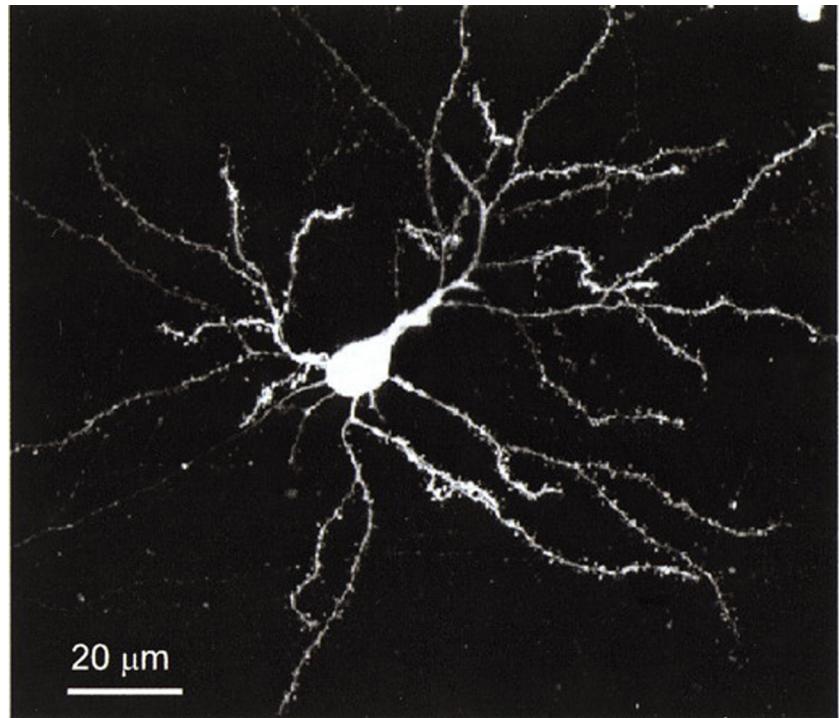


How memories are encoded?



How could experience be written into
neuronal memory?

Synaptic function
Intrinsic electrical properties
Morphology

Synaptic hypothesis of learning

Storage capacity: consider the neocortex $\sim 2^{11}$ cells, 2×10^{15} synapses, $\sim 10^{16}$ bytes
10,000Gbytes

