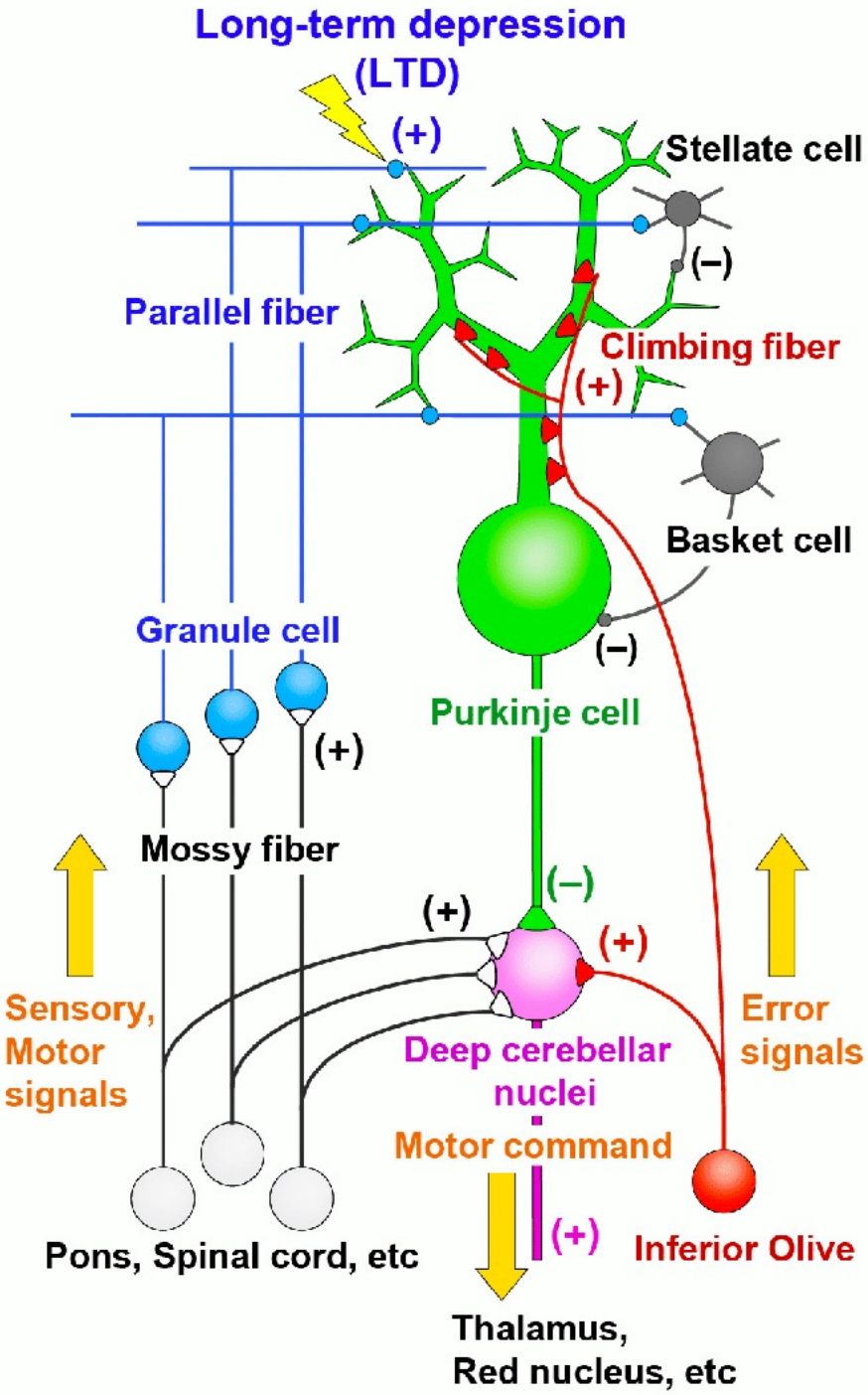
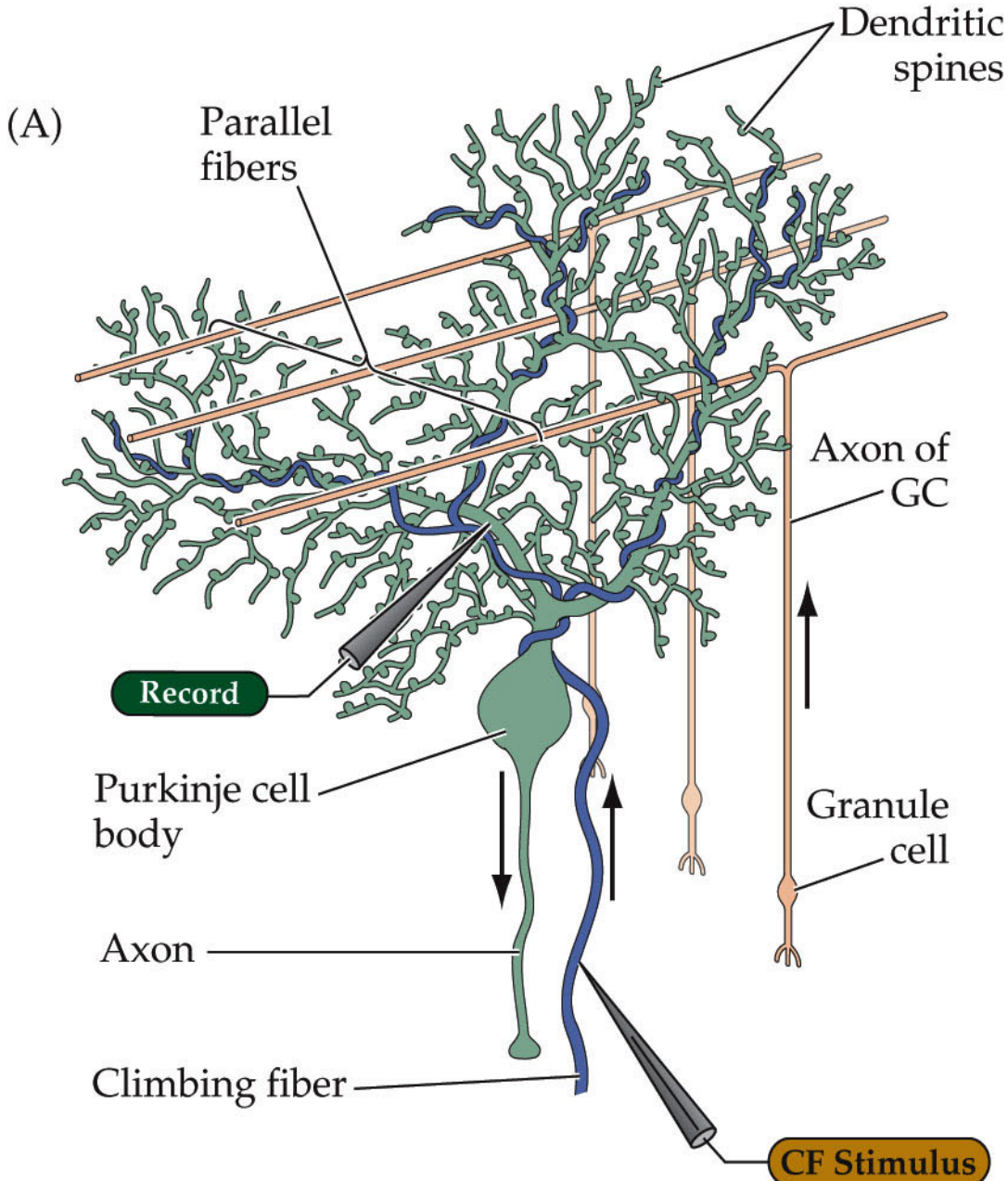
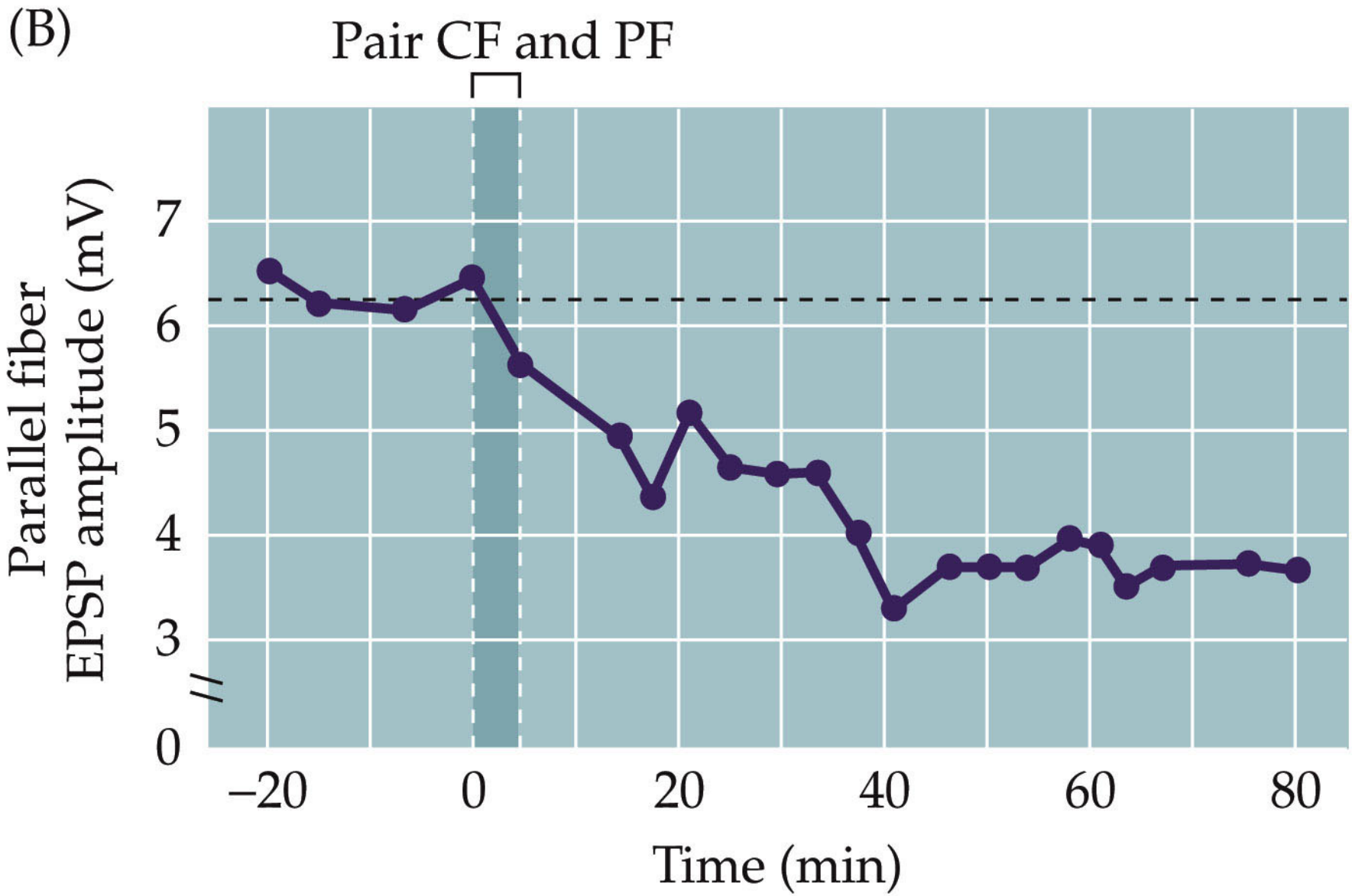



Long-term depression
(LTD)
(+)
Stellate cell
(–)
Parallel fiber
Climbing fiber
(+)
Basket cell
(–)
Granule cell
Purkinje cell
(+)
Mossy fiber
(–)
(+)
(+)
Sensory,
Motor
signals
Error
signals
Deep cerebellar
nuclei
Motor command
(+)
Inferior Olive
Pons, Spinal cord, etc
Thalamus,
Red nucleus, etc

