The efficacy of the transmission at a synapse is not fixed,

it depends on the frequency of stimulation and the history of prior activity

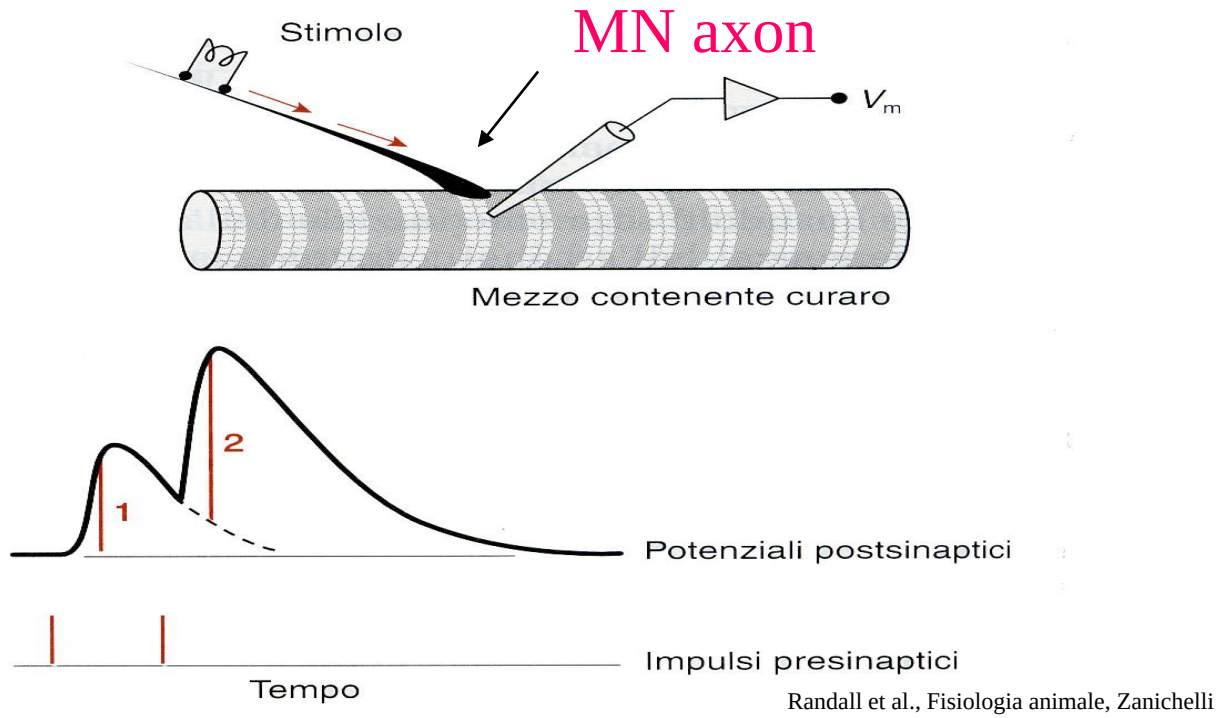
Short-term & long-term

synaptic plasticity

acts on different timescales

(from tens of milliseconds to hours).

Facilitation is a transient frequency-dependent increase in the amplitude of PSPs evoked when two presynaptic stimuli are delivered within a short time interval (100-200 ms).



Randall et al., Fisiologia animale, Zanichelli

It is caused by a transient increase in the probability of transmitter release following synaptic activation.

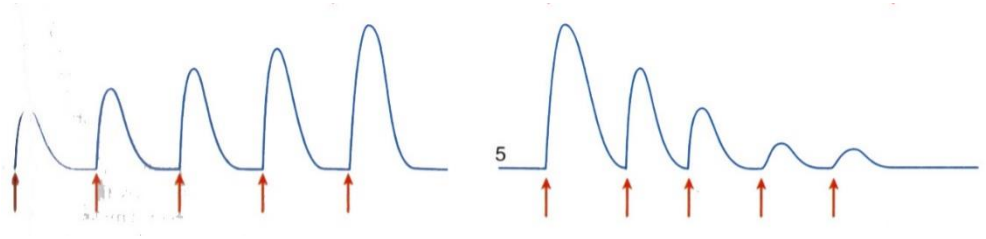
It depends on a small, residual increase in presynaptic internal [Ca^{2+}] that can bring to modification of proteins at the presynaptic terminal.

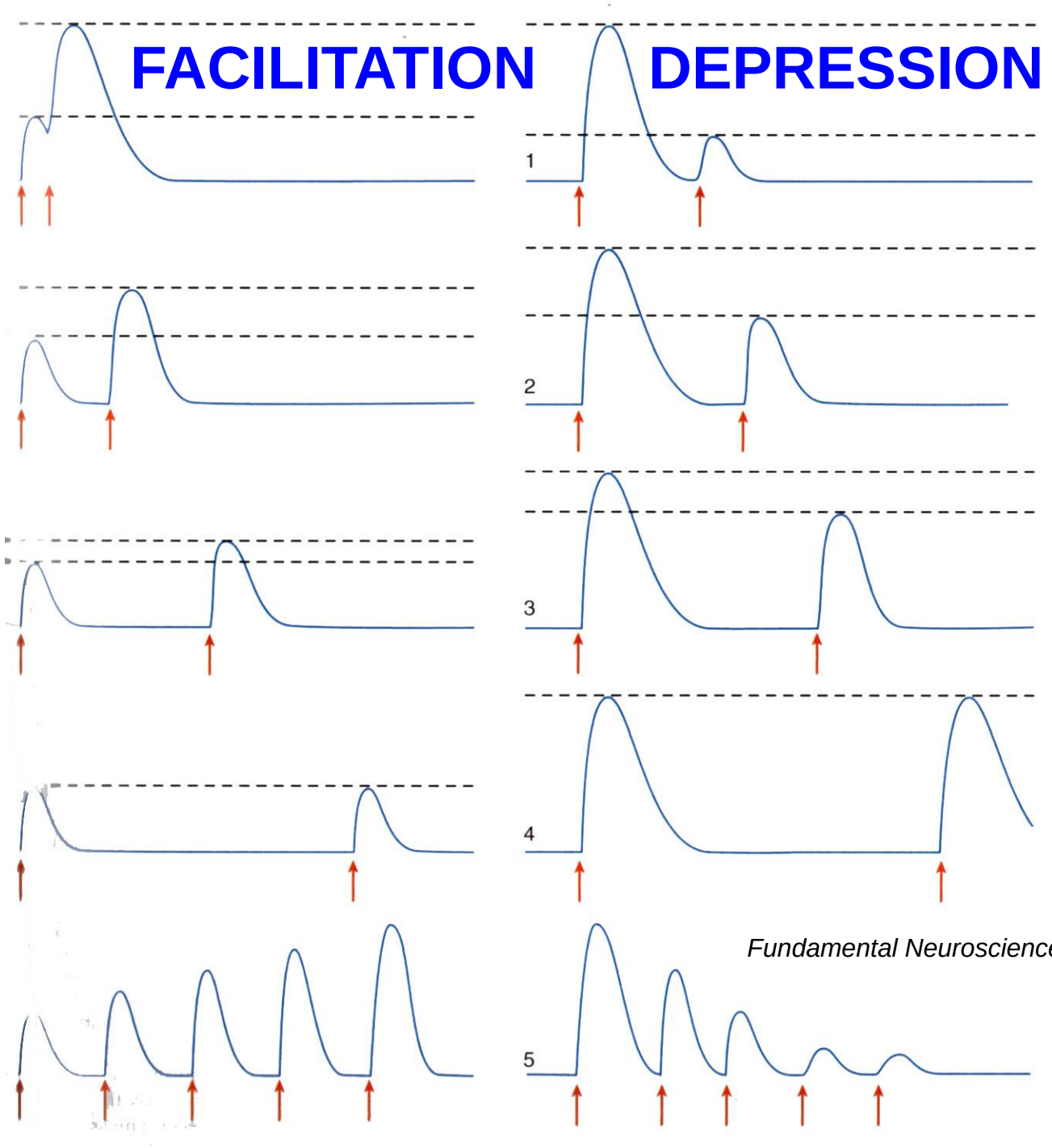
Ca^{2+} extrusion systems:
Plasma membrane ATPases, Na^{+}-Ca^{2+} exchange
Ca^{2+} uptake into organelles such as endoplasmic reticulum and mitochondria

Short trains of presynaptic action potentials can produce either FACILITATION of transmitter release from the presynaptic terminal (that persists for hundred milliseconds), or DEPRESSION of release (lasting for less than 20ms until seconds), or a combination of both.

Synapses that have a low probability of release tend to display large FACILITATION, because it is more likely that the second of a stimulus pair will evoke release.

Synapses with a high probability of release tend to display DEPRESSION, presumably because the pool of vesicles available for release becomes depleted after an initial successful release.





Fundamental Neuroscience, Academic Press

Depression may be due to:

1. a depletion of a readily releasable supply of vesicles.

2. to the inhibitory action of neurotransmitter on autoreceptors

3. to the desensitization of postsynaptic receptors.