Hebbian Learning

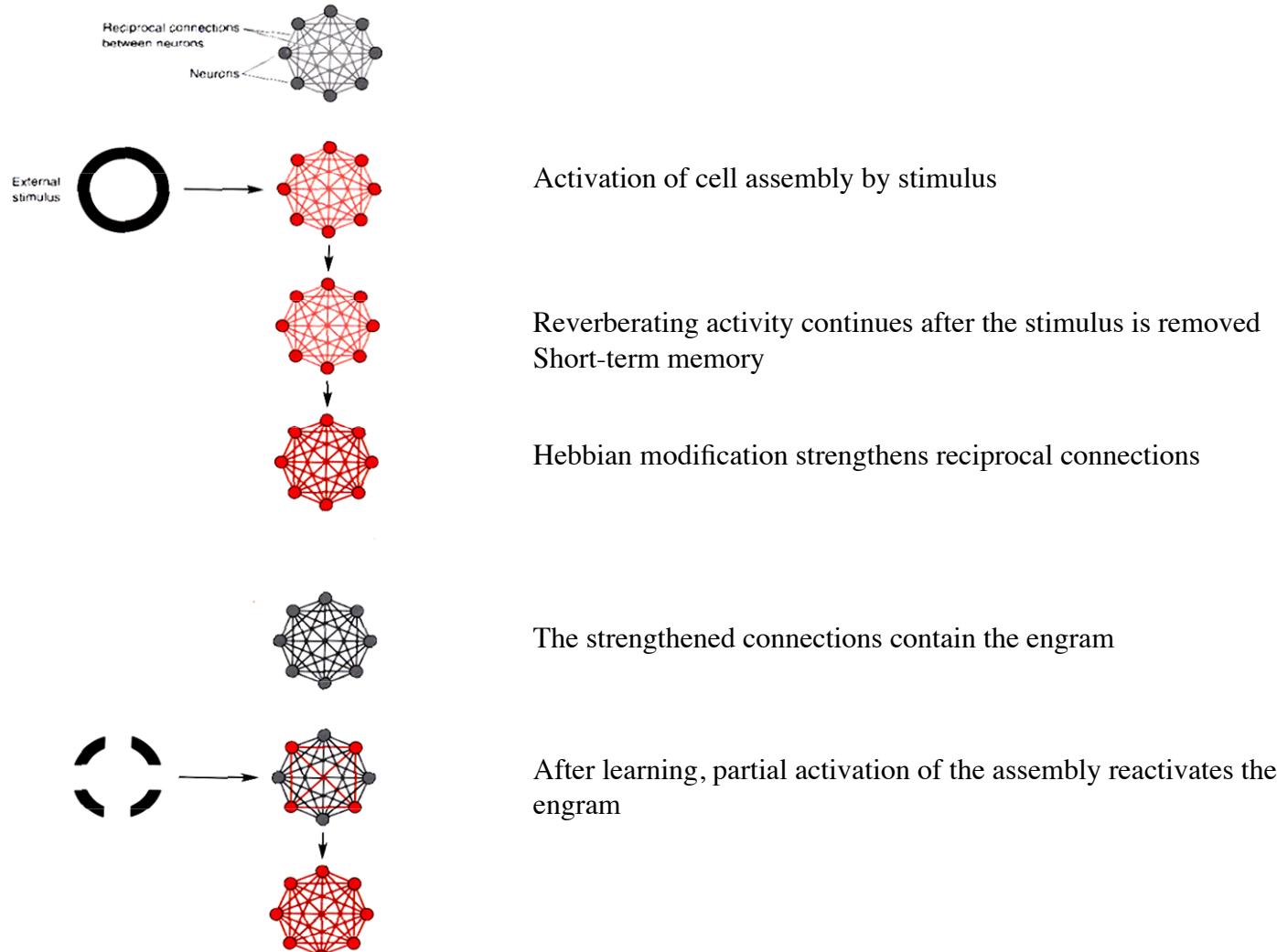


Figure 19.4
Hebb's cell assembly and memory storage.

Hebb's postulate

“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.”

From the “Organization of Behavior” by D. O. Hebb (1949)

Cells that fire together are wired together

(1949)