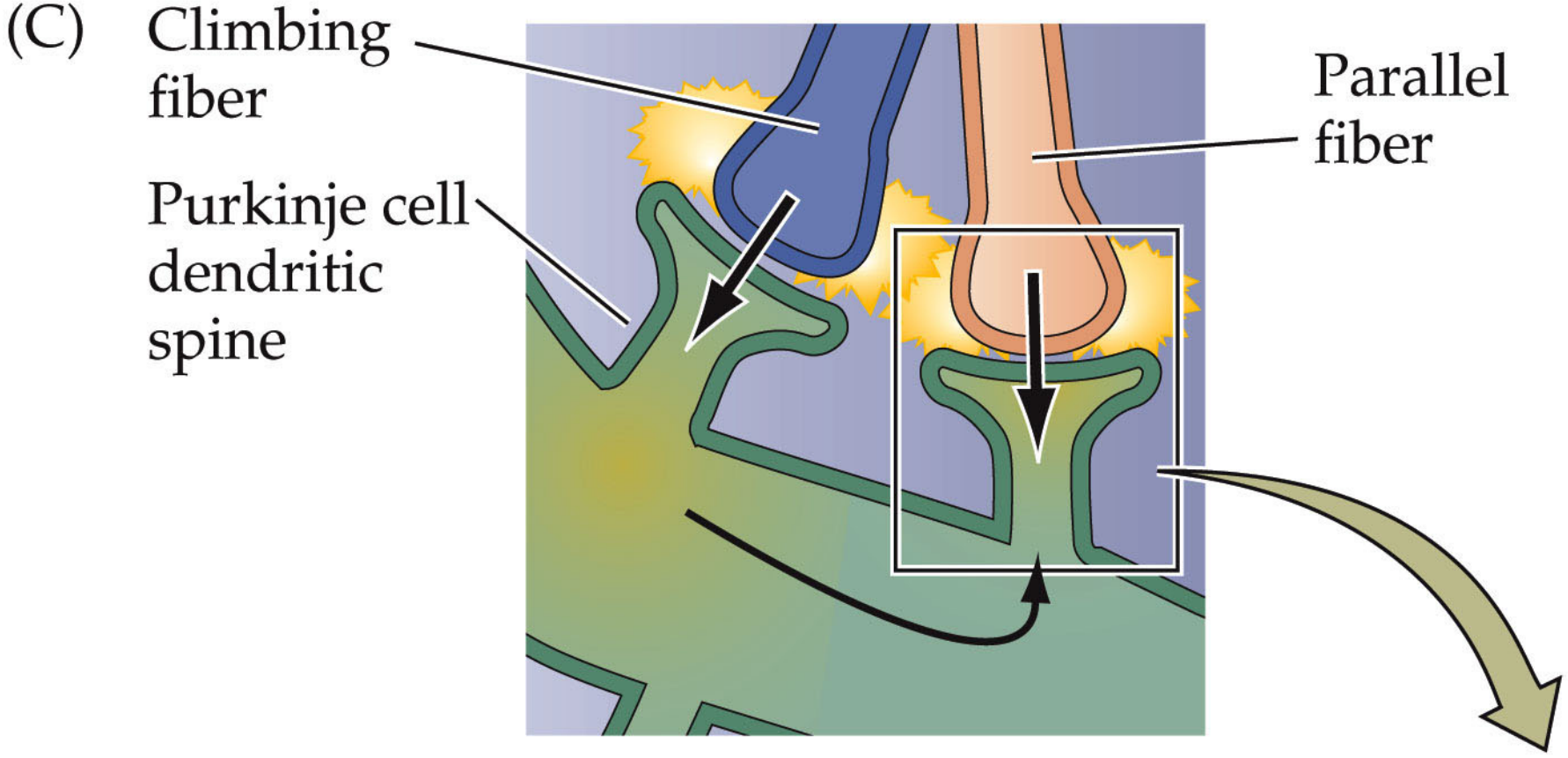
LTD in the cerebellum



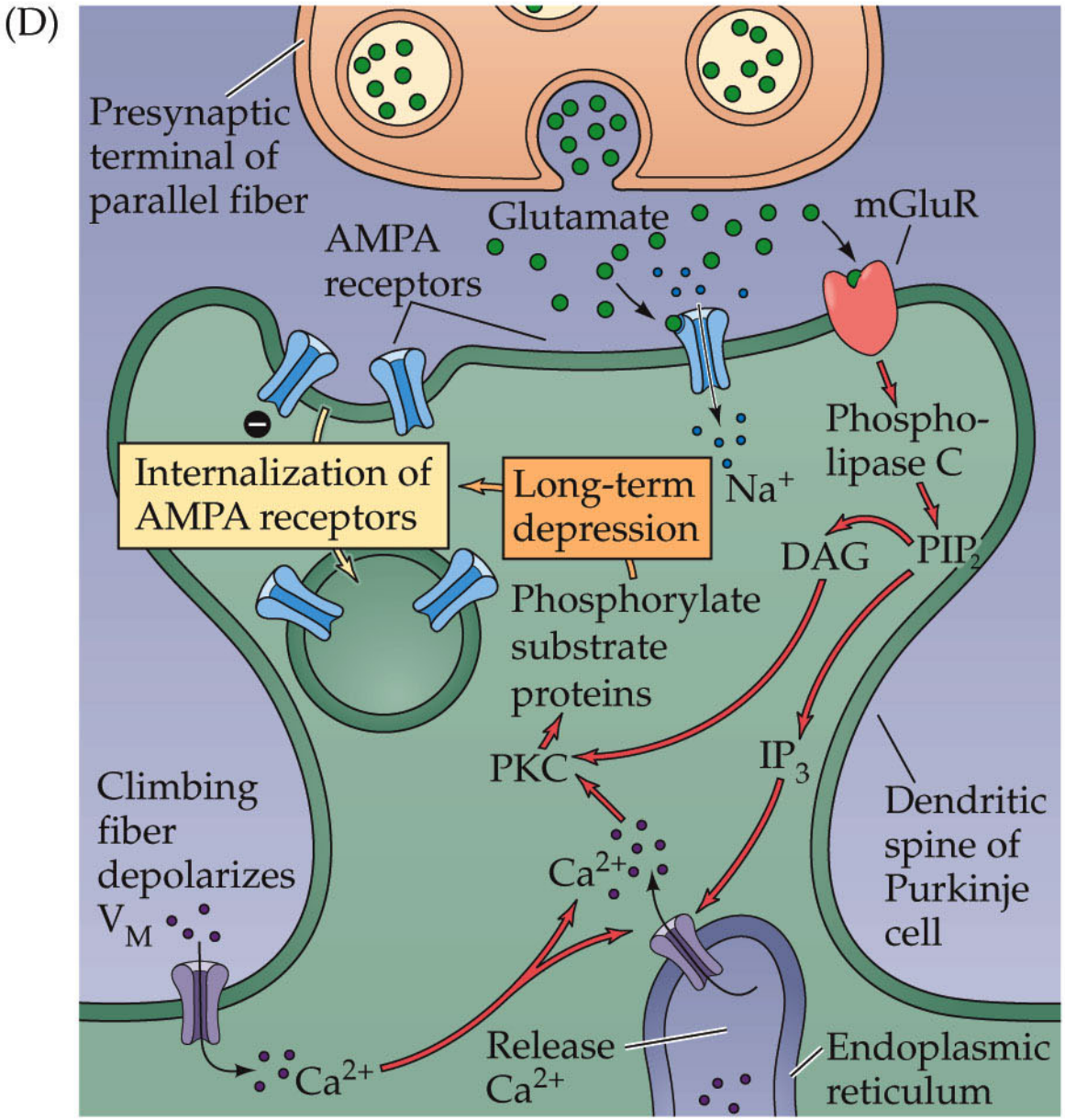
LTD in the cerebellum



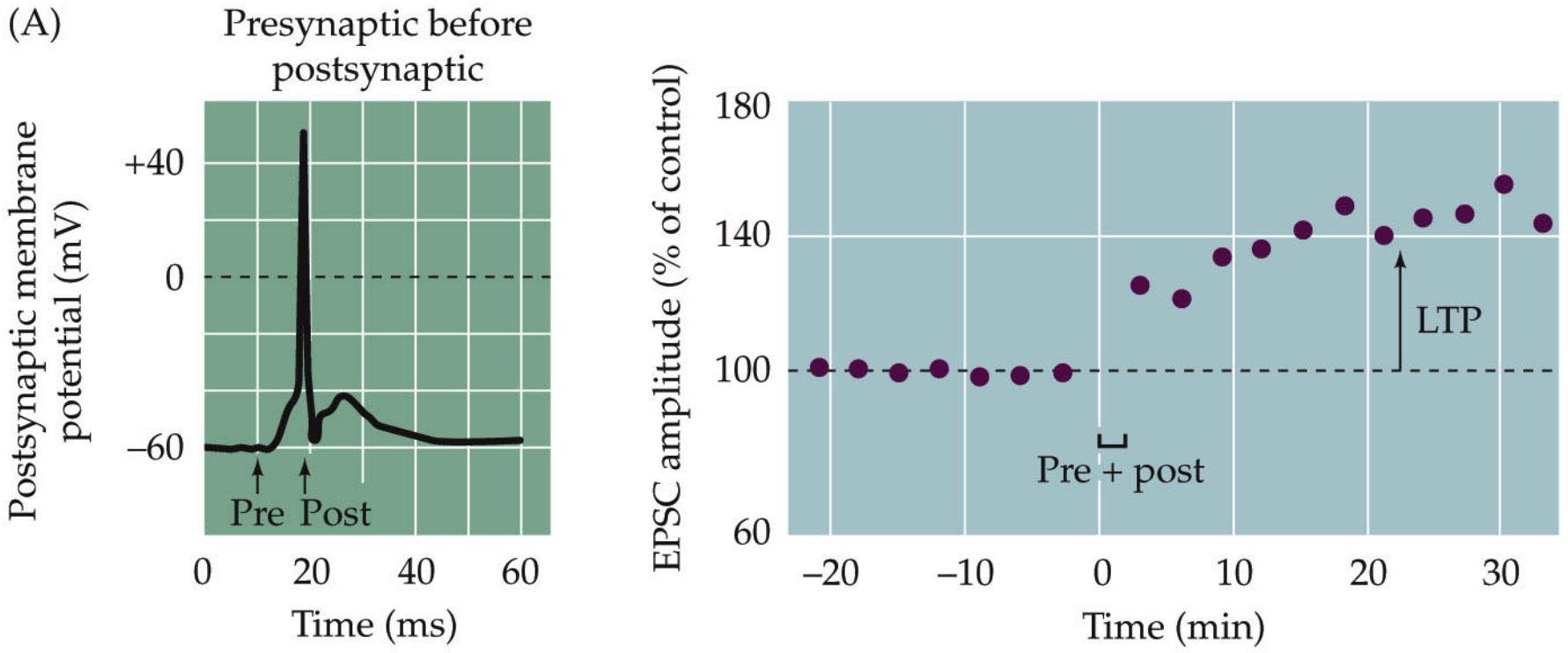
LTD in the cerebellum



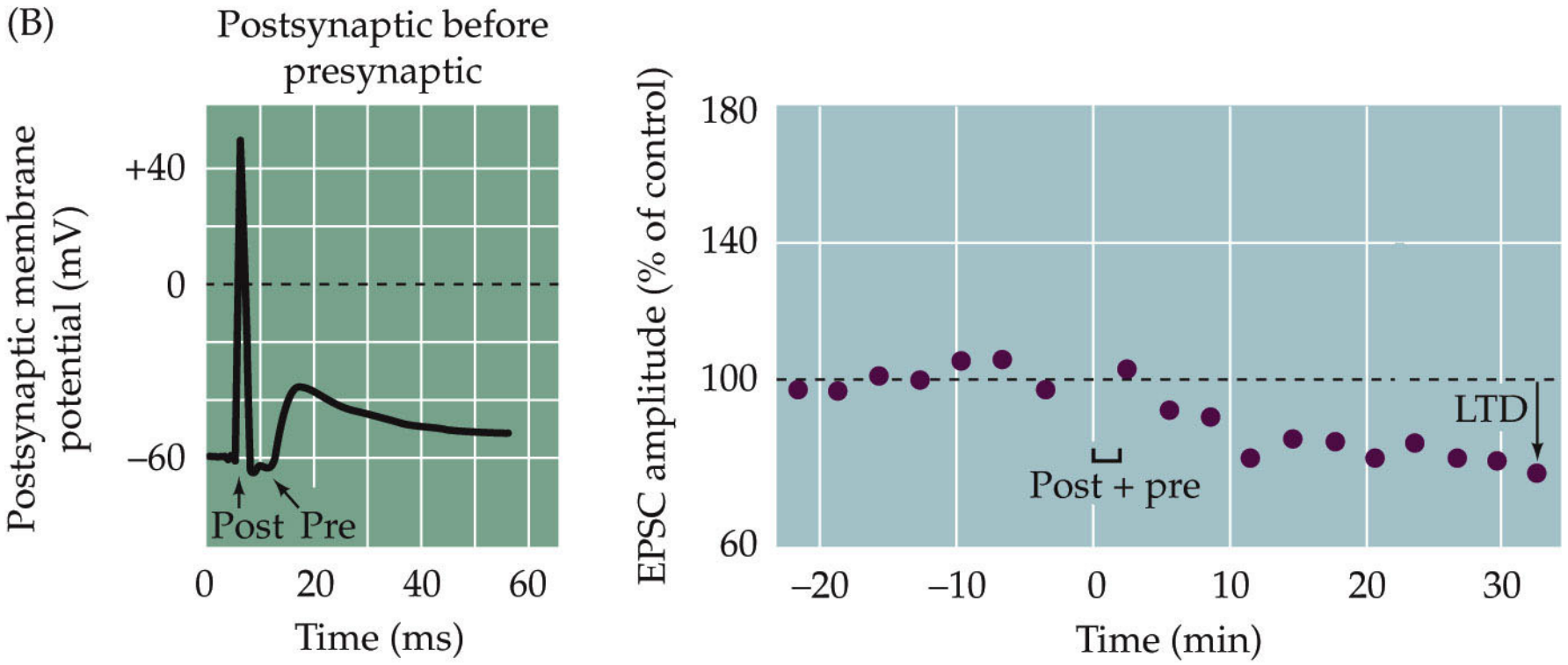
LTD in the cerebellum



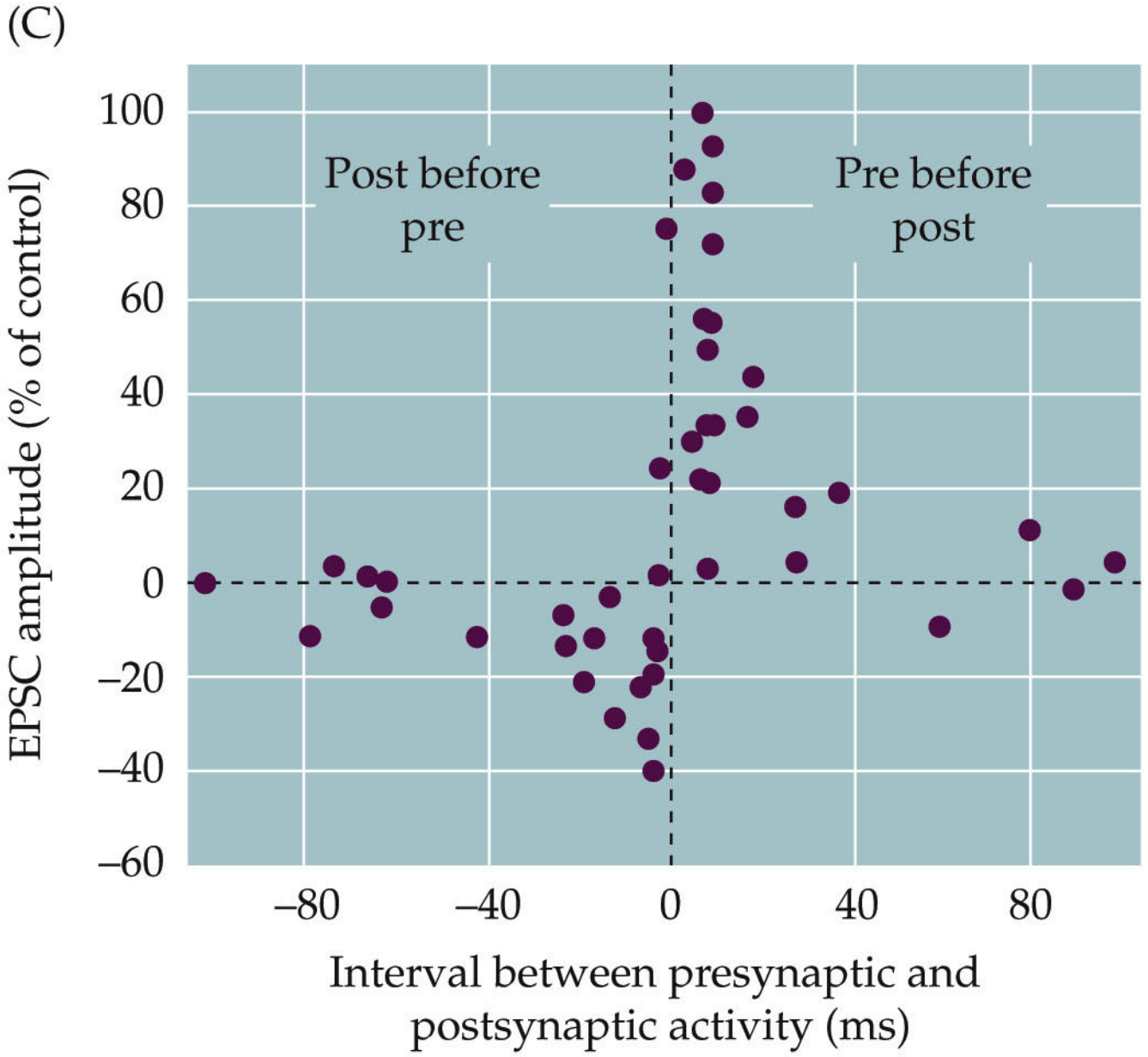
Spike timing-dependent synaptic plasticity in cultured hippocampal neurons



Spike timing-dependent synaptic plasticity in cultured hippocampal neurons



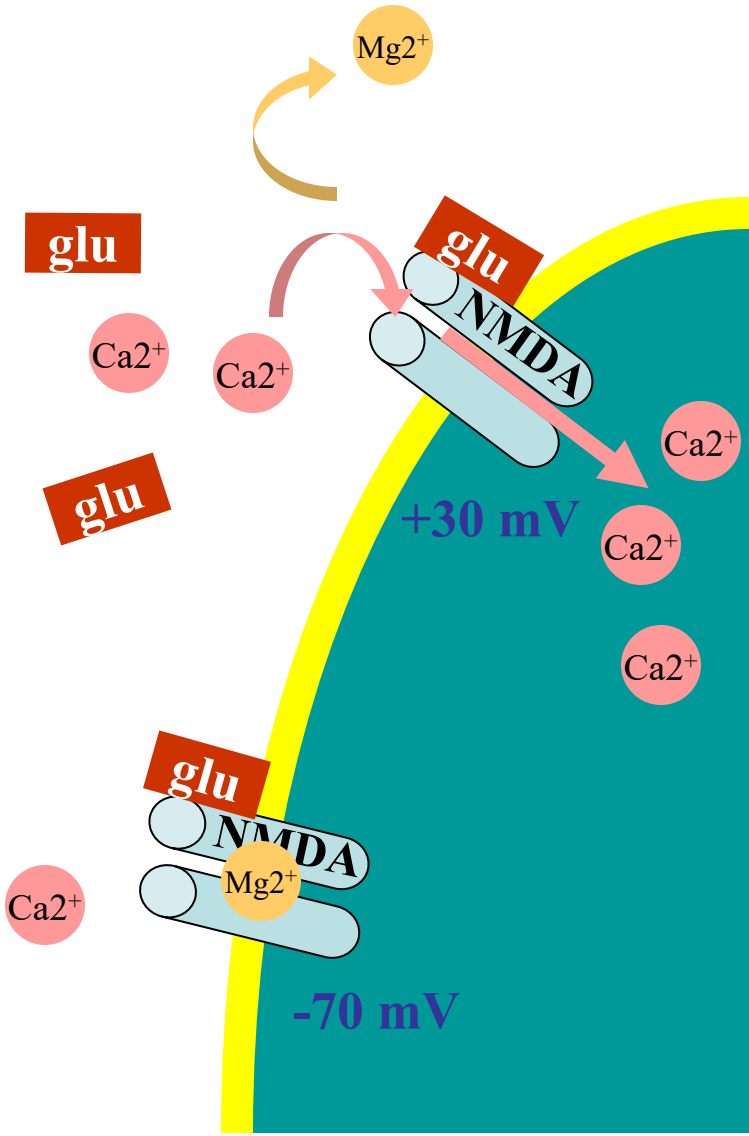
Spike timing-dependent synaptic plasticity in cultured hippocampal neurons



NMDA receptor-dependent LTP competitive antagonists of the NMDA receptor (D-AP5) prevent the induction

NMDAR properties suggest a role in LTP induction at Hebbian synapses:

- Permeable to Ca^{2+} (and Na^{+}, K^{+})