4. Fast paired-pulse depression (<20 ms) may derive from inactivation of voltage-gated Na^{+}/Ca^{2+} channels

Differences in basic release properties

Excitatory Neocortex pathway

Stimulating layer IV activates synapses in layer III pyramidal cells.
Probability of transmitter release is high

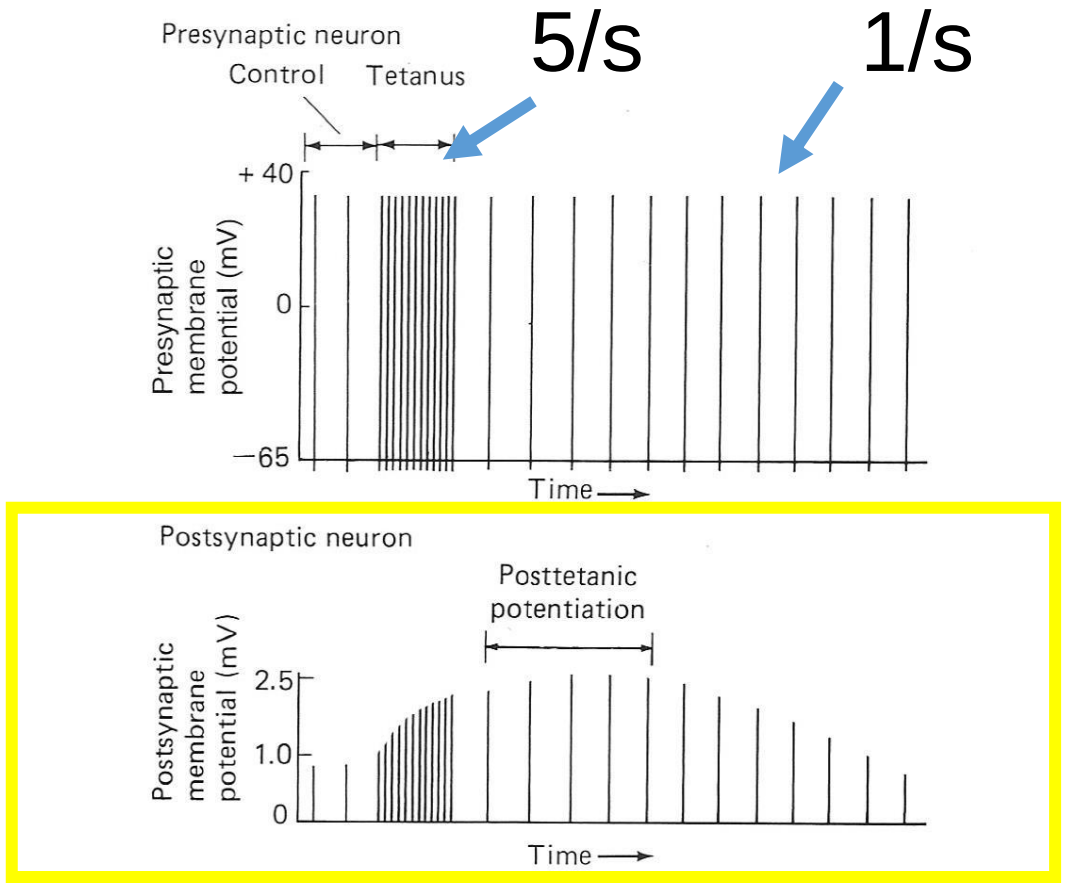
Hippocampus Pathways

Stimulating Shaffer collateral of hippocampal CA3 activates CA1 pyramidal cells.
Baseline probability of transmitter release is lower in hippocampus

Differences in Short-term synaptic plasticity

Although the hippocampal pathway shows strong facilitation, most neocortical pathways onto pyramidal cells display depression

Trains of repetitive stimulation result in POST-TETANIC POTENTIATION (PTP) of transmitter release, which *<u>can last for tens of minutes</u>* and, like facilitation, is mediated by a short-lasting accumulation of free Ca^{2+} in the presynaptic terminal.



Post-tetanic potentiation is quite potent in the hippocampus pathway but is largely absent in the neocortex pathway.

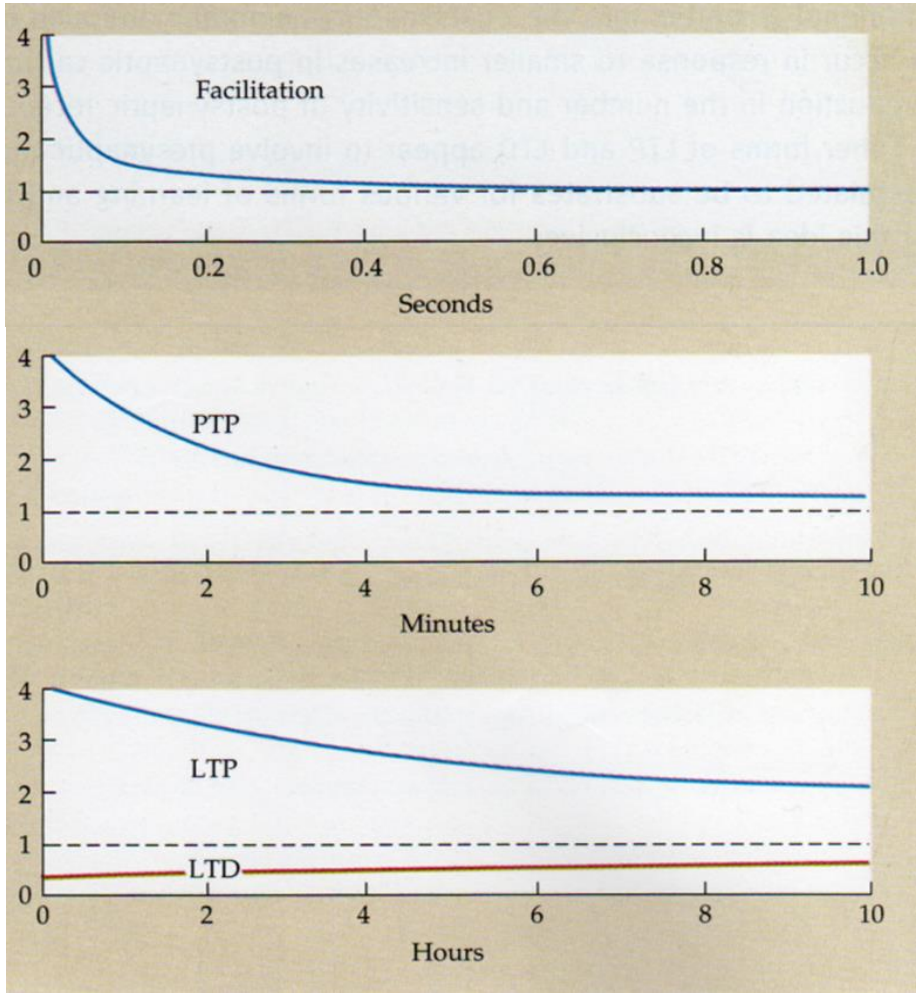
PTP post-tetanic potentiation

- Induced by “weak” tetanic stimulation (for frequency and duration)
- Duration ≤ few min
- Presynaptic mechanism

LTP long-term potentiation

- Induced by “strong” tetanic stimulation (≥ 100 Hz, ≥ 1 s)
- Duration: hours (*in vitro*), days (*in vivo*)
- Presynaptic and post-synaptic mechanisms

Time course of activity-induced changes



FACILITATION: < 1 sec

PTP: lasts for several sec to some min, generally seen after a series of presynaptic stimuli.

LTP/LTD last for a hour or more.

From Neuron to Brain, J. Nicholls

At most synapses depression and facilitation occur.

Depending on the nature of the single synapse and the time course of facilitation, depression and PTP (min), any of these phenomena, may predominate at a given moment.

Facilitation and post-tetanic potentiation change synaptic transmission for short periods.

They can not explain the mechanism for memory or other phenomena of behavioural plasticity that persist for weeks, months, years.

At many synapses repetitive activity can produce not only short-term changes, but also alterations in synaptic efficacy that last for hours, or even days.

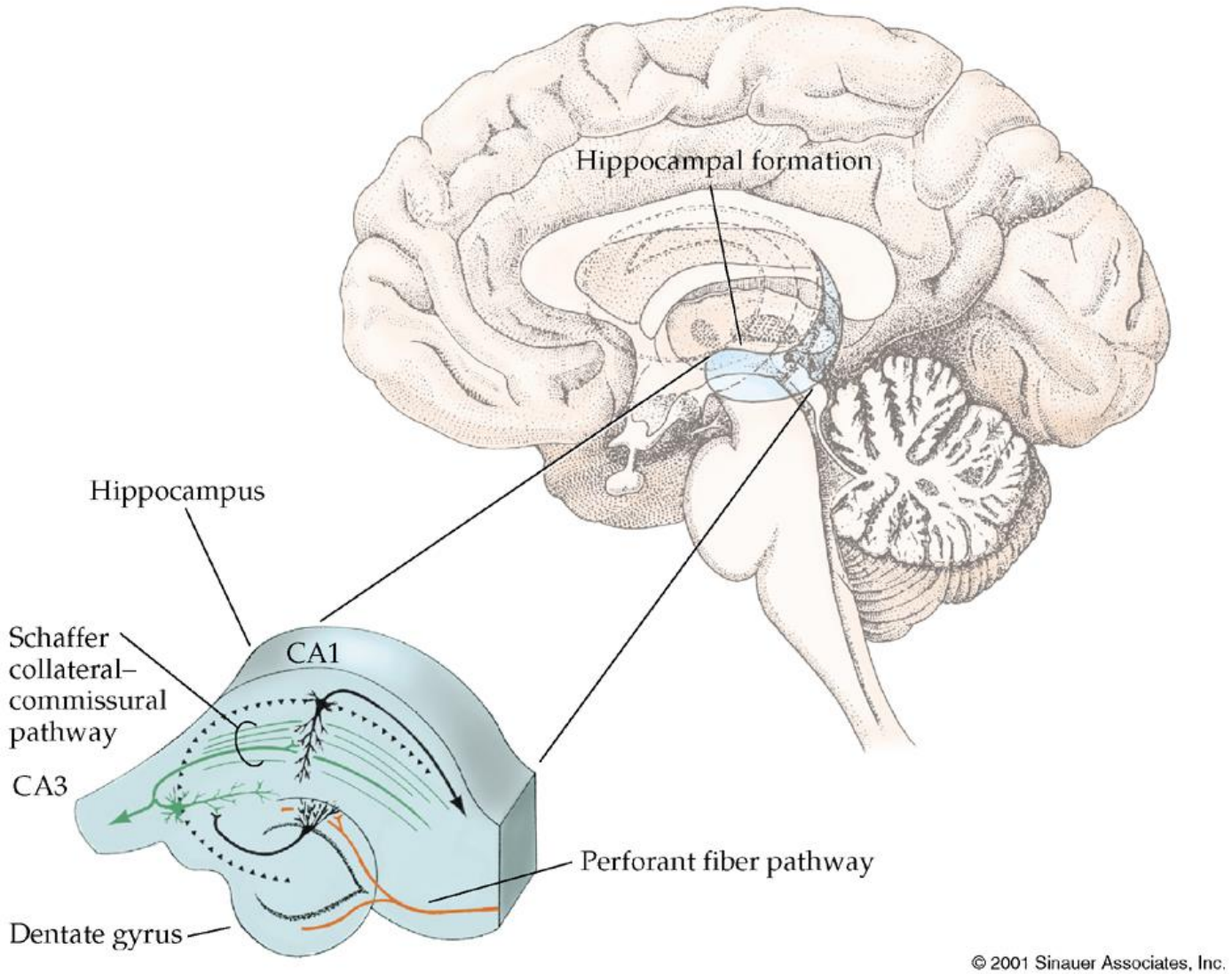
The two phenomena of this type are known as long-term potentiation (LTP) and long-term depression (LTD).