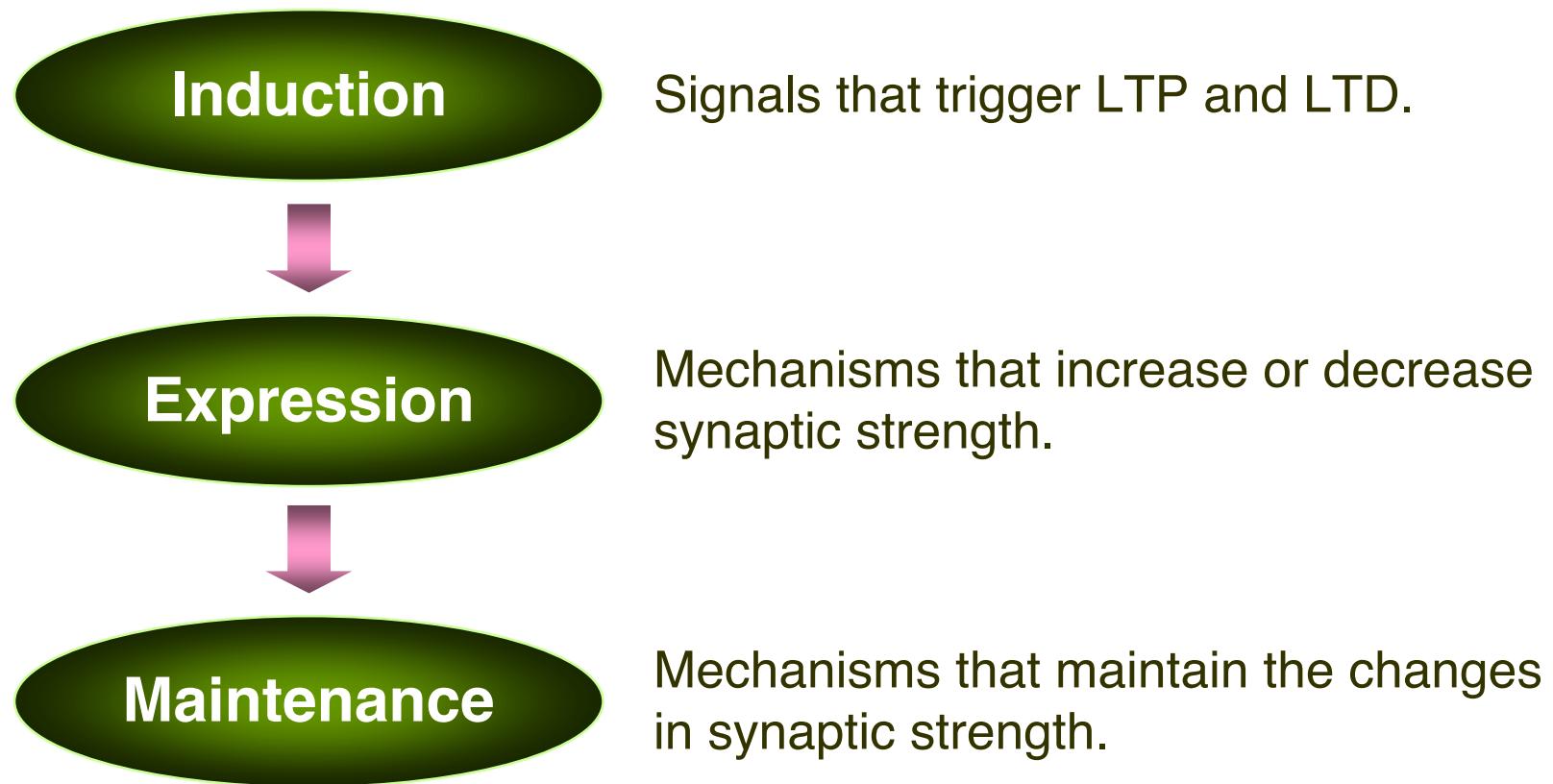
Stent's postulate

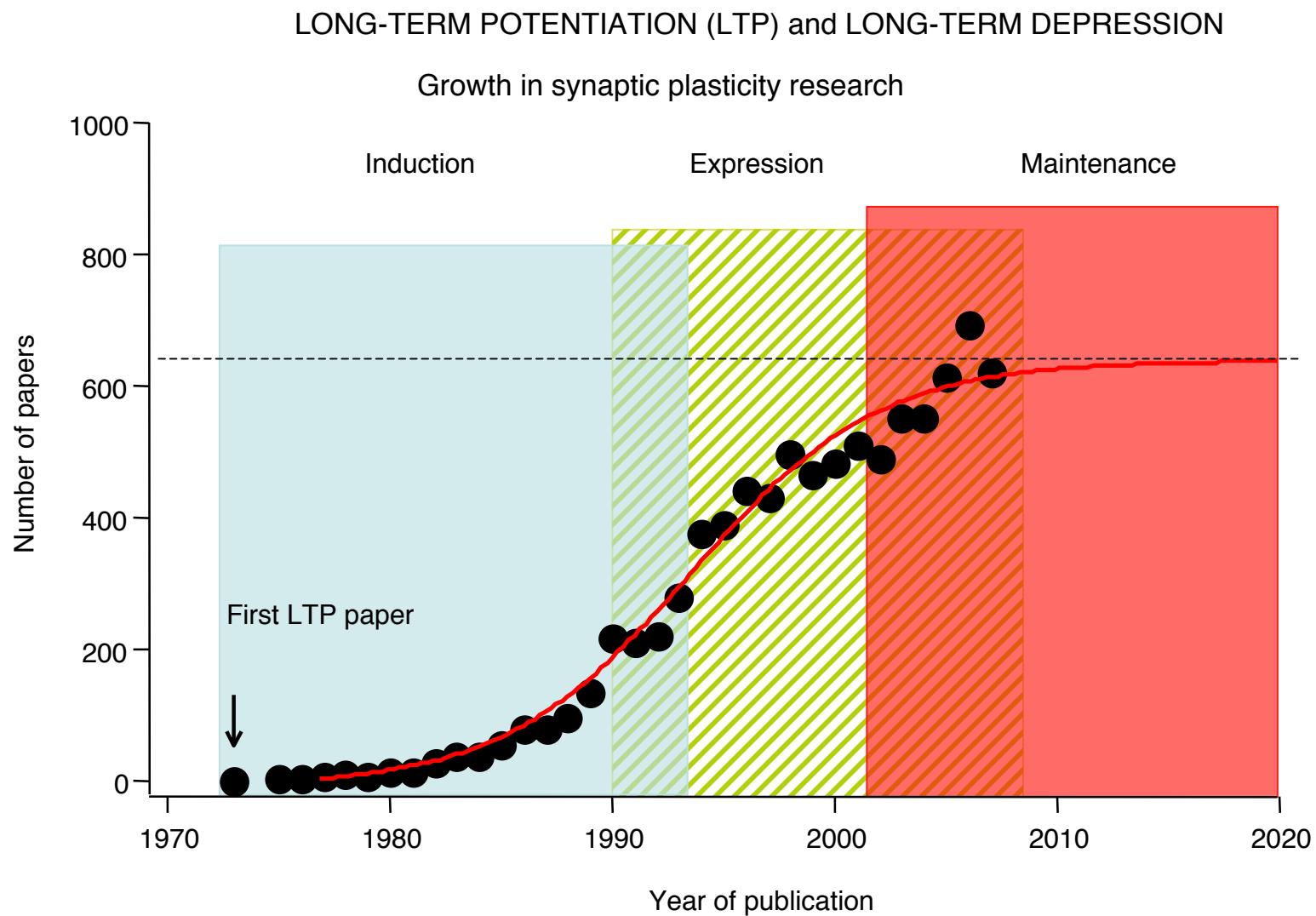
“When an axon of cell A repeatedly and persistently fails to excite the postsynaptic