- Blocked by Mg^{2+} at the resting potential
- If the postsynaptic membrane is depolarized, Mg^{2+} is expelled.



NMDARs "***coincidence detectors***" for presynaptic neurotransmitter release and postsynaptic depolarization.

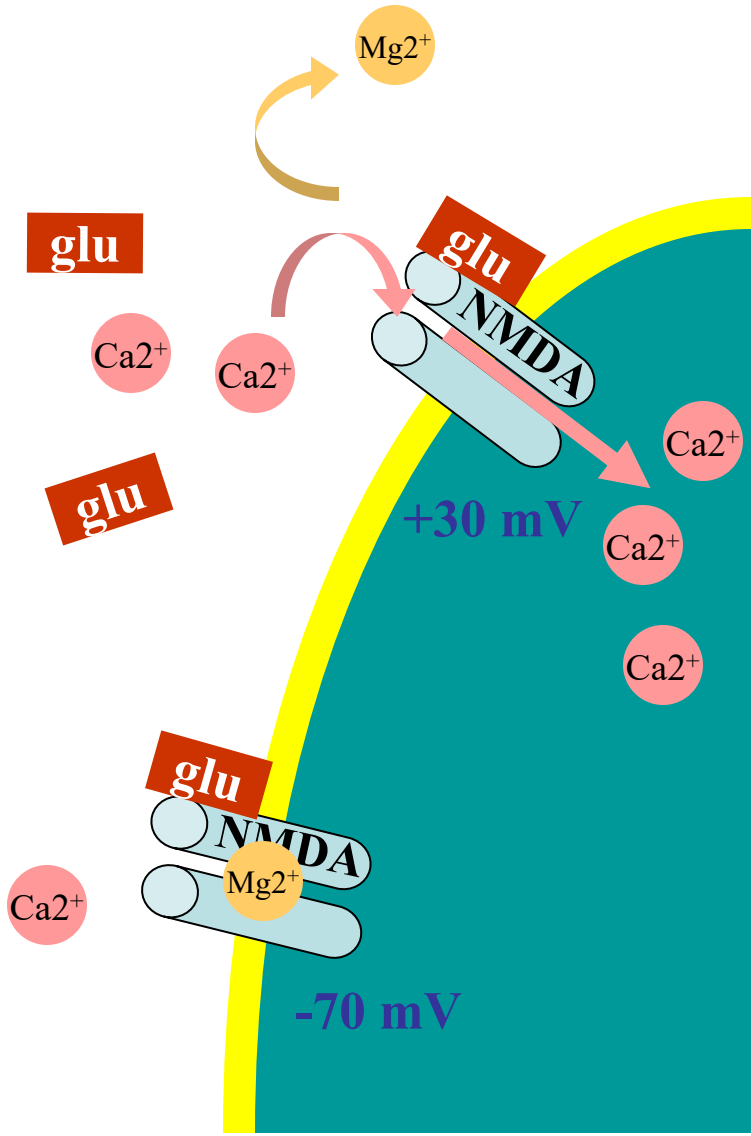
NMDA receptor-dependent LTP- Hebbian LTP

Schaffer collateral inputs to CA1 pyramidal cells

NMDA receptor-mediated Ca^{2+} conductance is voltage-gated

1. **postsynaptic membrane potential**
2. **glutamate availability**
   determined by presynaptic glutamate release in accordance with presynaptic action potentials.

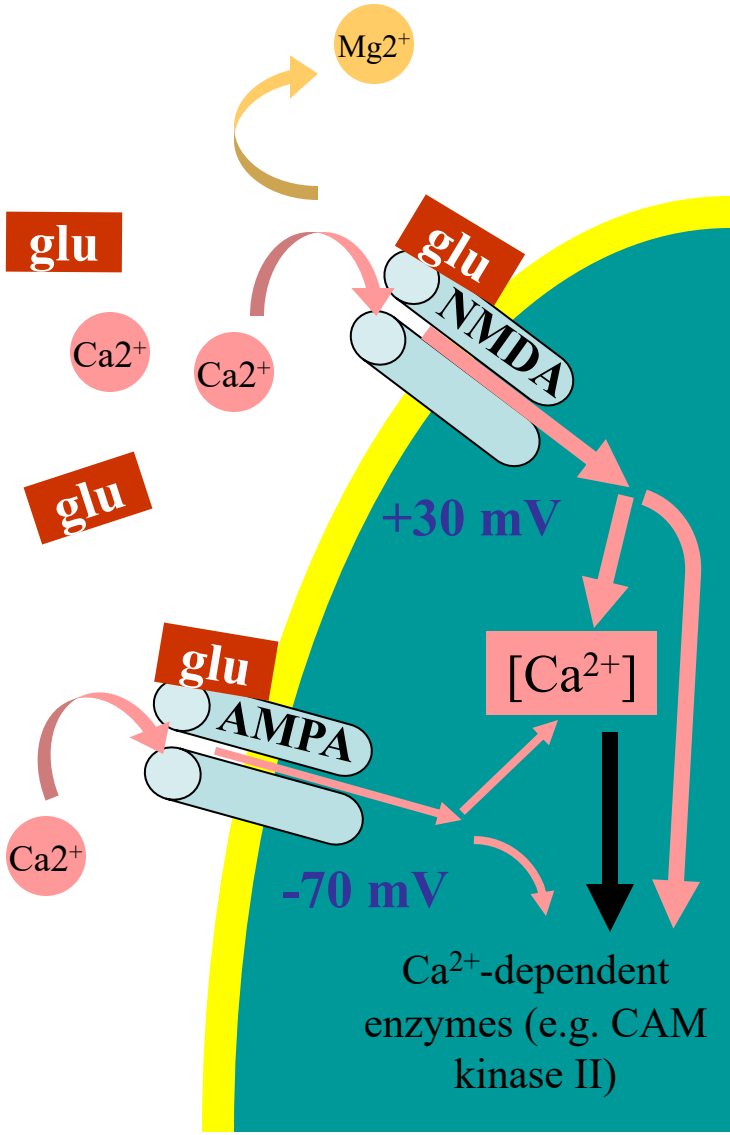
Activation of NMDAR is dependent on *contiguous* pre- and post-synaptic activity.



The **AMPA receptor**

- Does not exhibit voltage-dependent blockage by Mg^2
- Is less conductive of Ca^{2+} than the NMDAR.