Both LTP and LTD have been postulated to be substrates for various forms of learning and memory formation.

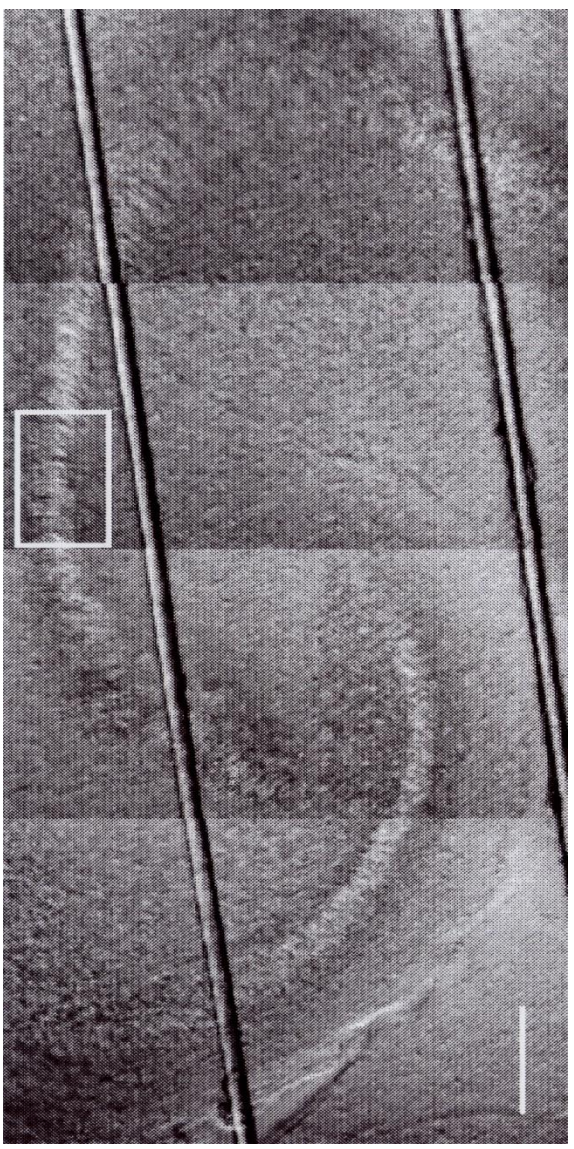
LTP in:

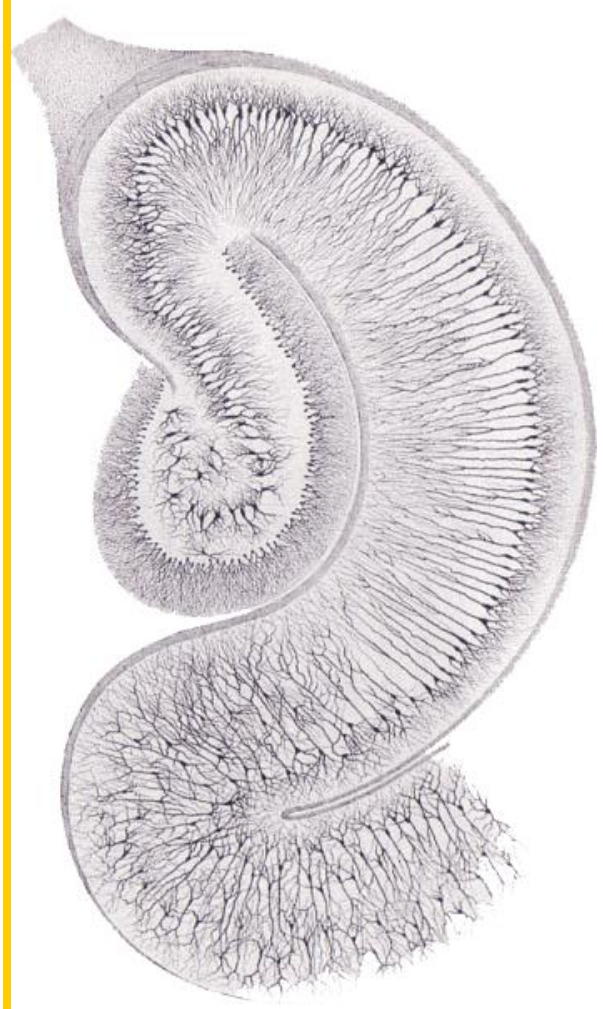
HIPPOCAMPUS
CEREBRAL CORTEX
AMYGDALA
CEREBELLUM
THALAMUS
STRIATUM
VENTRAL TEGMENTAL AREA

The hippocampus



Cellular level

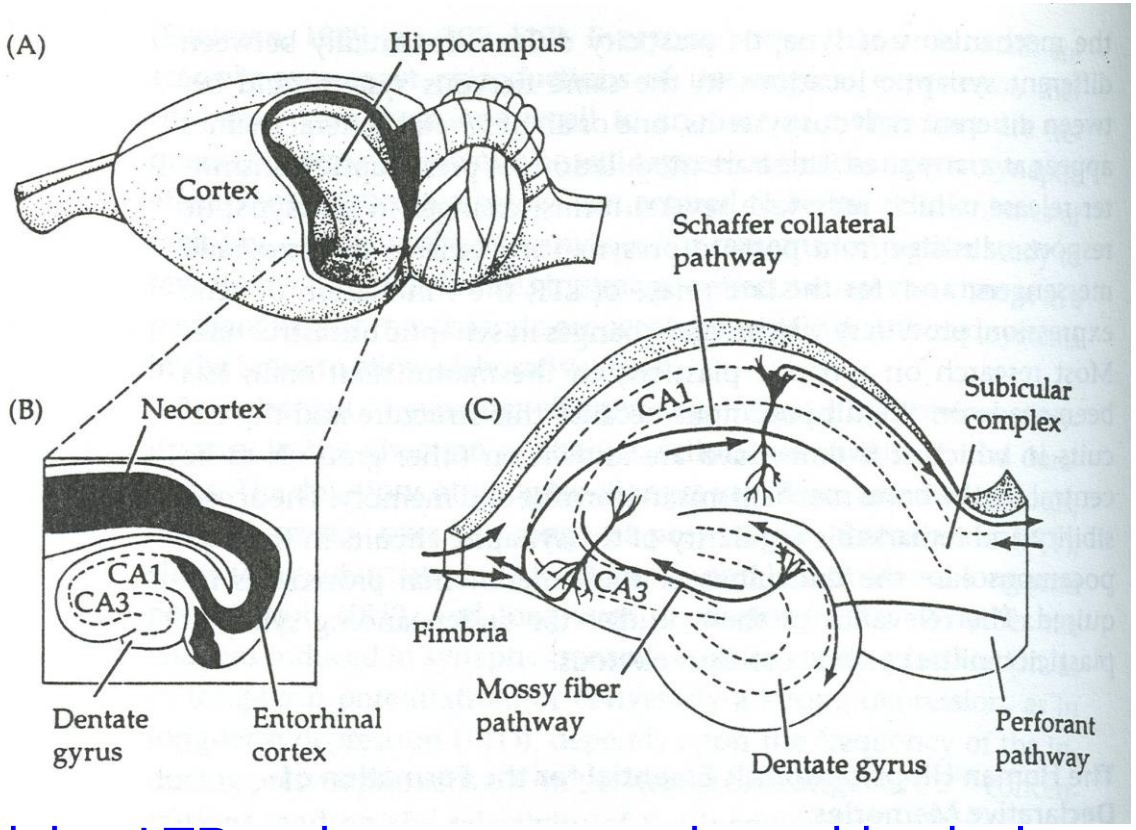




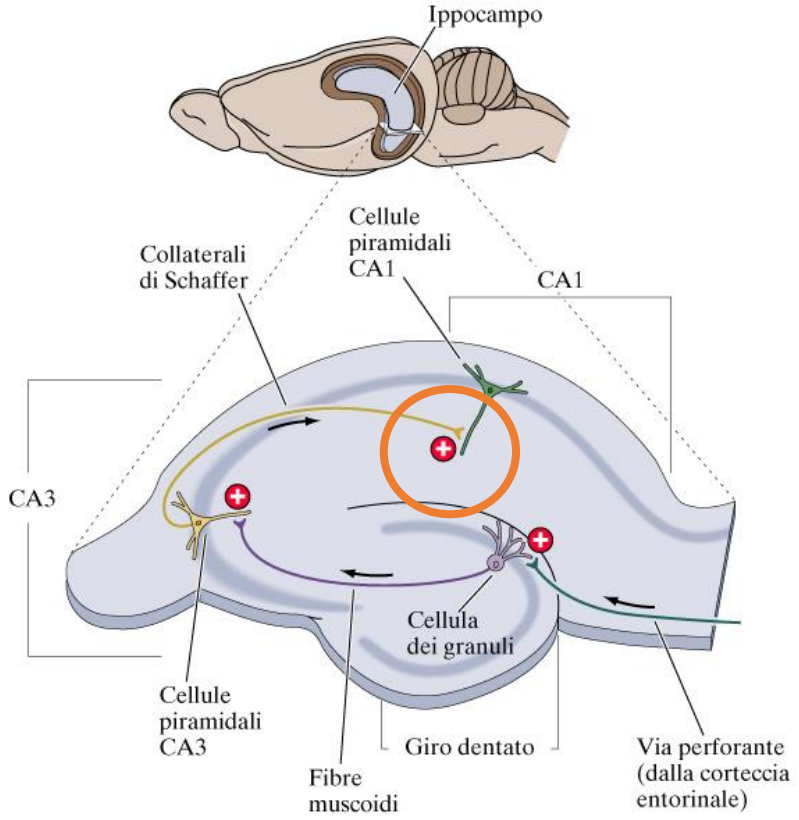
The hippocampus is by far the most investigated brain area in term of synaptic plasticity

Virtually all excitatory hippocampal synapses can present LTP or LTD under some experimental protocols:

1) Perforant path-DG
2) Mossy fibers-CA3
3) Schaffer collaterals-CA1



Various studies demonstrated that LTP at these synapses is not identical

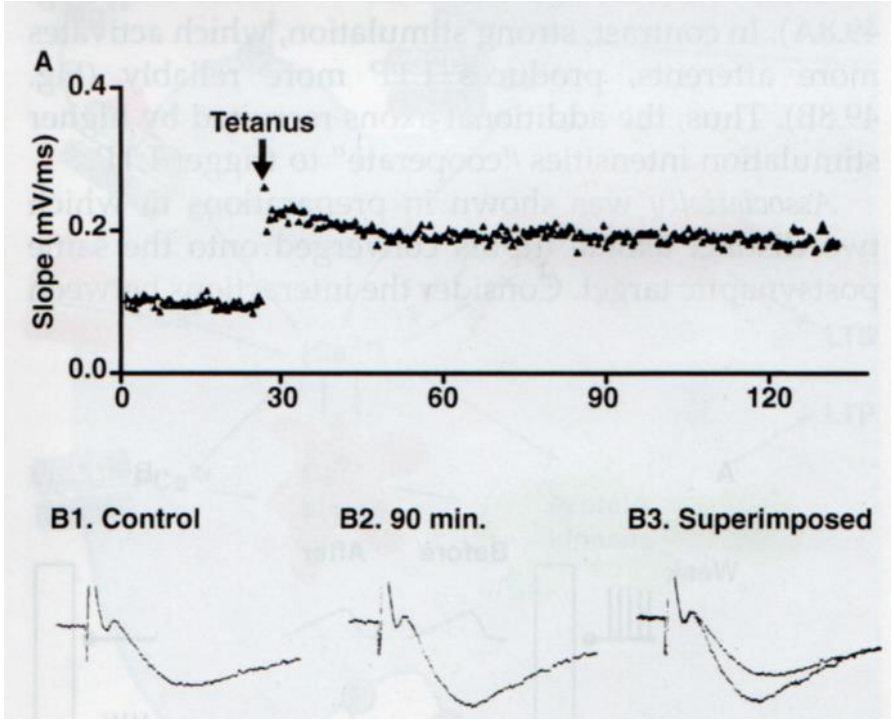


Neuroscienze, Zanichelli

Single electrical stimulation of Schaffer Collaterals (SC) gives origin to EPSP in CA1 region.

A tetanic stimulation of SC gives origin to LTP in CA1 pyr neurons.

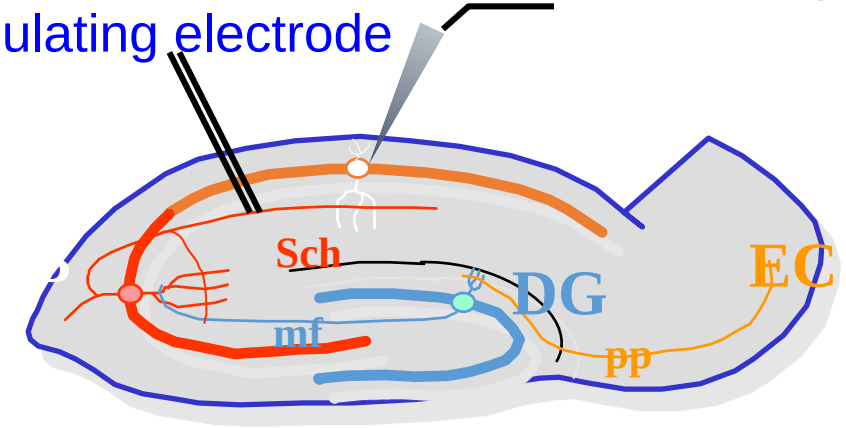
LTP PROPERTIES



4 trains, 100 Hz

Field extracellular recordings

stimulating electrode

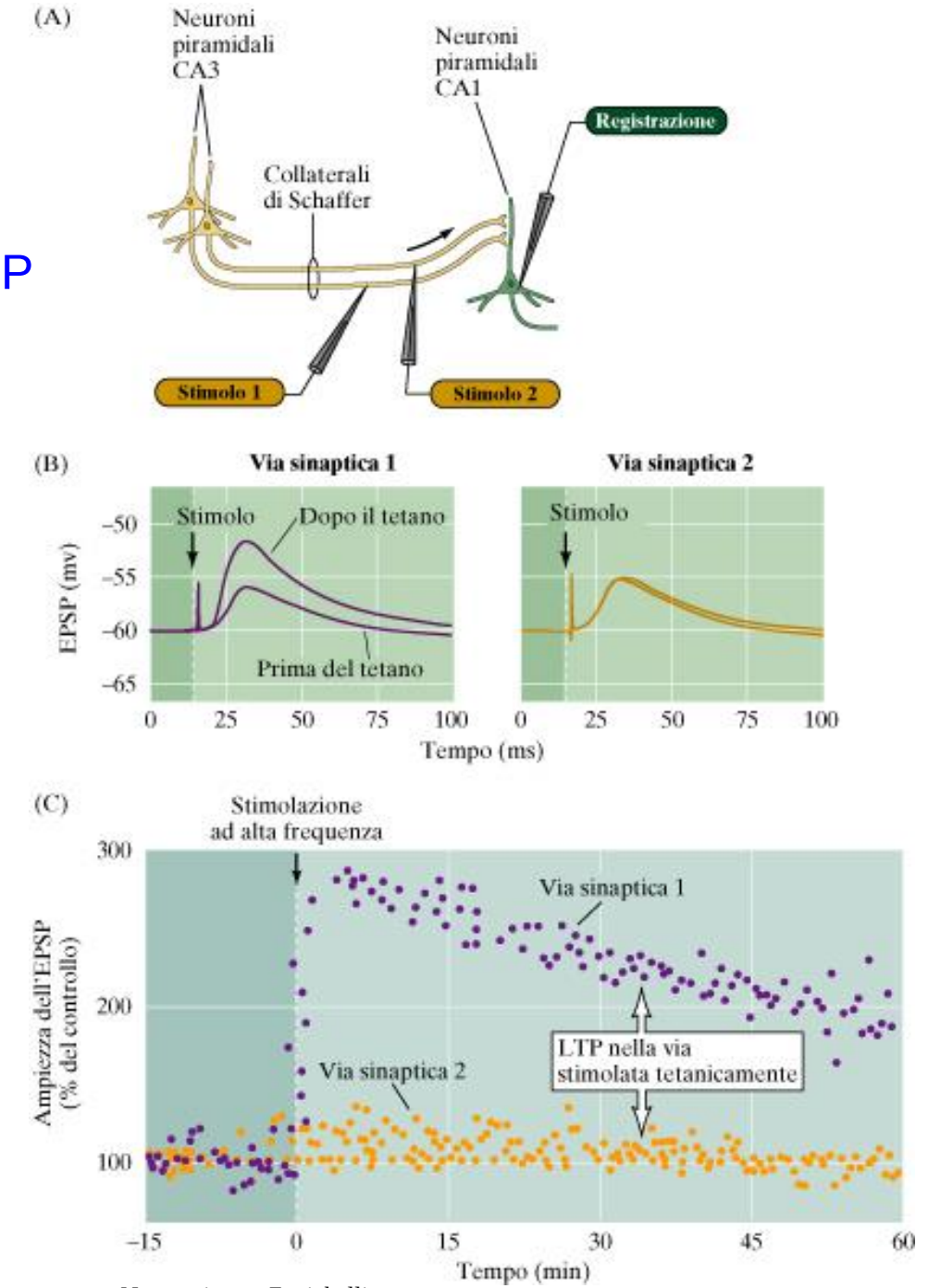


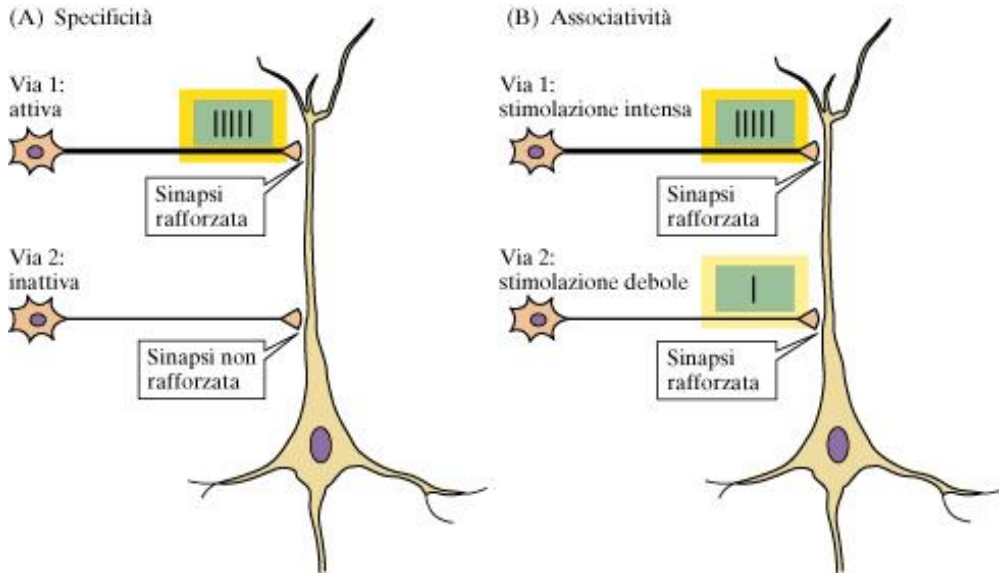
- SPECIFICITY
- COOPERATIVITY
- ASSOCIATIVITY

INPUT SPECIFICITY

Only the potentiated set of synapses shows LTP

If the activation of one set of synapses led all other synapses being potentiated, it would be difficult to selectively enhance particular set of inputs as presumably required for learning and memory.





Input specificity a strong tetanic stimulation induces LTP only in the activated synapses. Weak synapses are not modified.

Cooperativity: more than one fiber must be activated to obtain LTP

Associativity: for successful pairing of two inputs to occur, their activation must be temporally correlated. If the weak and strong inputs are separated in time by more than 100 ms, no associative LTP will result.