cell B while cell B is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is decreased.”

Cells that fire out of sinc lose their link

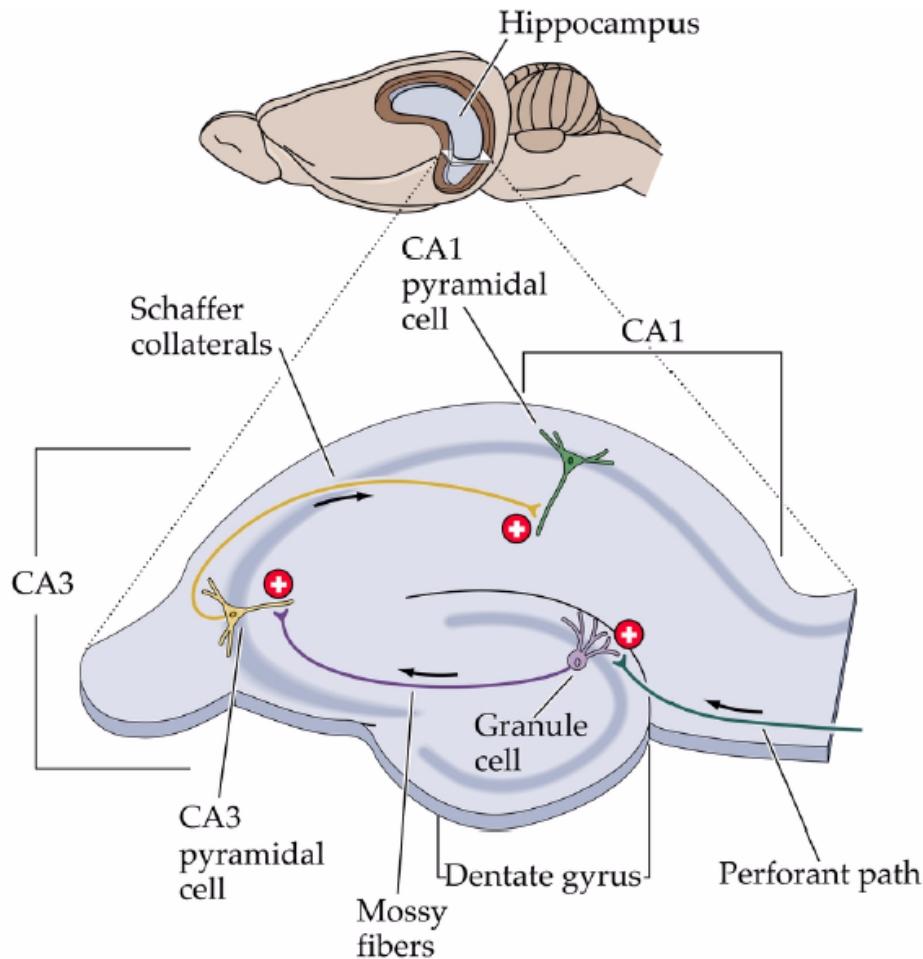
(1973)