Ca^{2+} influx through AMPAR and NMDAR activate Ca^{2+}-dependent enzymes **CaM kinase II.**



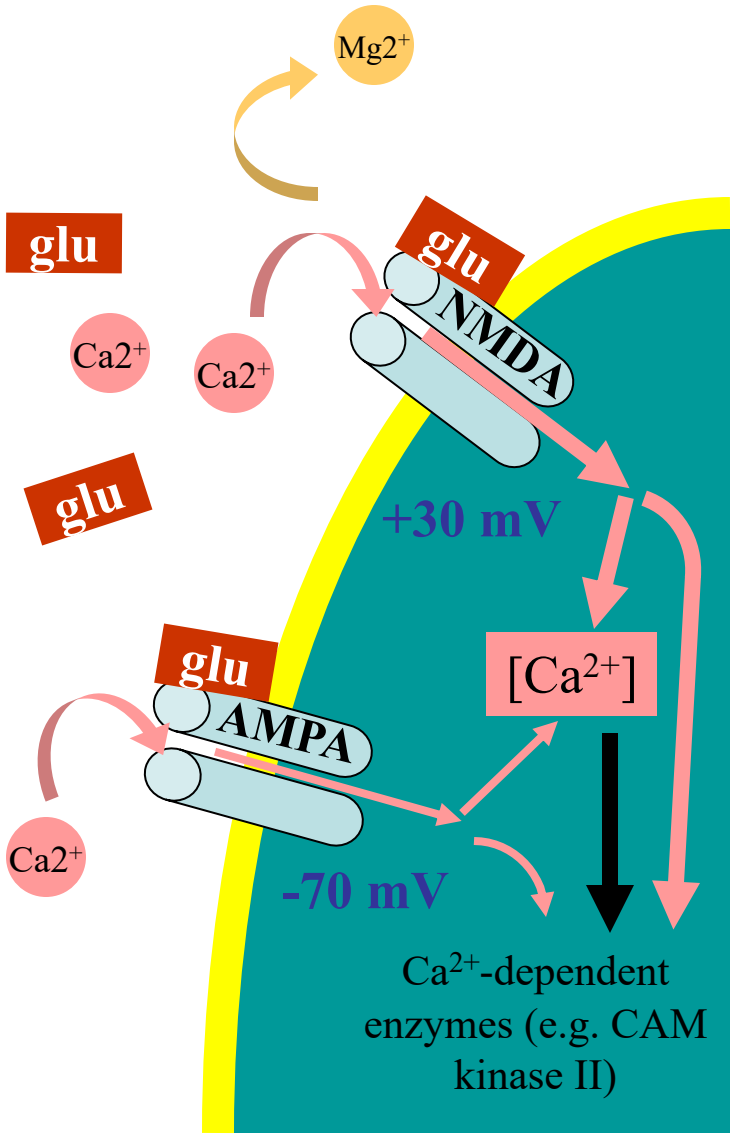
weak inputs

- Allow a small amount of Ca^{2+} influx through AMPARs
- Do not produce enough depolarization to remove the Mg^{2+} block from NMDARs

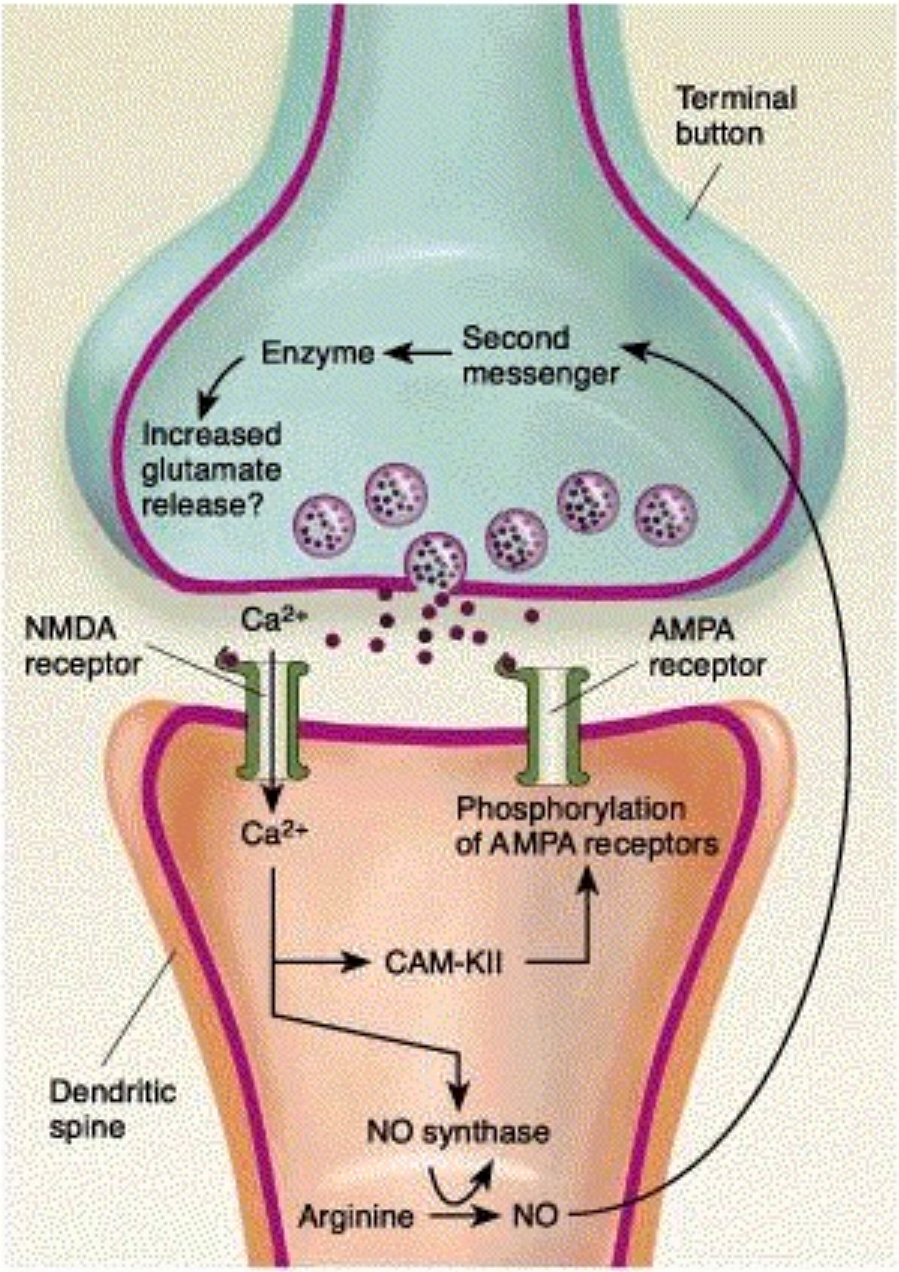
A weak input can activate large amounts of Ca^{2+} influx through NMDA receptors if that weak input is properly timed in relation to a strong input.

All occurs in *dendritic spines*.

- compartmentalizing the intracellular Ca^{2+} signal
- concentrate the signal in the head of the spine where Ca^{2+}-dependent enzymes are localized.



▶ Long-Term Potentiation



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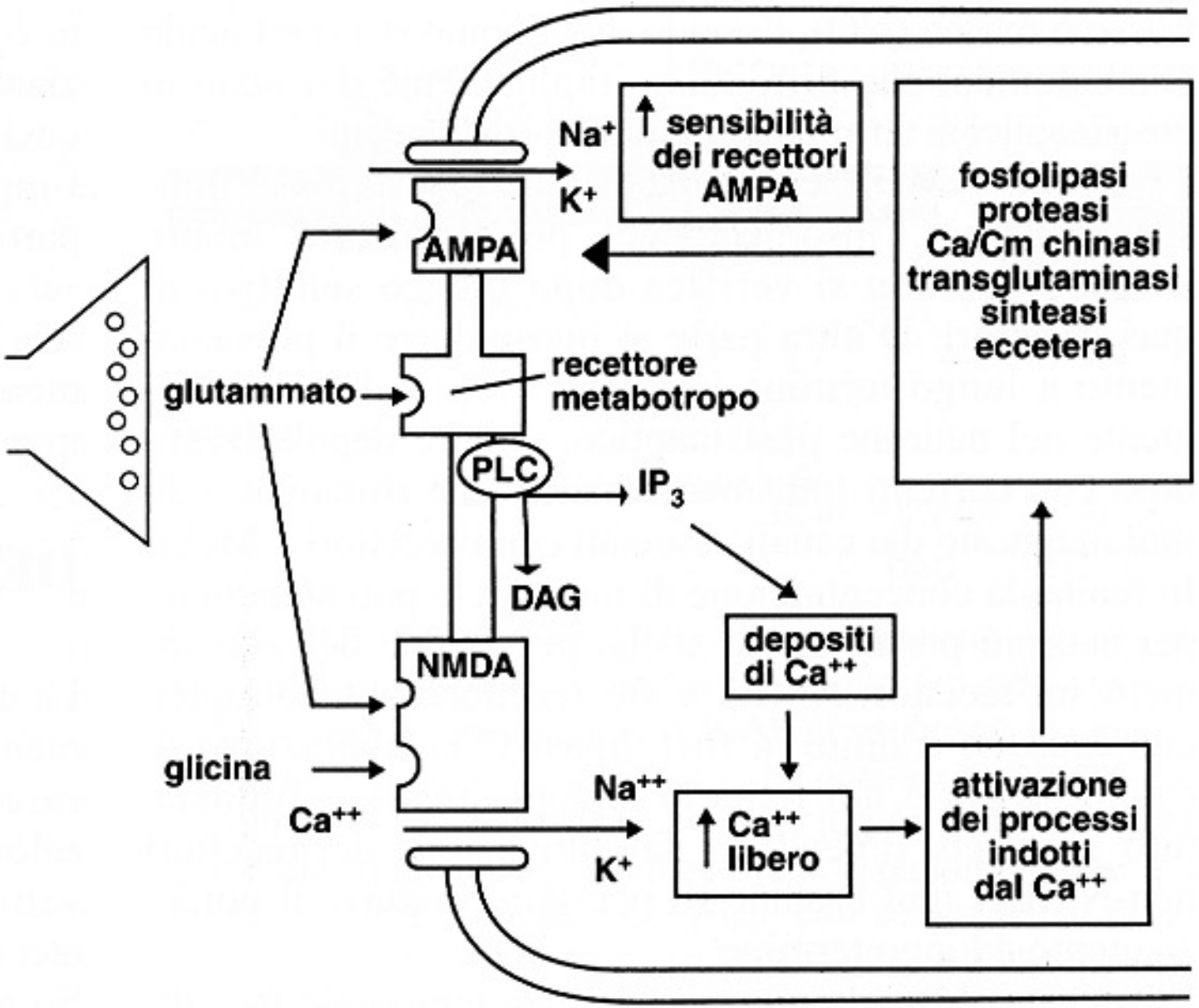
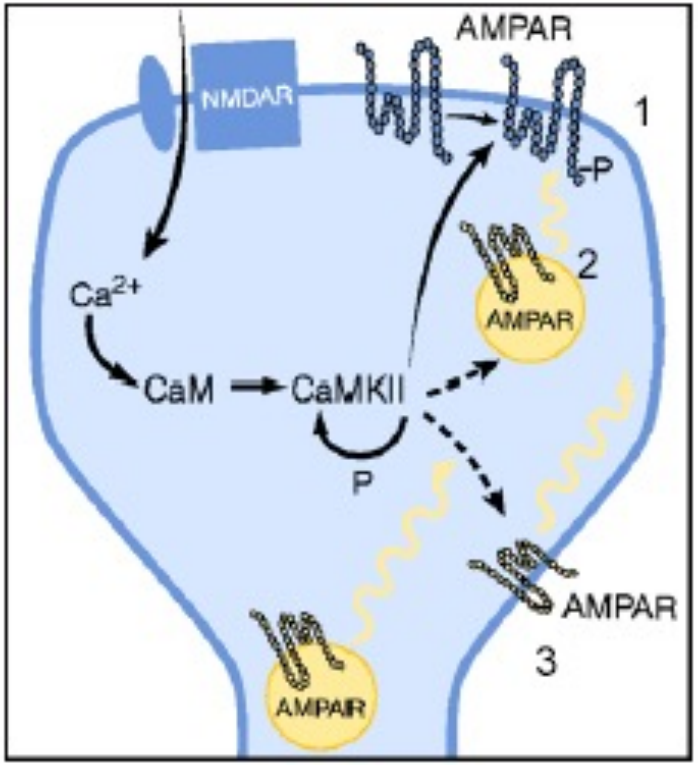
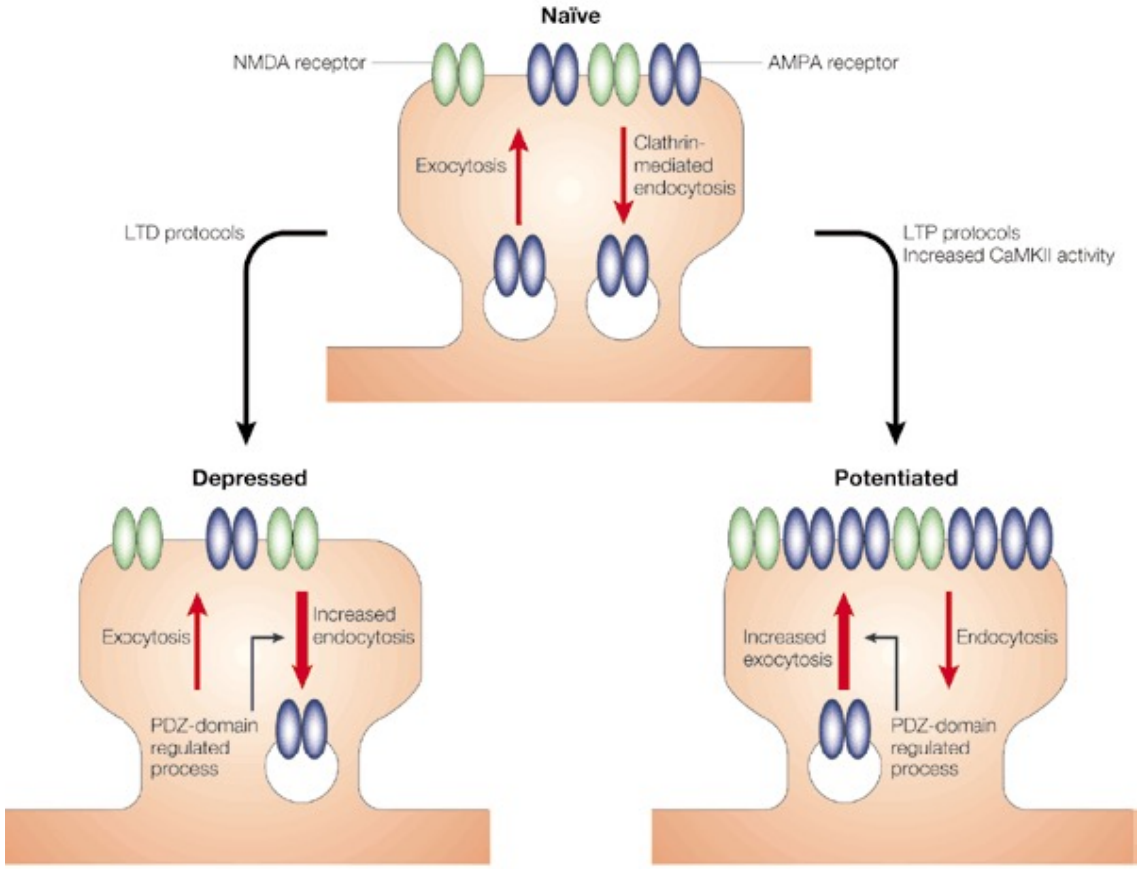
modificazioni a breve termine