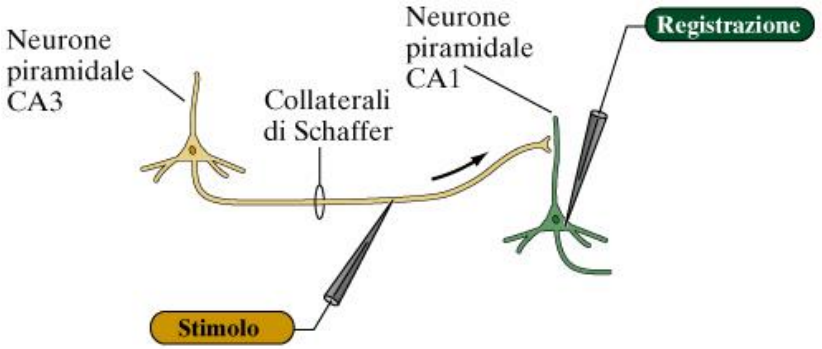
Neuroscienze, Zanichelli

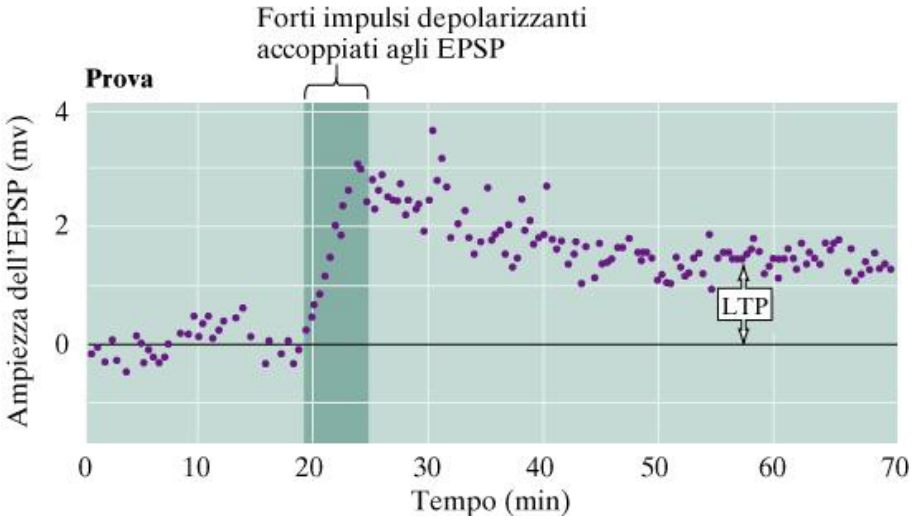
Hebb postulate:

Synaptic efficacy increases when pre- and post-synaptic activities are strongly correlated

(Hebb: The organization of Behaviour, Wiley, New York, 1949)

The degree of depolarization of postsynaptic cell determines whether or not LTP occurs





Neuroscienze, Zanichelli

Low-frequency activation of SC, paired with strong depolarization of CA1, makes the size of EPSP higher.

(Collingridge, 1983)

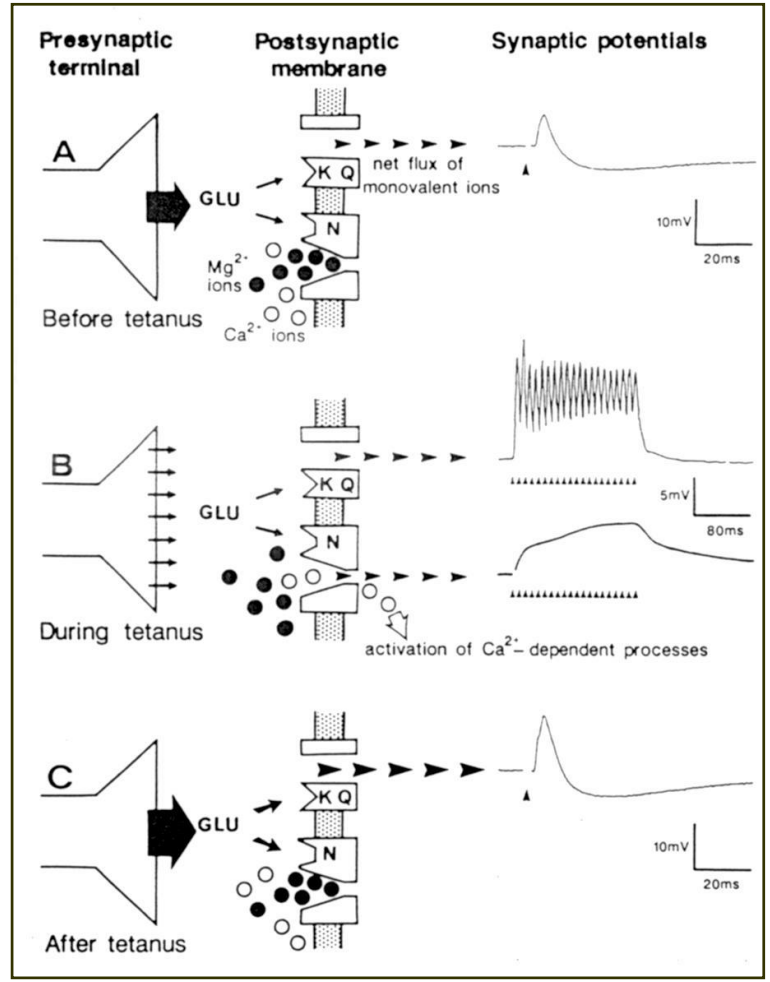
Key molecules for LTP induction:

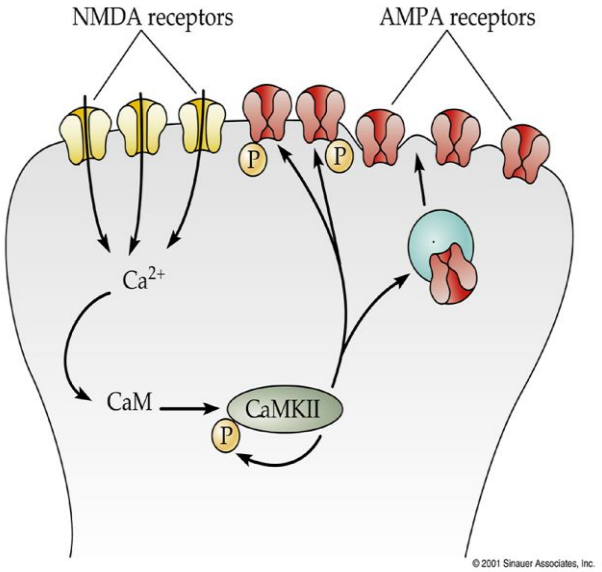
NMDAR

antagonists (see APV) block LTP

$[Ca^{2+}]_i$

Ca^{2+} chelators (EGTA) blocks LTP


Presynaptic terminal
Postsynaptic membrane
Synaptic potentials
A
GLU
K Q
N
net flux of monovalent ions
10mV
20ms
Mg2+ ions
Ca2+ ions
Before tetanus
B
GLU
K Q
N
5mV
80ms
During tetanus
activation of Ca2+- dependent processes
C
GLU
K Q
N
10mV
20ms
After tetanus



Early LTP lasting~1 hour

CaMKII induces phosphorylation of AMPARs promoting the insertion of new receptors in the membrane

Post-translational modifications of existing proteins

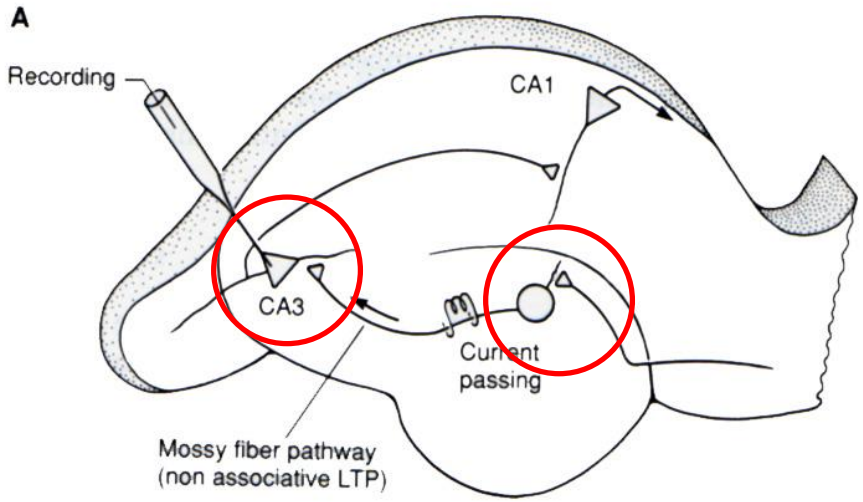
Late LTP- «LTP consolidation»

genetic transcription and synthesis of new proteins:
Transcription factors, growth factors

Transcription-dependent LTP (>4h)

In MF-CA3 synapse LTP has different properties

- It does not require associativity
- it does not depend on NMDA receptor activation
- It involves an enhancement of presynaptic release



Possible presynaptic mechanisms for LTP

Increase in the release probability can be induced by:

- Increase in the amplitude of Ca^{2+} transients
- Higher sensitivity to $[Ca^{2+}]_i$ increase

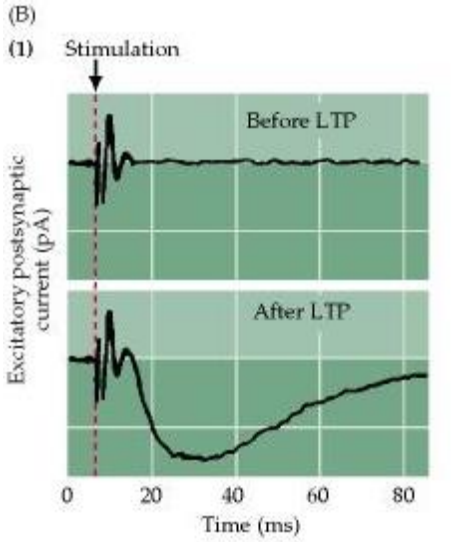
Decrease in failures of neurotransmitter release suggests an increase in probability of transmitter release.