Different aspects of LTP and LTD



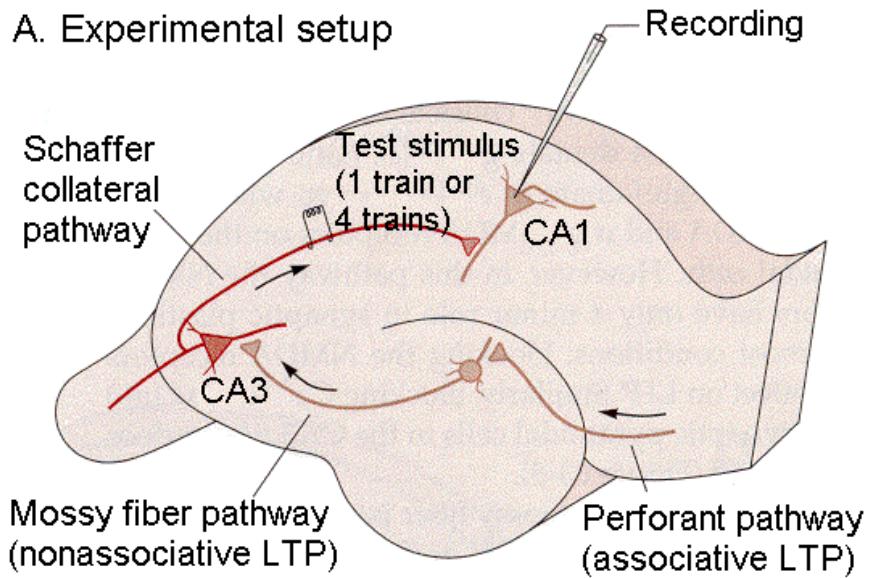


The hippocampus and hippocampal slice

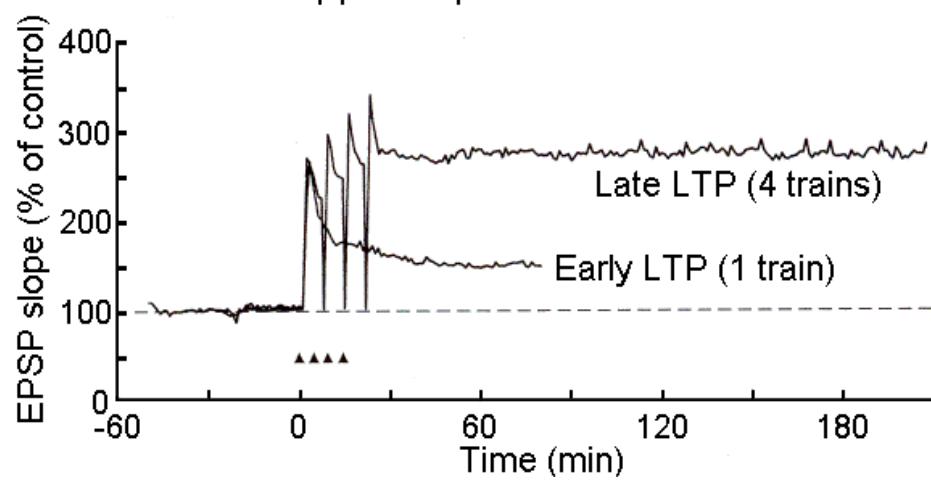


© 2001 Sinauer Associates, Inc.