After Ca^{++} entry: Molecules for storing memories

- CaMKII auto-phosphorylates
- CaMKII phosphorylates the AMPA receptor (1)
- CaMKII is involved in trafficking of AMPAR (2) and (3)





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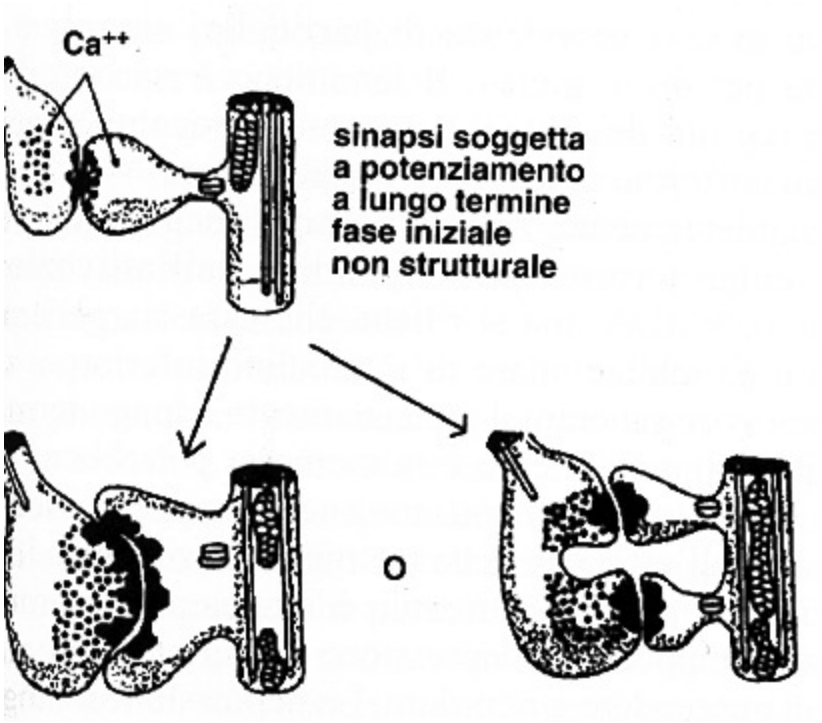
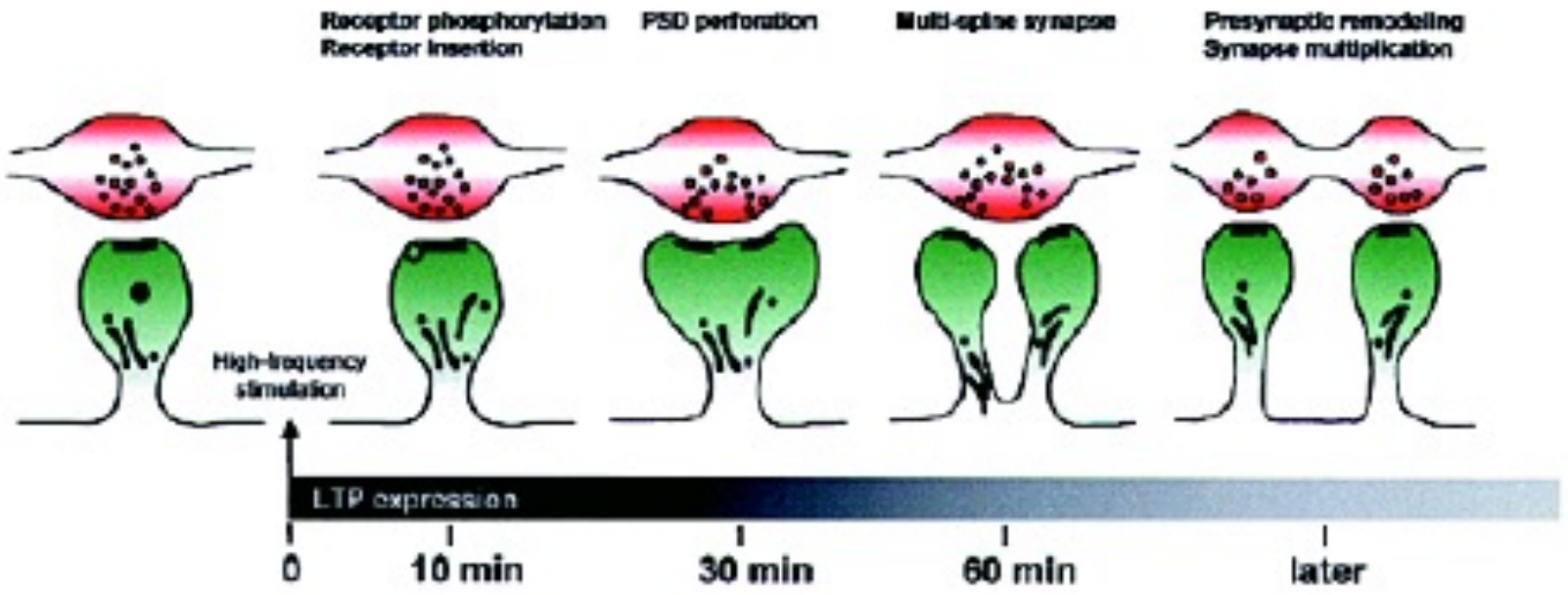
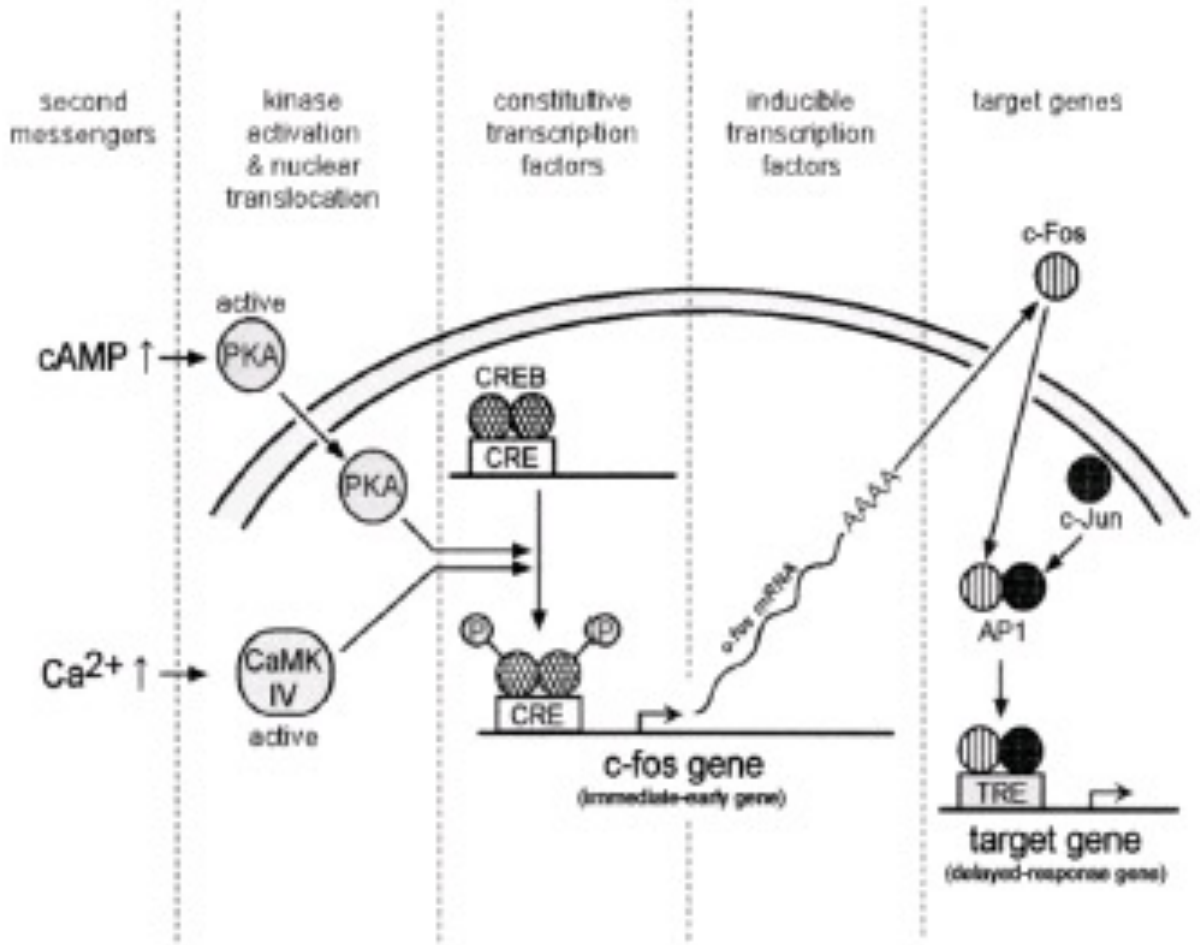
modificazioni a lungo termine