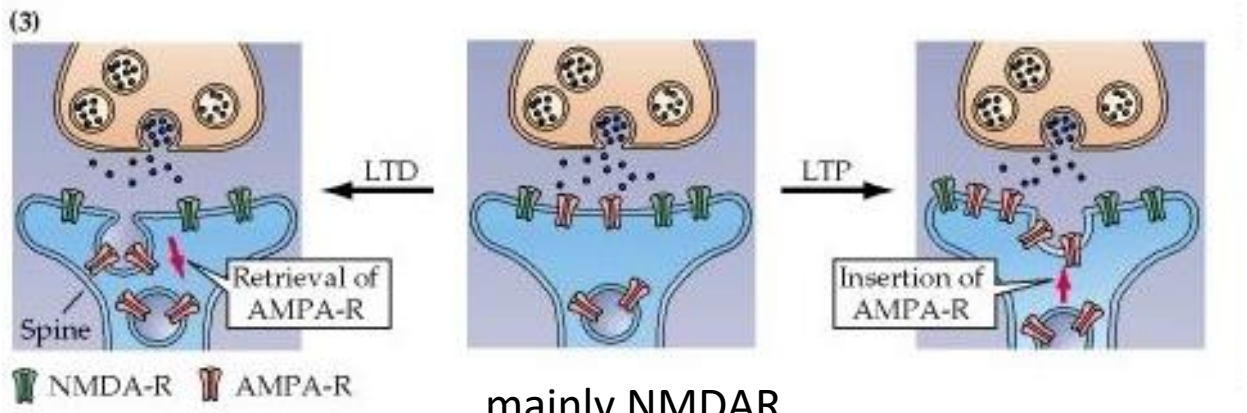
Postsynaptic mechanisms of LTP

- Activation of postsynaptic NMDA-R can induce a CaMK II-dependent AMPA-R phosphorylation
- Change in the expression of different AMPAR isoforms
- Activation of “silent synapses” (decrease in failures)

An increase in the amplitude of mEPSCs could indicates an increase in the number of functional postsynaptic receptors revealed by an increase of AMPA mediated currents after the application of exogenous agonists.

LTP might induce AMPA receptor-mediated responses at silent synapses.





mainly NMDAR

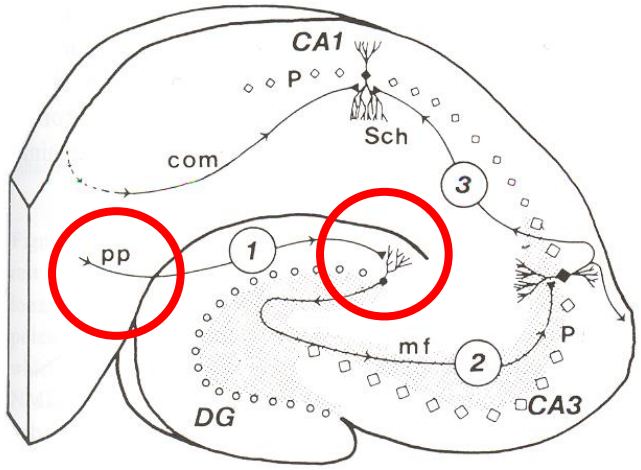
AMPAR silent at resting

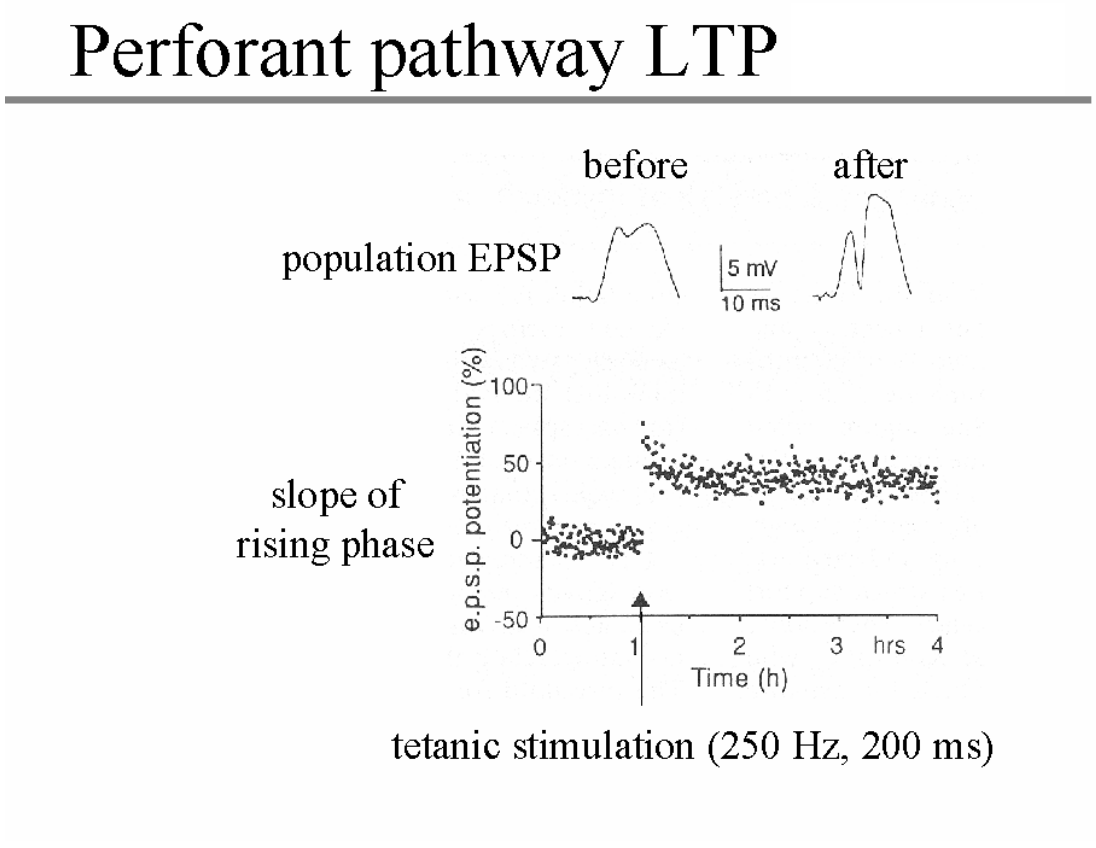
LTP

This can explain the decrease in failures after LTP

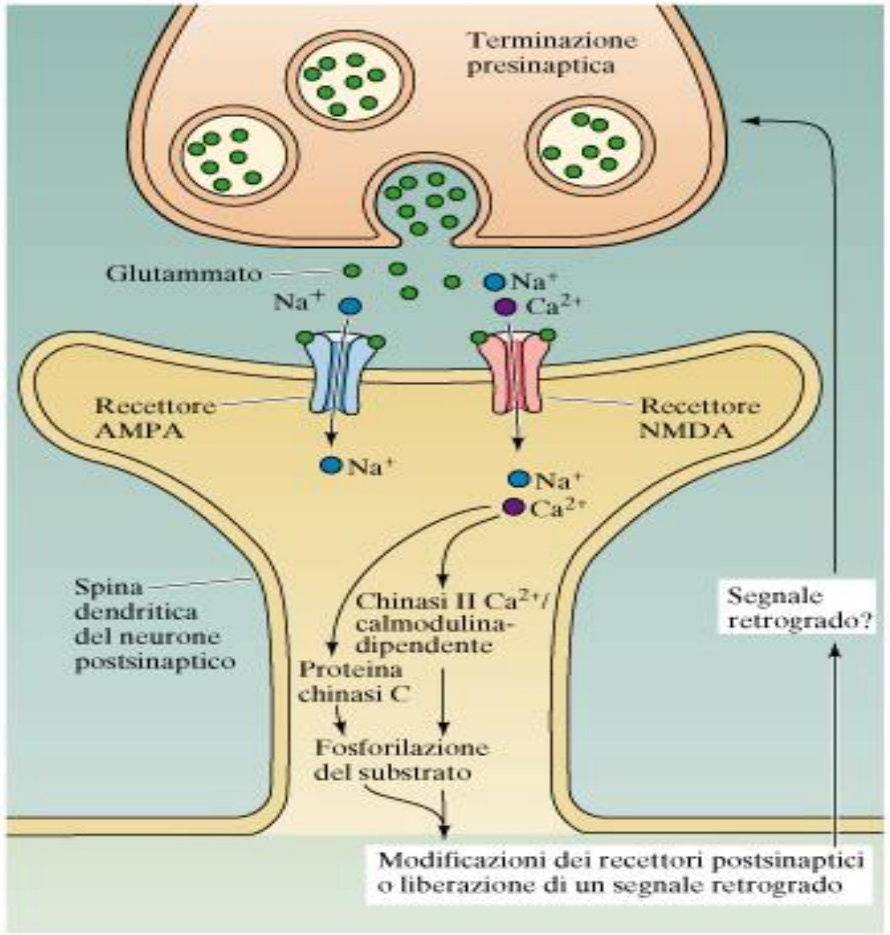
PP stimulation, recording from dentate gyrus (Bliss and Lomo, 1973)

NMDA-dependent LTP





Retrograde signaling

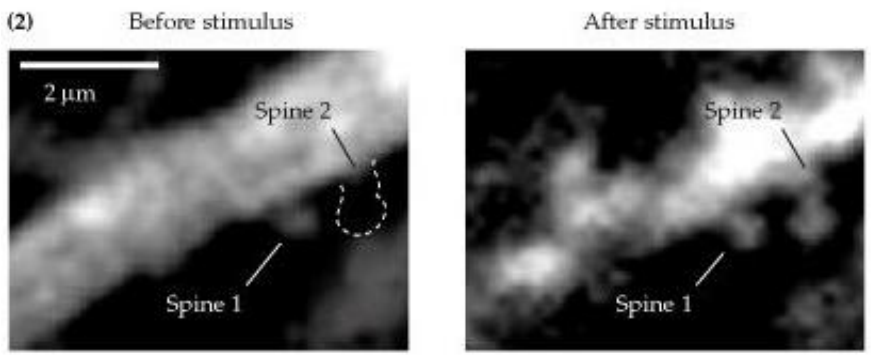


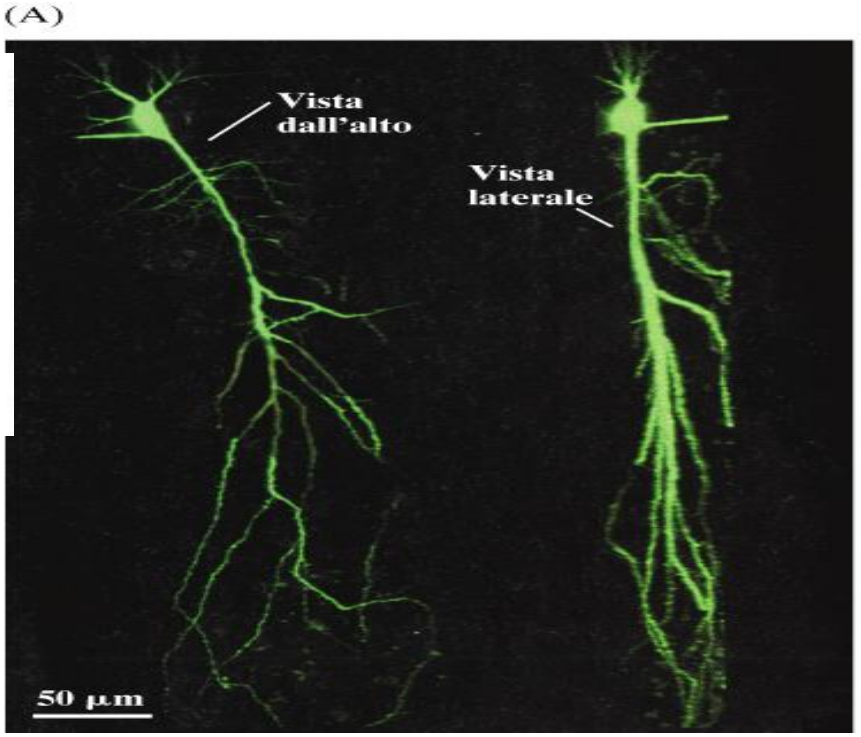
Protein kinases:

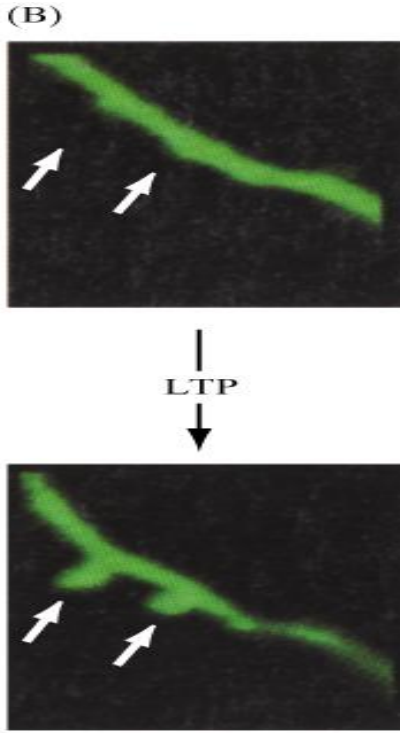
CaMKII
PK C

Neuroscienze, Zanichelli

How are the changes in synaptic strength maintained for long periods?

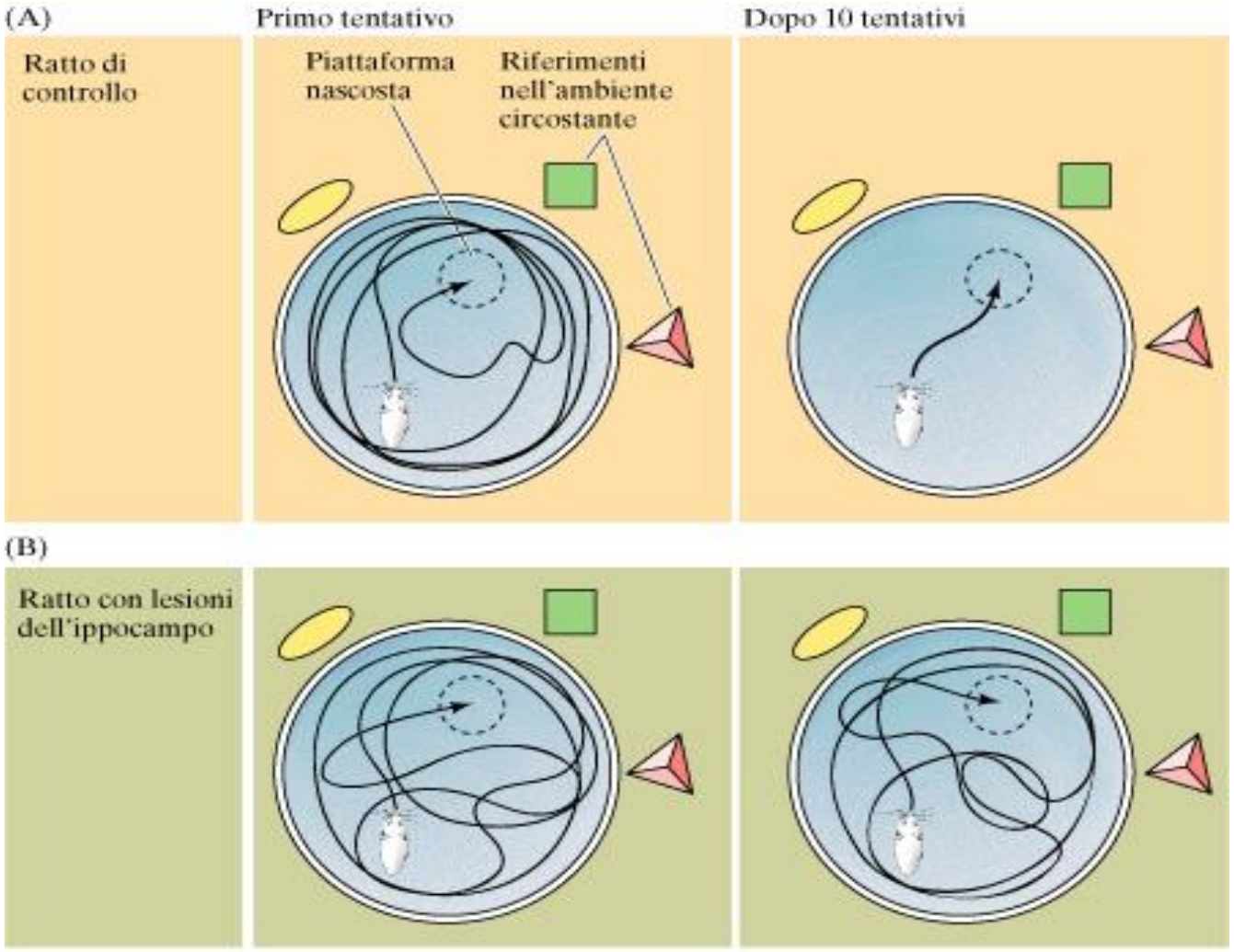






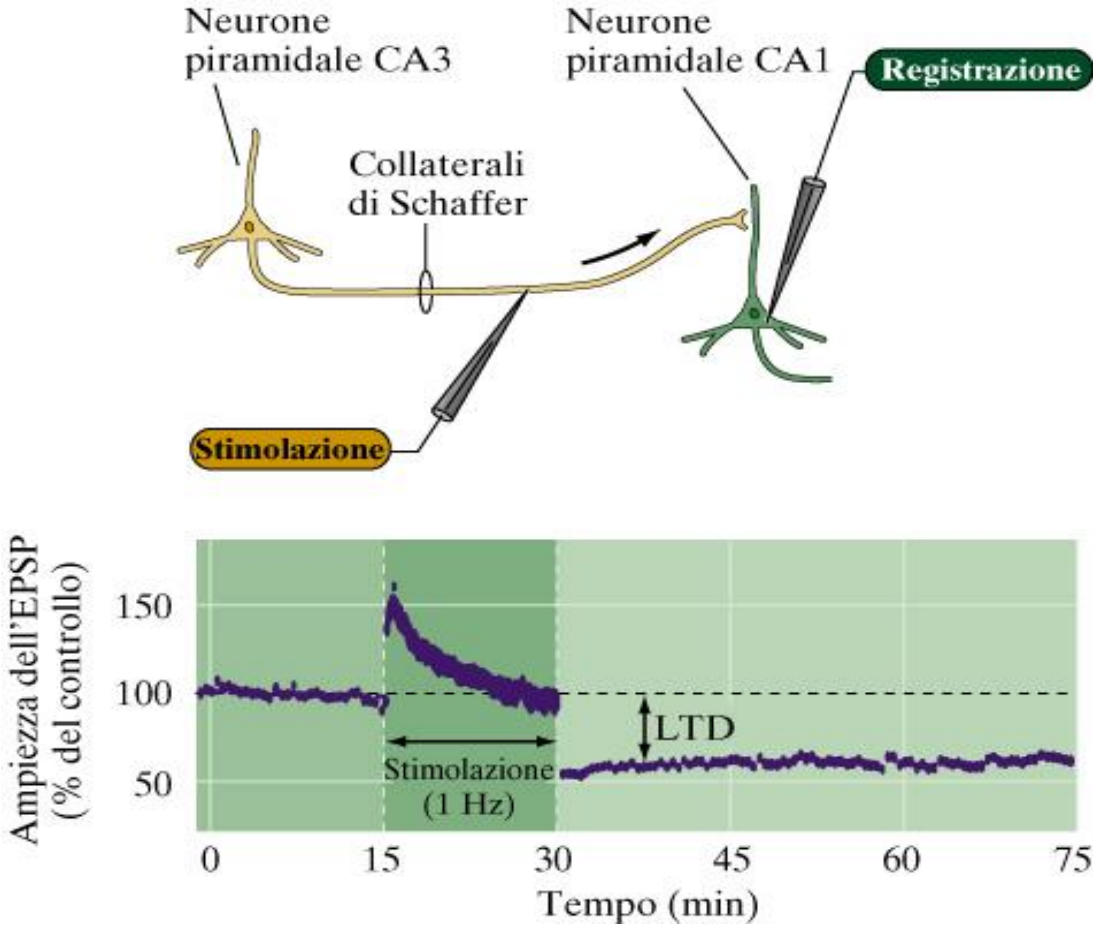
Spine remodelling during LTP in hippocampus. Neosynthesis of proteins can facilitate new synaptic contacts.