A. Experimental setup



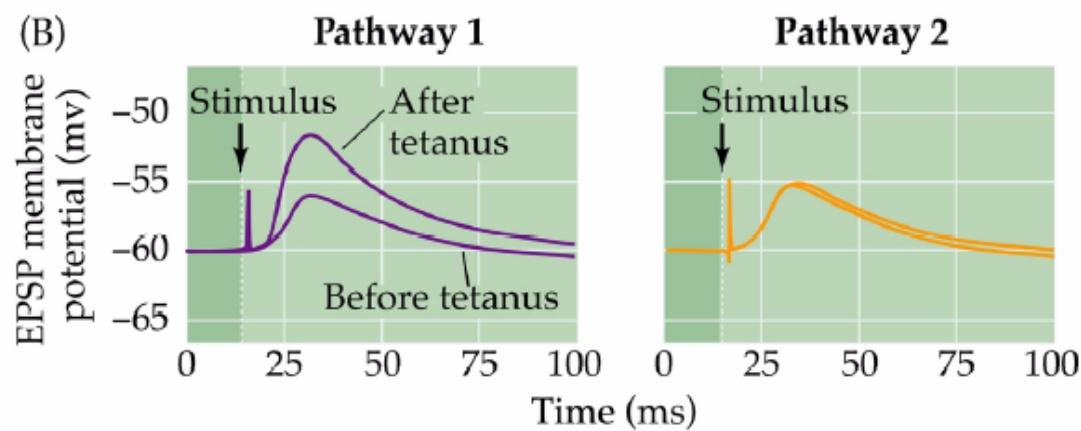
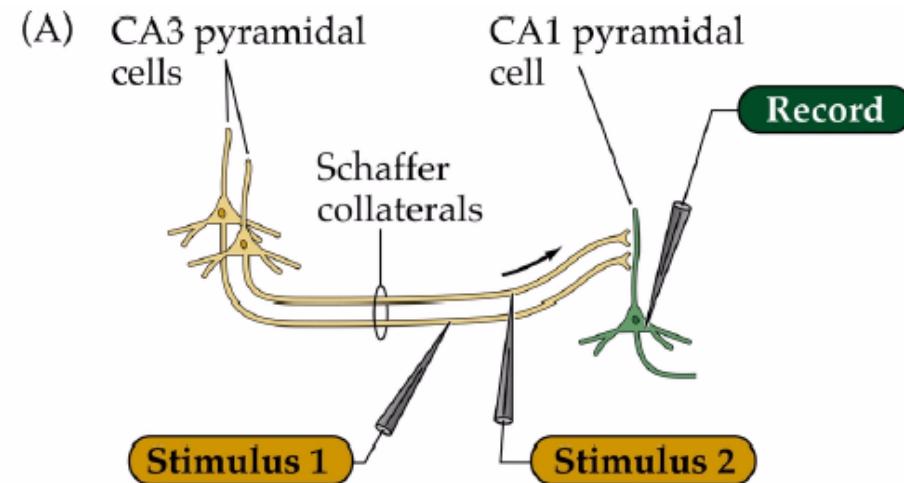
B. LTP in the hippocampus CA1 area



Long-term potentiation (LTP): lasting, non-decremental increase in the synaptic response magnitude.

In this case it was induced with tetanic stimulation (high frequency)

LTP is input-specific (mostly confined to activated synapses)