Strengthening of Synapse at different time-scales

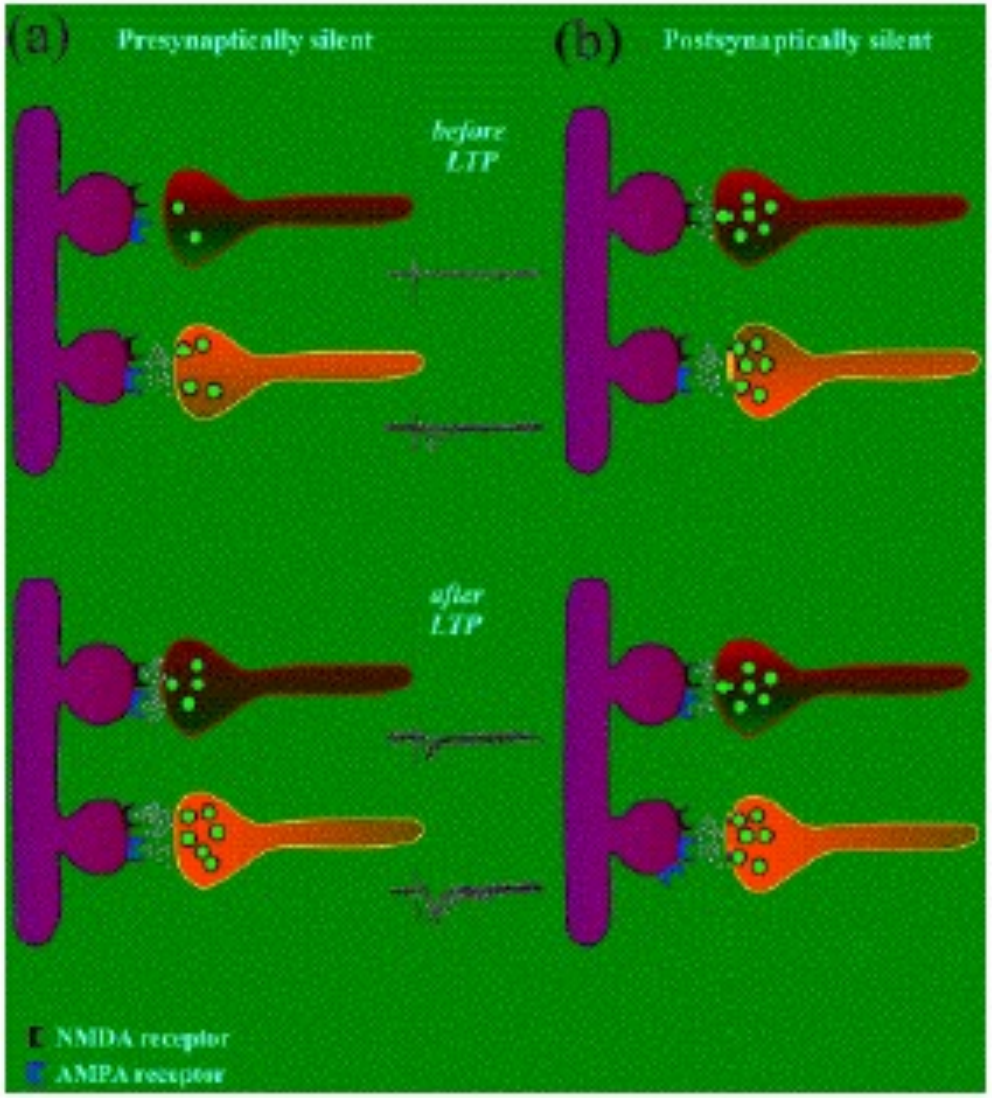


Activation of Genes for Long-Term Memory

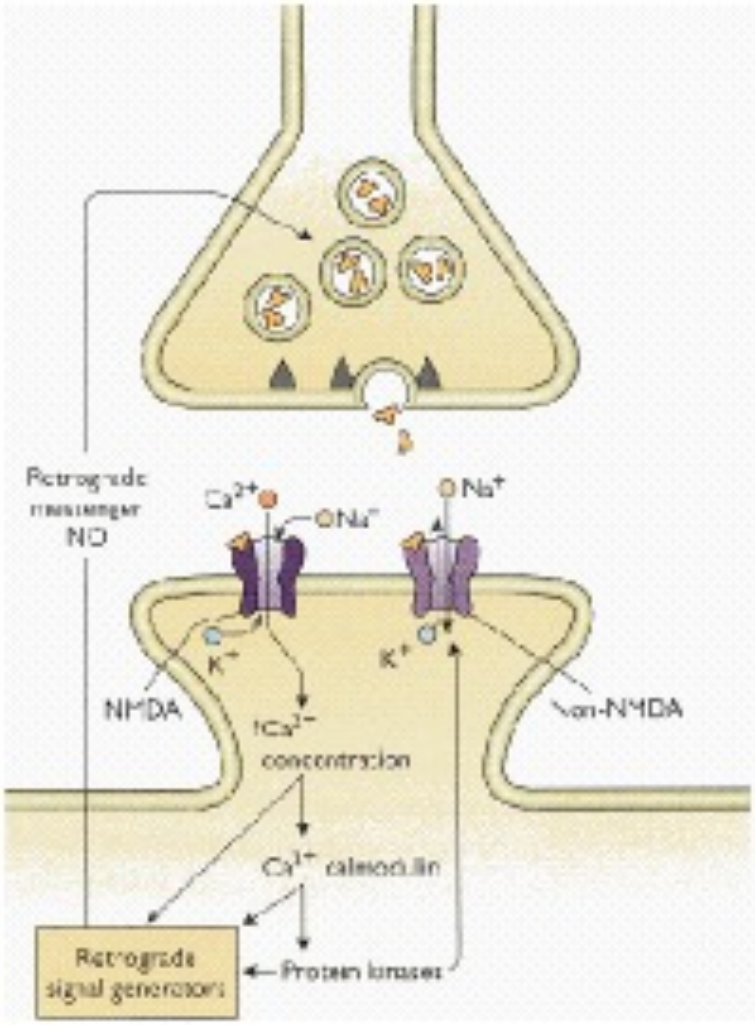


- Plasma membrane AMPA-Rs are also phosphorylated and become more active.
- CamKII is not the only relevant kinase.
- The dendrite may sprout new spines.
- Gene expression is necessary for long-lasting changes.
- Something happens presynaptically.

Involvement of presynaptic and postsynaptic “silent” synapse to LTP



Retrograde messenger



- nitric oxide
- carbon monoxide
- arachidonic acid

Mechanisms of LTP expression

Once LTP has been induced, what physical modifications mediate its expression?

A variety of models has been proposed.
These models focus on increased neurotransmitter release (presynaptic) or increased receptivity to neurotransmitter (postsynaptic).

[Reciprocal communication has been identified between pre- and post-synaptic elements across the synapse.]

In the crayfish neuromuscular junction it has been clearly
is produced by increased quantal release of neurotransmi
Analyses of the mechanisms of LTP expression in mammals have produced contradictory results.

In mossy fiber inputs to CA3, there appear to be increases in neurotransmitter release, but in other hippocampal synapses there appear to be postsynaptic changes.

Changes in neurotransmitter release –

1- Preexisting but “silent” release sites that could be “unsilenced”:

- failure of neurotransmitter vesicles to dock appropriately at the release site
- absence of functioning postsynaptic receptors opposite the release site
- absence of functioning VGCCs adjacent to the release site.

2- Formation of new release sites.

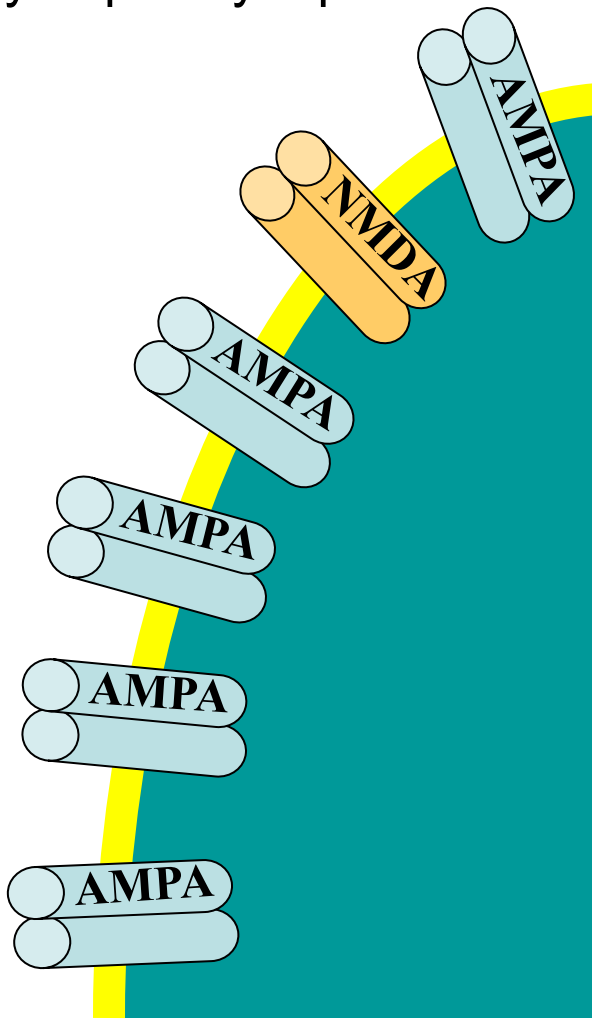
3- Altered coupling of the action potential to neurotransmitter release.

4- Alteration in the action potential in the nerve terminal itself (as in *aplysia*).

Changes in receptivity to released neurotransmitter –

1- Decrease in the axial resistance of dendritic spines (unlikely).

2- Increase in the probability that released neurotransmitter will bind to postsynaptic receptor (increase in the number or affinity of postsynaptic AMPA receptors).



How can a synaptic change endure over long periods of time in the face of constant molecular turnover?

Alterations in gene expression -
High frequency stimulation of the rat hippocampus increases overall hippocampal RNA concentrations.
Long term memory is associated with protein synthesis.

- High frequency stimulation applied to a hippocampal section. LTP is observed, lasting more than 4 hours.
- When actinomycin is applied to a hippocampal section, synaptic potentiation is observed for the first 2 hours, and then it declines back to baseline. Actinomycin administration just 2 hours after stimulation does not impair LTP. Accordingly,

LTP has 2 components - a brief, protein synthesis-independent component, and a long-lasting protein synthesis-dependent component. Protein-synthesis dependent later stages of LTP have been observed in a broad variety of organisms. These actions must involve second messenger cascades (cAMP, PKA, CREB…).

Long-Term Potentiation

Mechanisms of LTP maintenance -

Question: How can a synaptic change endure over long periods of time in the face of constant molecular turnover?

Alterations in gene expression -

However, general changes in nuclear gene transcription should affect all synapses associated with the affected neuron. This raises the question "How is synaptic input specificity achieved?"

This issue is unresolved. One potential solution is for the synapse to produce a local "marker" that makes it more susceptible to the effects of upregulated transcription of particular proteins. Another possibility is the generation of an enduring modification of local transport of transcribed proteins.

Summary and Conclusions

1) Recent investigations on the biological basis of learning and memory focused on synaptic plasticity. Research is concentrated on the cellular and molecular mechanisms mediating alterations in synaptic strength.

2) Investigations of LTP focused almost exclusively on the role of NMDA receptors until very recently.

3) It is now clear that VGCCs and mGluRs (as well as other mechanisms) play important roles in LTP - particularly in the induction of LTP.

4) LTP and LTD may share a variety of cellular and molecular mechanisms.

5) The expression and maintenance of LTP appears to consist of multiple stages in which differing biological mechanisms are invoked. Protein synthesis appears to be very important in the longer-term stages of LTP.

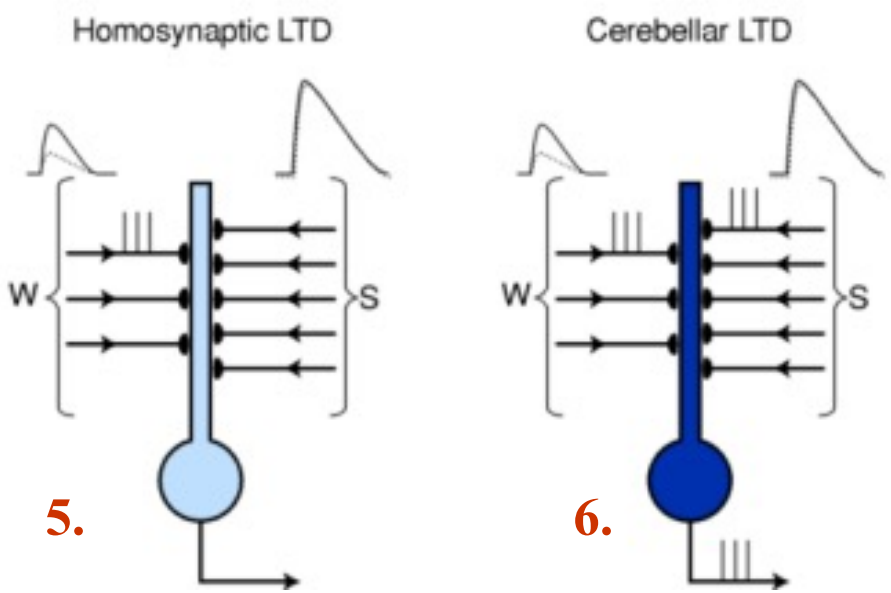
6) The functional significance of LTP and LTD in specific aspects of learning and memory (encoding, storage and retrieval of information) have yet to be established.

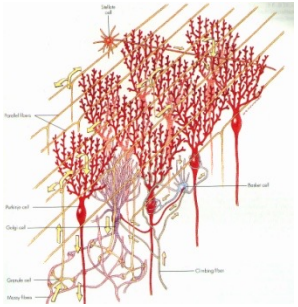
Long-Term Depression

Mechanisms of LTD induction differ from mechanisms of LTP induction -

5. Low frequency stimulation (1-5 Hz) of a weak input produces LTD in that specific synapse.

6. Contiguous low frequency stimulation of a cerebellar parallelfiber and of a cerebellar climbing fiber produces LTD in the parallel fiber synapse, but not in the climbing fiber synapse.





Mechanisms of LTD induction -

LTD is observed in many brain regions in which LTP has been observed

Hippocampus, cortex, and cerebellum.

- Thought to oppose LTP in the hippocampus and cortex.
- Thought to be the mechanism of learning encoding in the cerebellum.

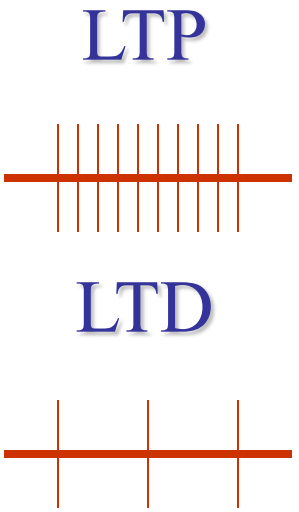
In the hippocampus and cerebellum

- Brief, high-frequency trains of stimulation (4 trains of 10 shocks at 100 Hz) induce LTP
- Low frequency stimulation (1 Hz for 10 minutes) induce LTD.

- NMDA receptor-mediated
- NMDA receptor-independent, mediated by VGCCs.