Deficit of spatial memory in rats with hippocampal lesions



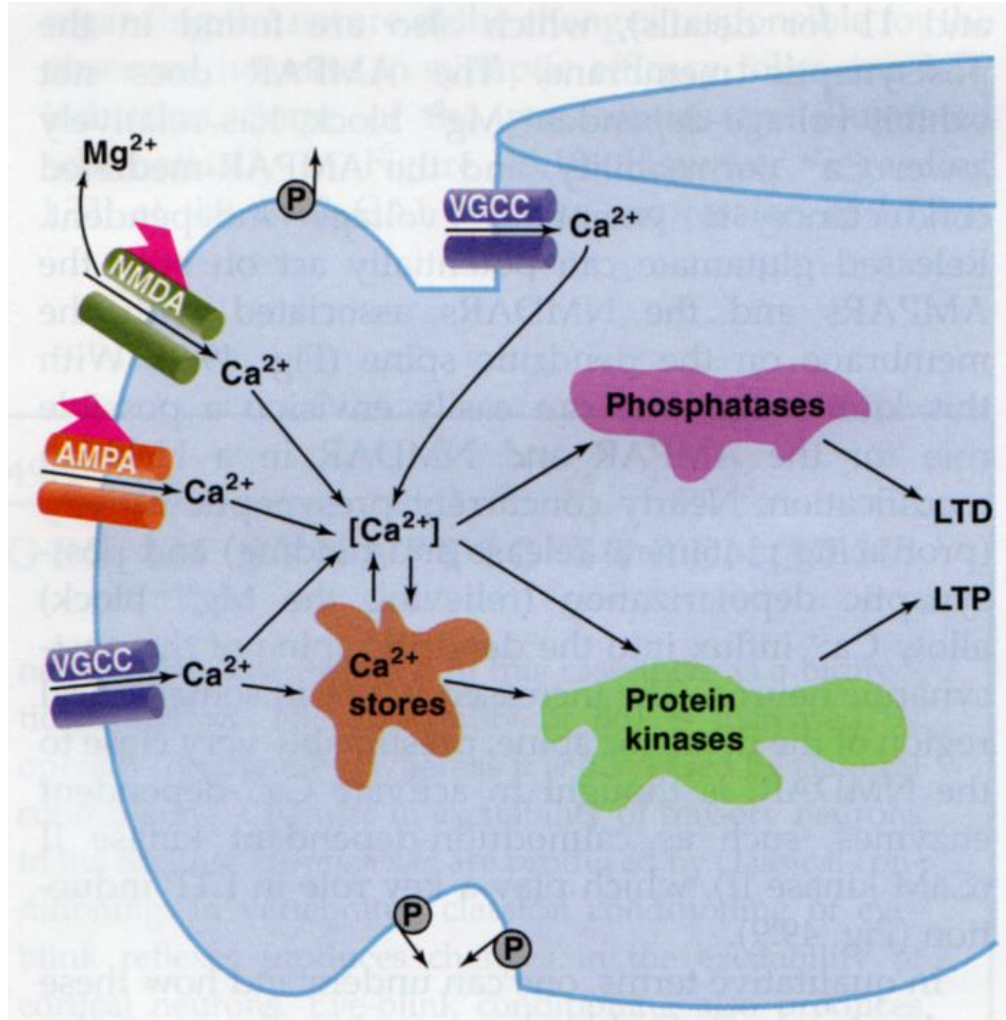
Long term depression- LTD

LTD appears to occur in response to smaller increases in postsynaptic $[Ca^{2+}]_i$ and is accompanied by a reduction in the number and sensitivity of postsynaptic receptors.

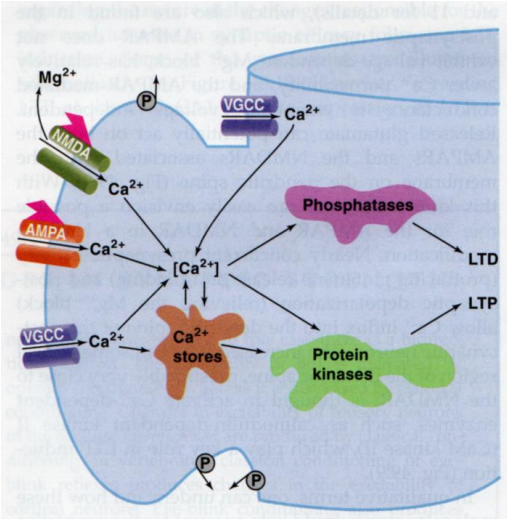


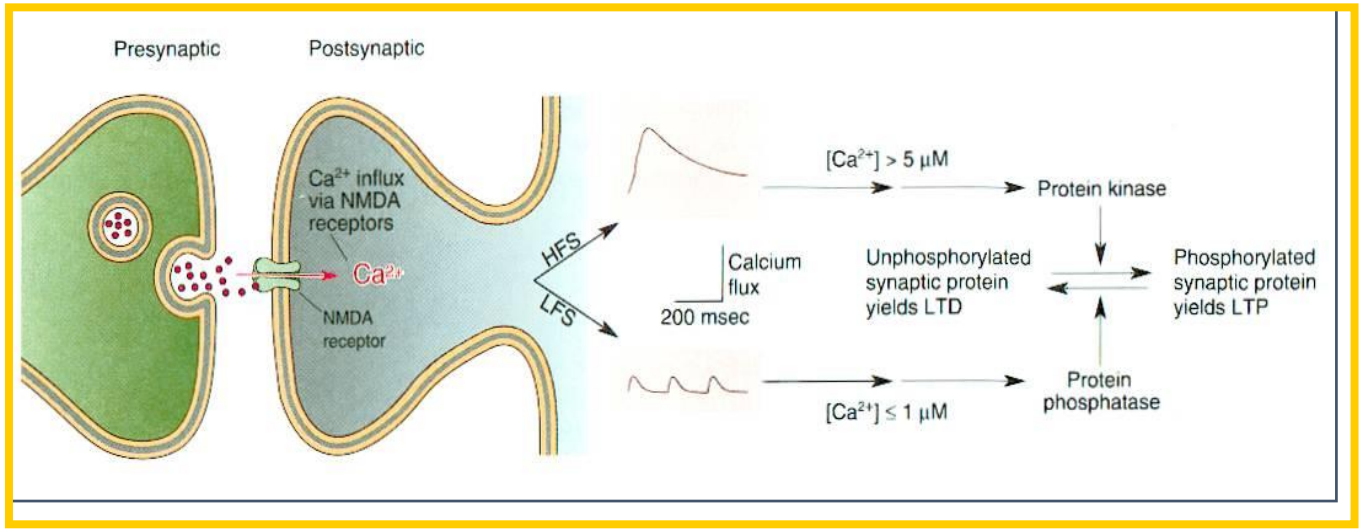
Neuroscienze, Zanichelli

If the Schaffer's Collaterals are stimulated **for long periods (10-15 min) at low frequency (1 Hz)** a persistent (hours) reduction of EPSP amplitude is observed. As for LTP, also LTD is related to NMDAR and Ca^{2+} influx.


Mg^{2+}
P
VGCC
Ca^{2+}
NMDA
Ca^{2+}
Phosphatases
AMPA
Ca^{2+}
LTD
$[Ca^{2+}]$
LTP
VGCC
Ca^{2+}
Ca^{2+} stores
Protein kinases
P
P

LTP or LTD depend on $[Ca^{2+}]_i$



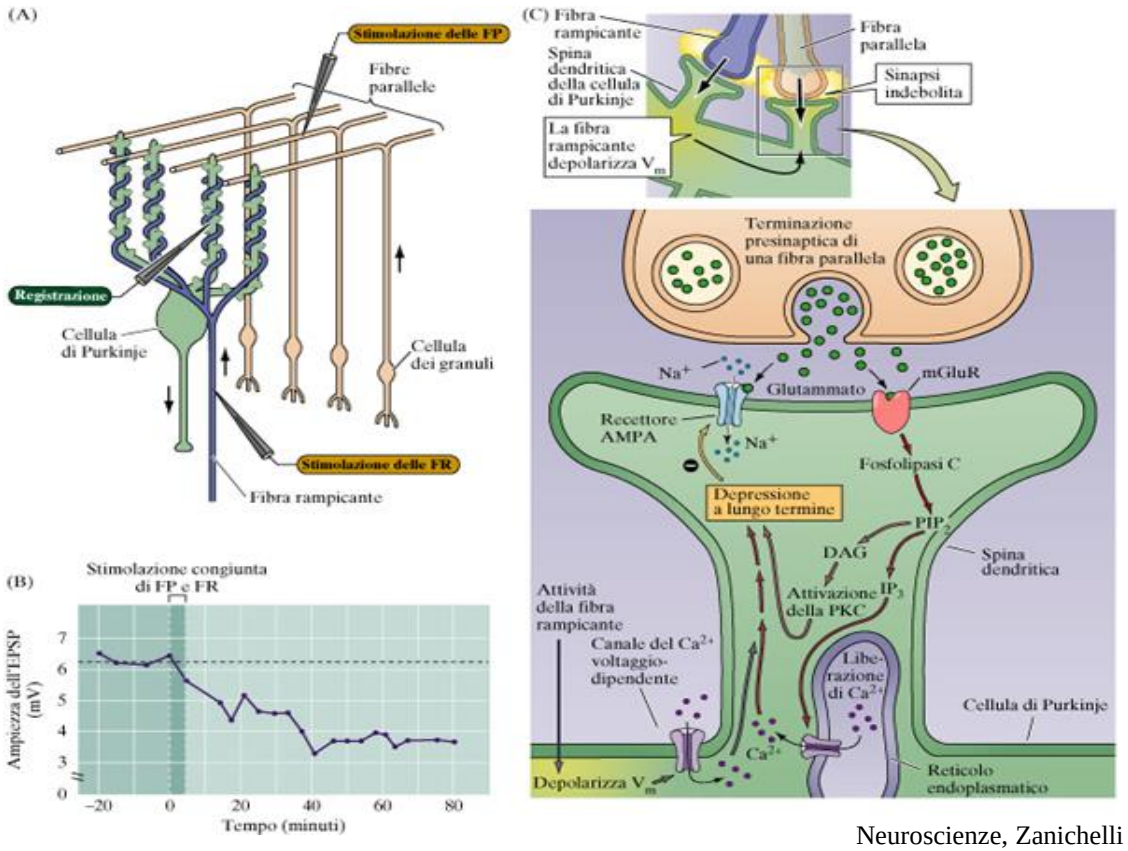


Ca^{2+} dependent Phosphatases activated during LTD separate the posphate groups from the target molecules. LTP and LTD could induce phosphorylation or dephosphorylation in the same regulatory proteins and control the efficacy of synaptic transmission.

Also the temporal properties of $[Ca^{2+}]_i$ increase can be important

Motor learning in cerebellum improves the accuracy of movements

Associative LTD-reduction in parallel fiber response



Neuroscienze, Zanichelli

Climbing fibers code error signals which have to be eliminated!!

Motor learning improves the accuracy of movements
Associative LTD-reduction in parallel fiber response

Possible roles of LTD in cerebellum are the elimination of those synaptic connections associated with errors during repeated exercises, while preserving other connections leading to the successful execution of movements.