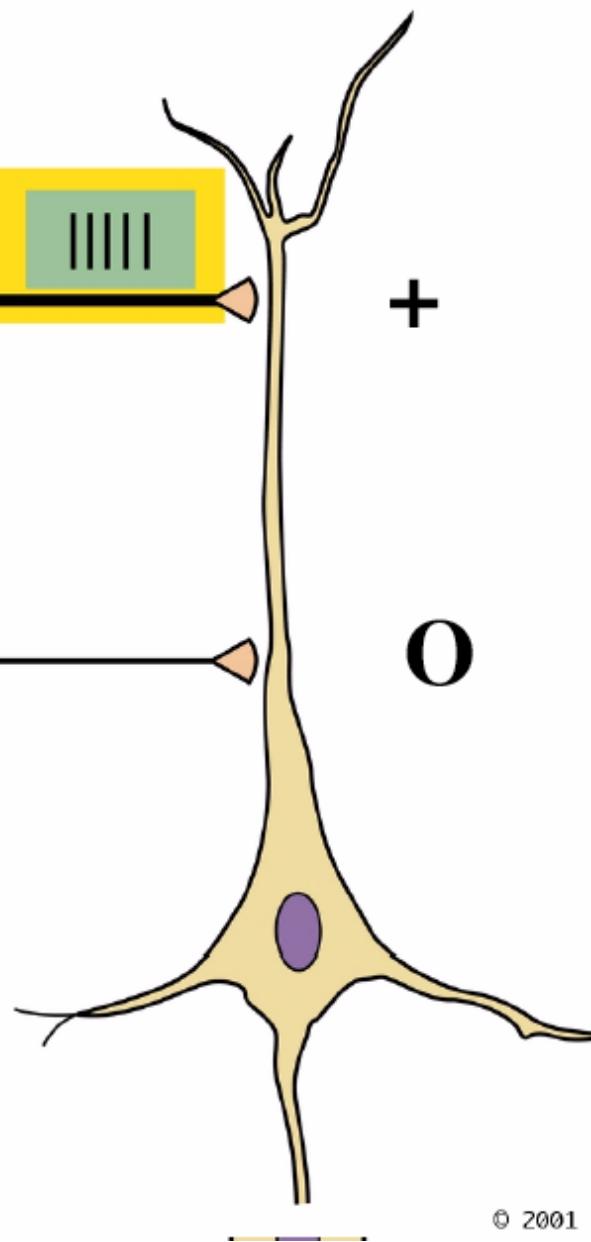
© 2001 Sinauer Associates, Inc.