LTP and LTD are Ca^{2+}-mediated

blocked by injecting Ca^{2+} chelators into the postsynaptic cell.



How can Ca^{2+} entry into postsynaptic cells be involved in bi-directional induction of both LTP and LTD?

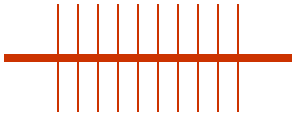
More Ca^{2+} influx occurs at high frequency (LTP-inducing) trains of stimulation than at low frequency (LTD-inducing) trains

High intracellular concentration of Ca^{2+} activates a **protein kinase** that phosphorylates a protein, producing LTP. Low intracellular Ca^{2+} concentration activates a **protein phosphatase**, causing LTD

The balance between these competing reactions will determine the synaptic strength

LTP

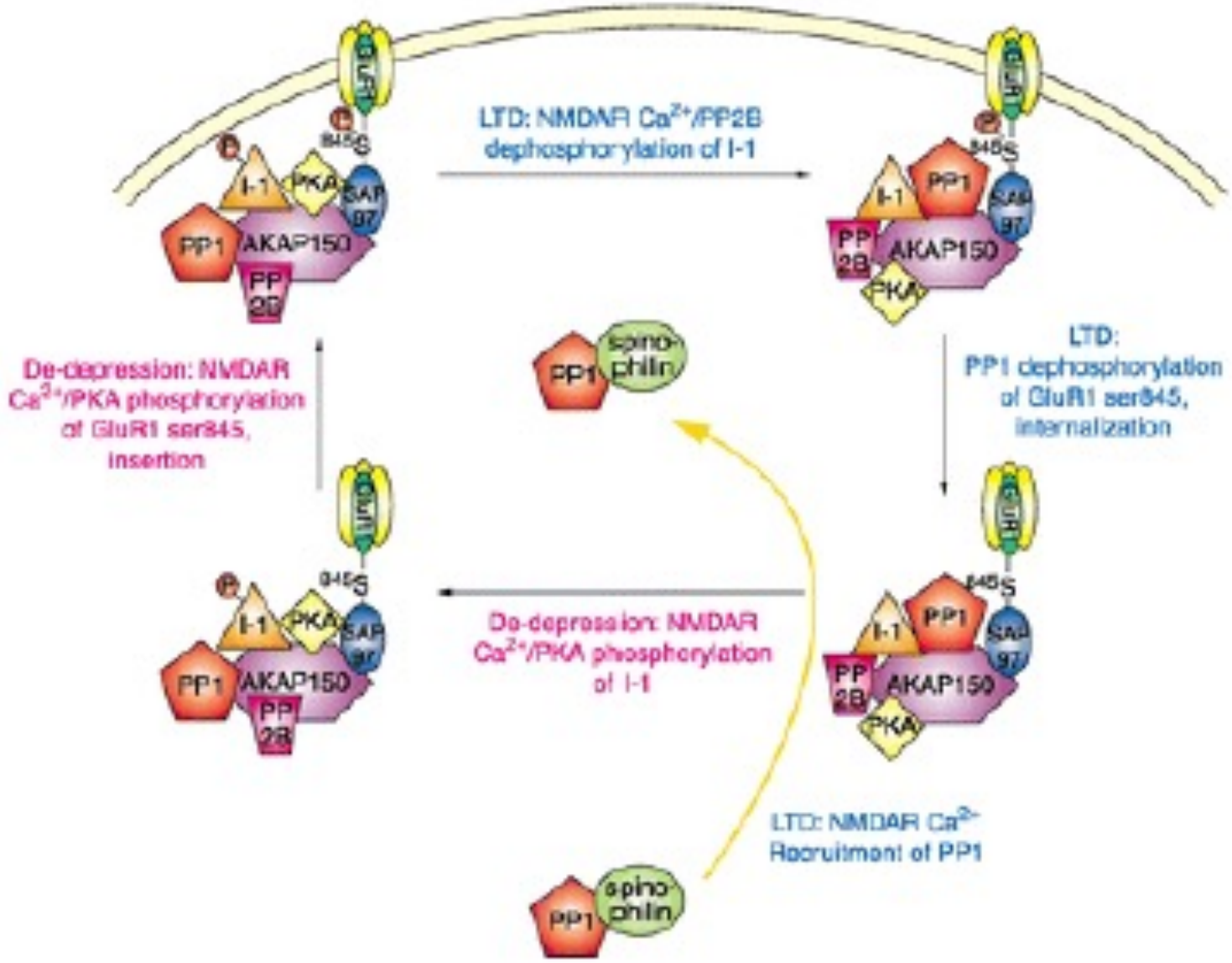
$[Ca^{2+}] >$



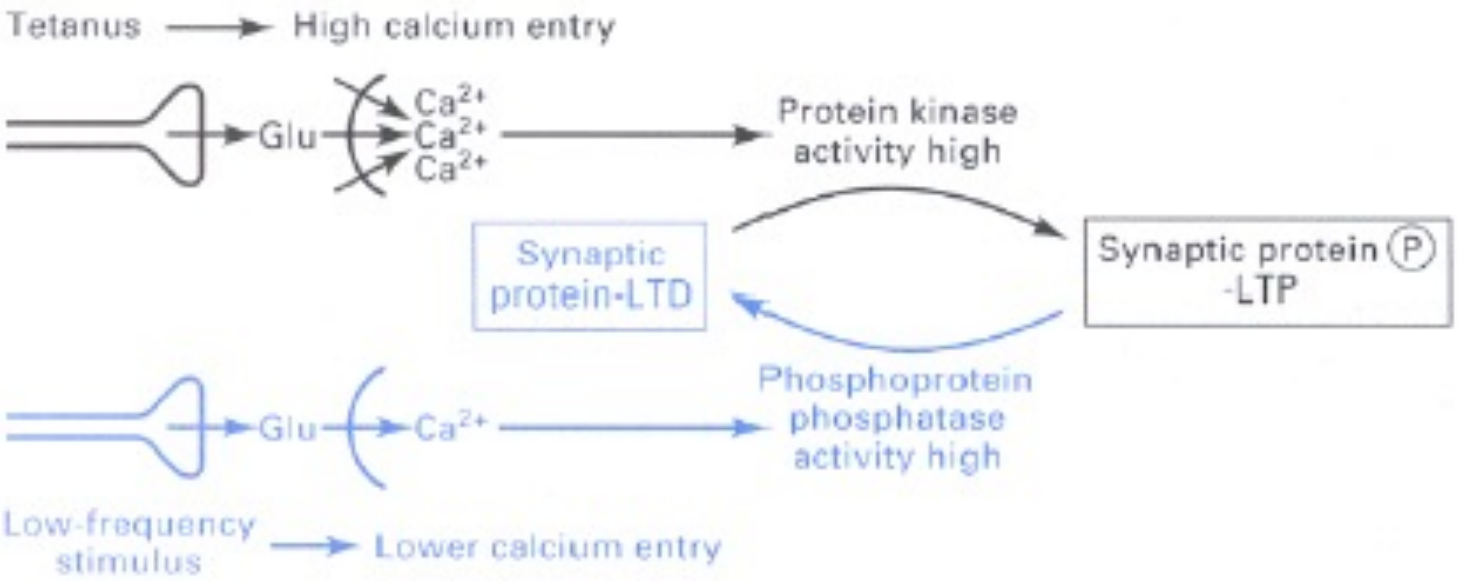
LTD

$[Ca^{2+}] <$

LTD requires Phosphatase



STDP Mechanism: Overview

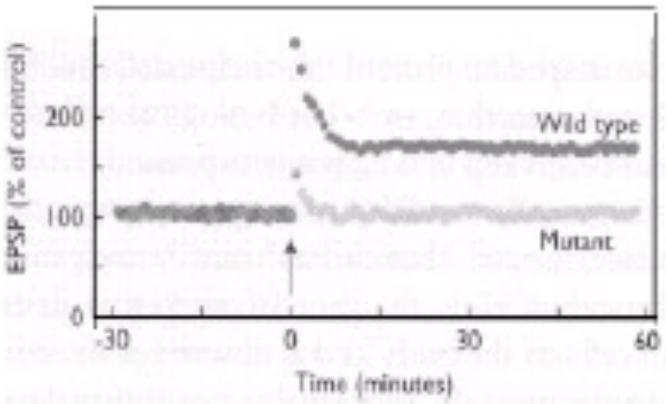


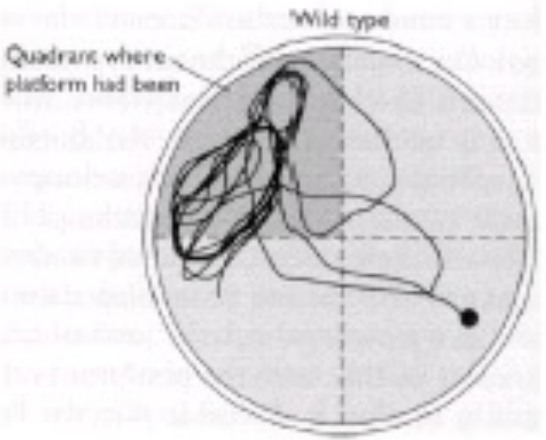
LTP: NMDAR → Ca2+ → CaMKII → AMPAR + P → Short Term/ Less Permanent

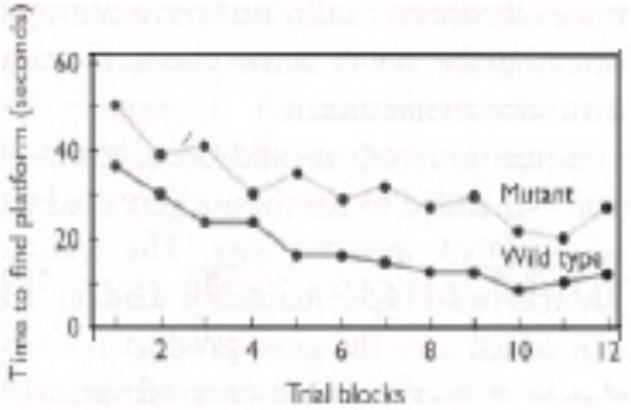
↳ cAMP → CaMKIV + PKA → CREB + P → IEG → Long Term

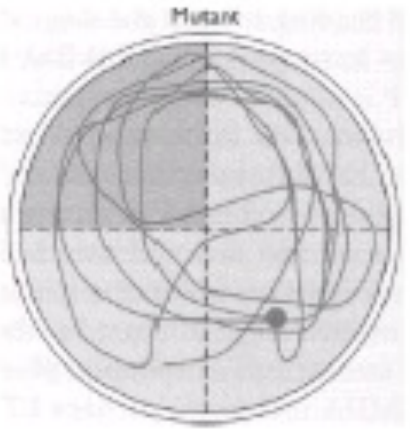
LTD: NMDAR → Ca2+ → PP1 → AMPAR - P

NMDAR-KO Mouse









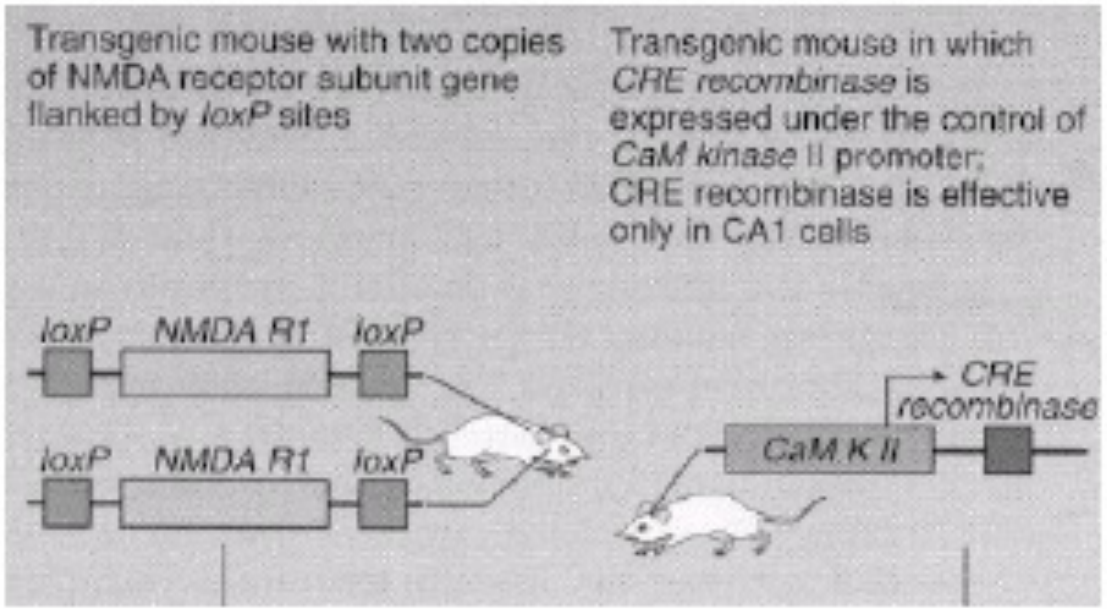
No NMDAR → No LTP in Hippocampus → No Spatial Learning

Summary of Genetic Experiment linking LTP with Declarative Memories

- **Disrupts LTP, stability of place cells and spatial learning:**
  - 1. Knockout of NMDA-R1 in CA1 only. *(Tsien and Tonegawa. Textbook)*
  - 2. Reversible over-expression of CaM-KII in CA1. *(Mayford and Kandel. Texbook)*. The original CaM-KII knockouts (without the reversible feature) was obtained by Silva et al. *(Science 10 July 1992.)*
- **Disrupts LTP but not spatial learning:**
  - 3. Knockout of AMPA receptor subunit called GluR-A. This is the receptor that is phosporilated by CaM K II and that increases the current going through the AMPA channel. *(Sprengel et al. Science 11 June 1999.)*
- **Improves Learning:**
  - 4. Over-expression of NMDA subunit 2B in the "Doogie" mice leads to longer lasting NMDA currents and mice with better performance in novel-object recognition, fear learning (both contextual and not) and spatial learning. *(Tsien et al. Nature 2 Sept 1999)*
  - 5. Inhibition of Protein phosphatase 1 (PP1) by overexpression of Inhibitor 1 (I1) leads to stronger long term memories and reduces age related decline in mice. (*David Genoux* et al. Nature 418:970-972, 2002*)
- **Disrupts LTP and Learning but deficit can be reversed by "rich" environment:**
  - 6. The NMDAR1 CA1-KO mice of experiment 1 are shown to be able to learn spatial tasks if raised in an enriched environment. *(Tsien et al. Nature Neuroscience. March 2000)*

Experiment 1. NMDAR1 – KO in CA1 Region Only

Spatial Specificity is obtained using a CaMKII Promoter



CA1 no NMDA R1

Other brain regions ~ Normal

Visualization of NMDA-R1 shows the specificity of the effect

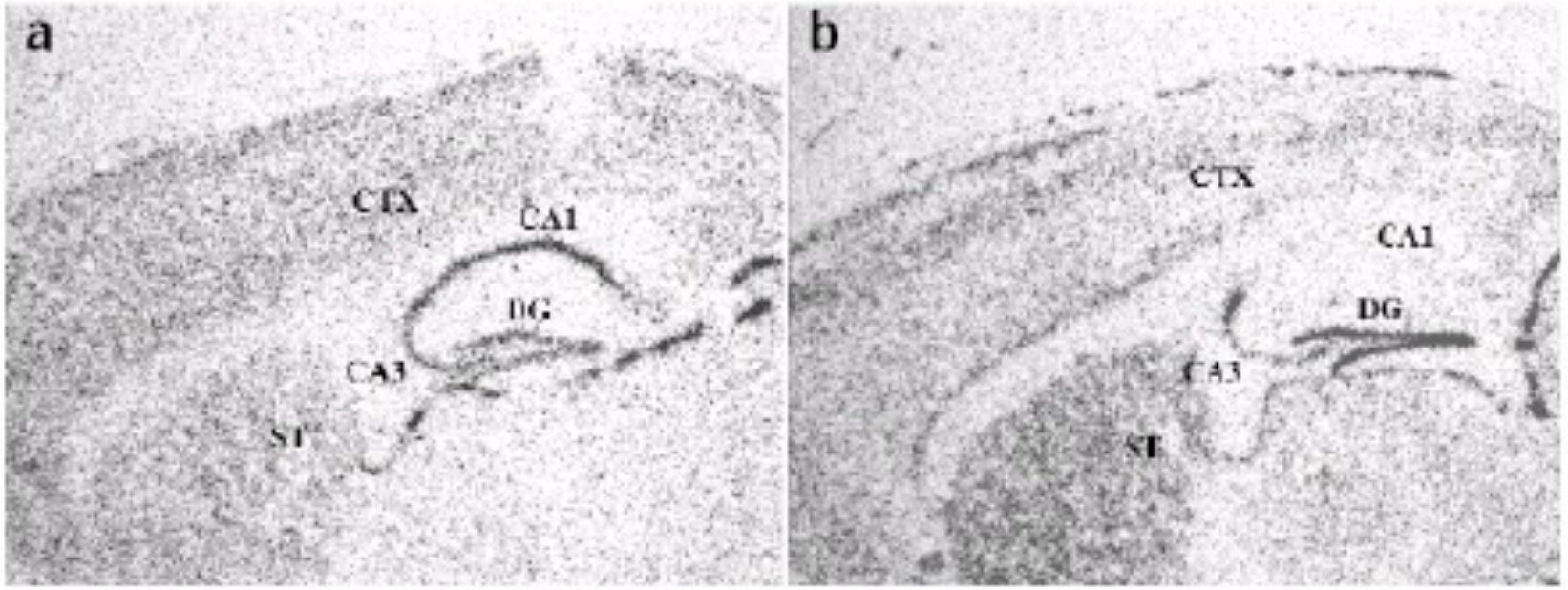
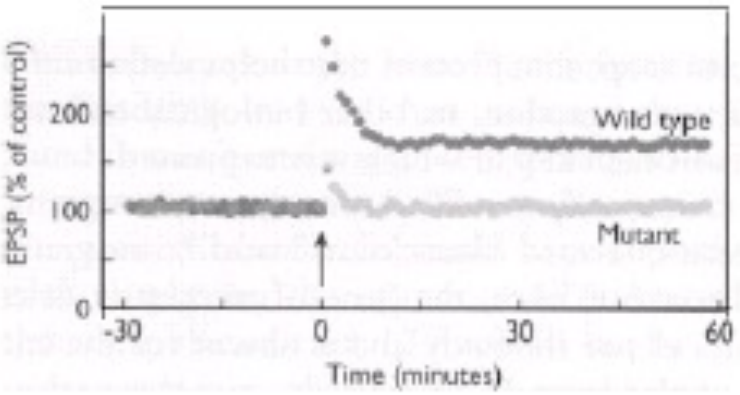
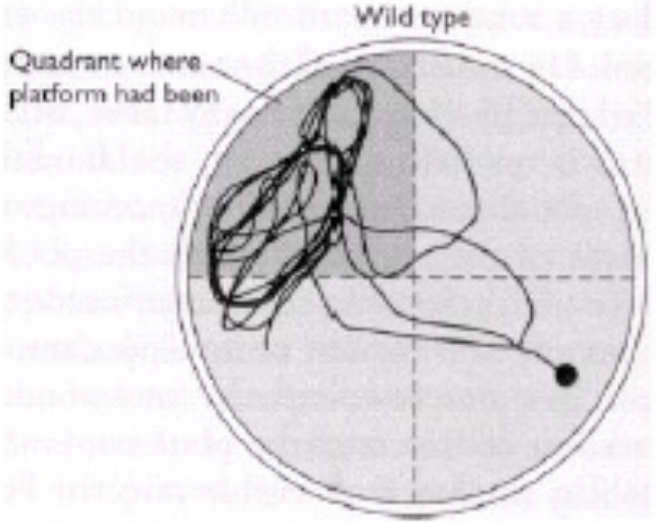
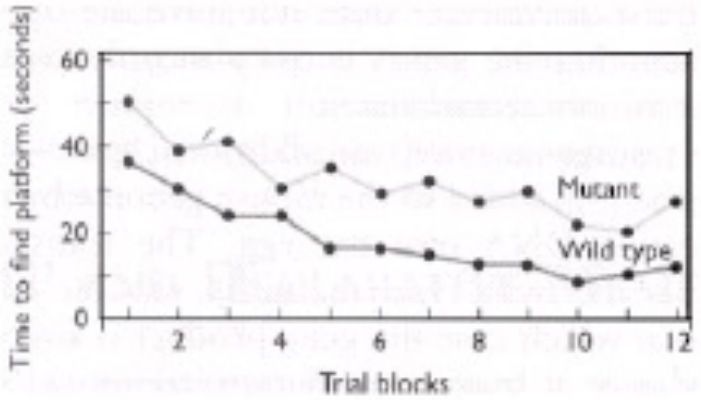


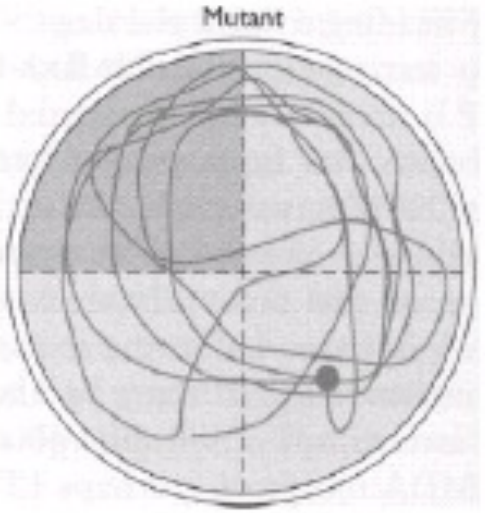
Fig. 1. Cre/loxP-mediated deletion of NR1 gene in CA1-KO mice (2.5 months old) is complete. An antisense 42-mer oligonucleotide recognizing the NR1 gene was used for *in situ* hybridization. CTX, cortex; ST, striatum; DG, dentate gyrus.

NMDAR-KO in CA1 is deficient in LTP and Spatial Learning

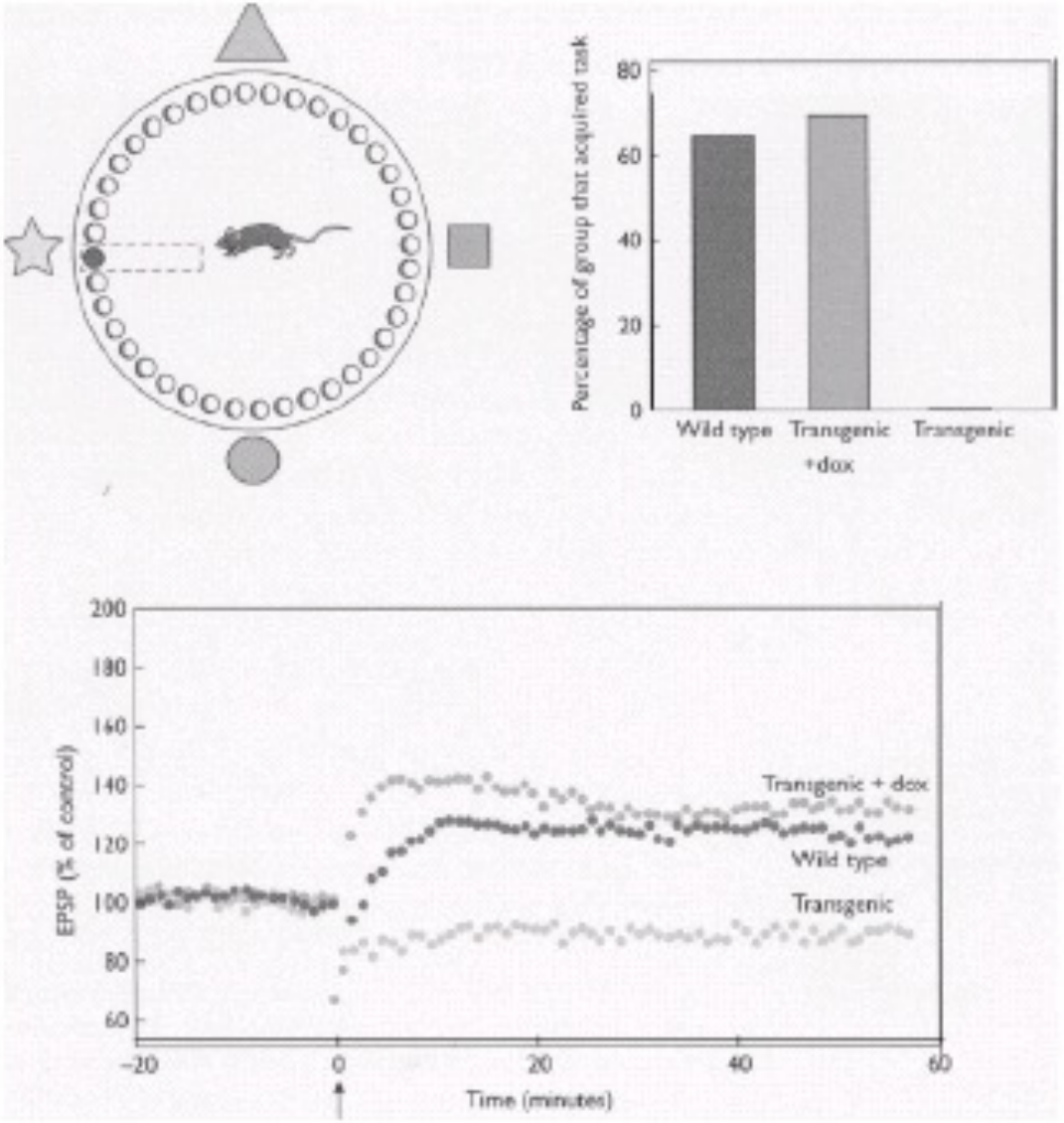








Reversible Overexpression of CaMKII in CA1 → deficient in LTP and Spatial Learning



Summary of Genetic Manipulations for impairment or enhancement of memory

- NMDAR KO or over-expression of CAMKII in hippocampus affects spatial learning.
- NMDAR-2B over-expression leads to an enhancement in all forms of declarative memory and also non-declarative memories.
- PP1 inhibition leads to increase in long-term memory and reverses the age related memory decline
- Blocking AMPA phosphorilation in CA1 prevents LTP but not spatial learning
- Development in a rich environment can overcome genetically induced deficits in hippocampal function.