(A) Specificity

Pathway 1:
Active

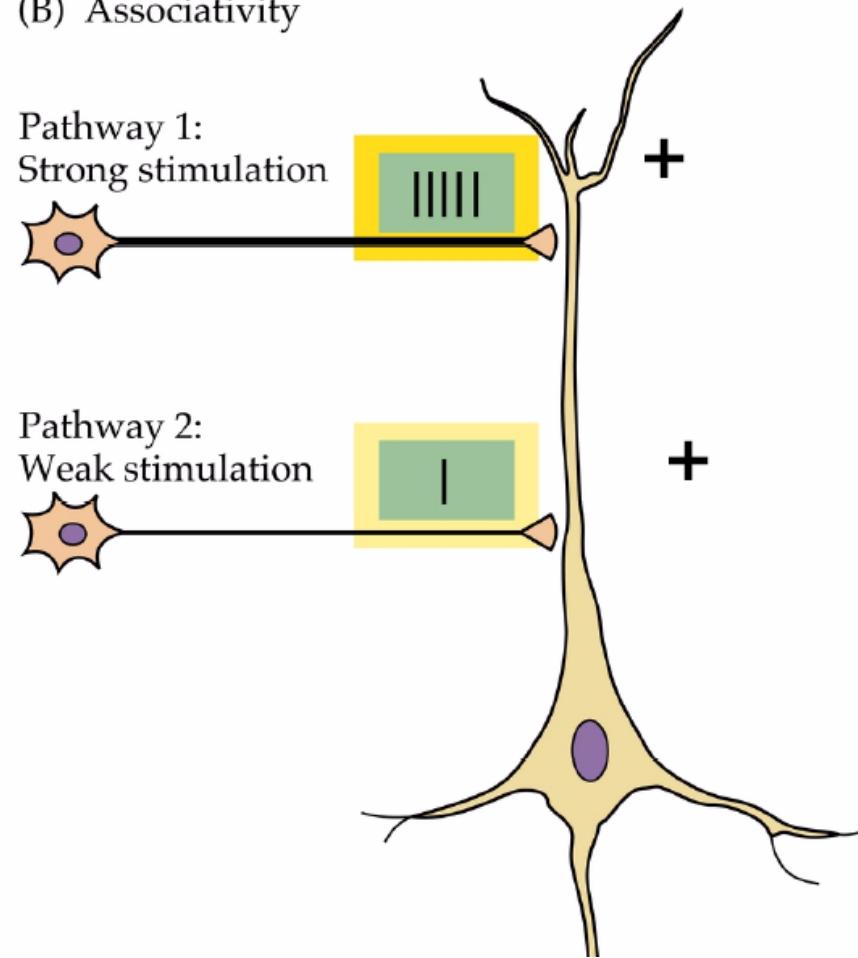


Pathway 2:
Inactive

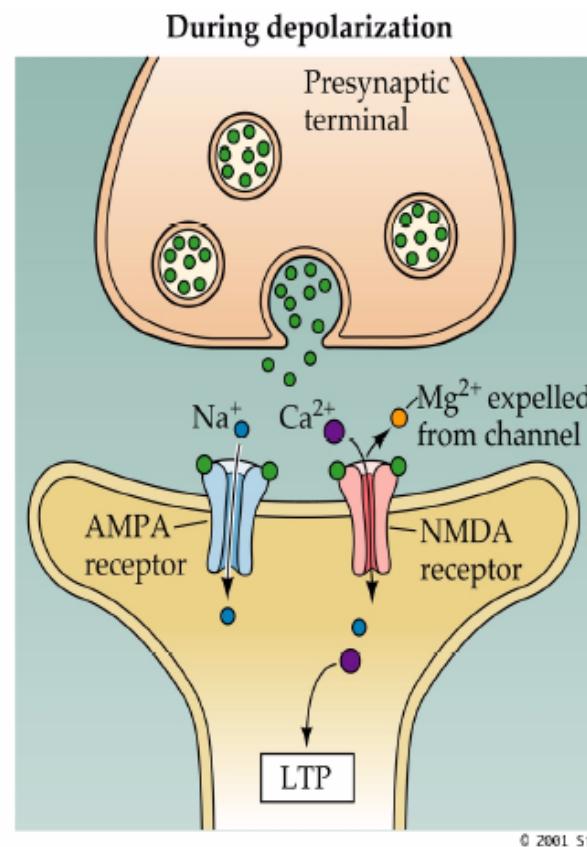
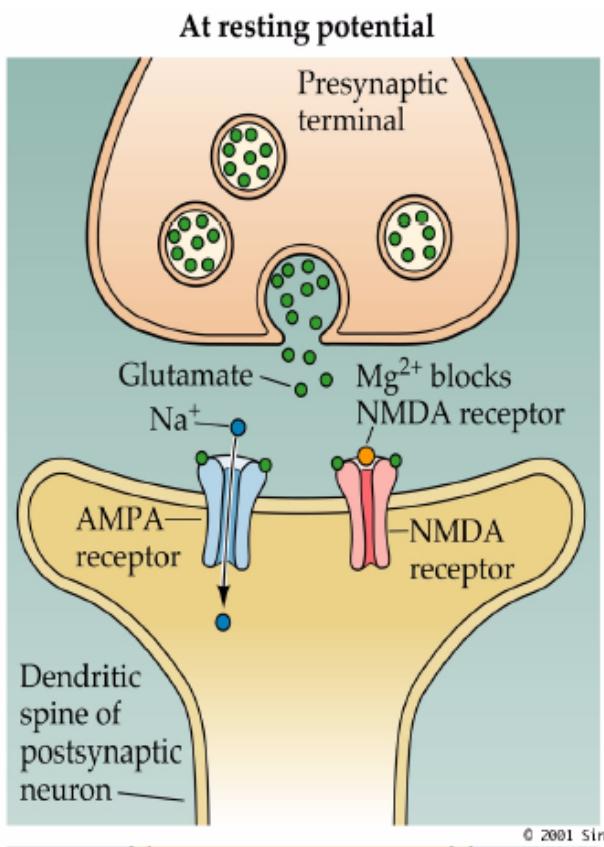


LTP is associative

(B) Associativity

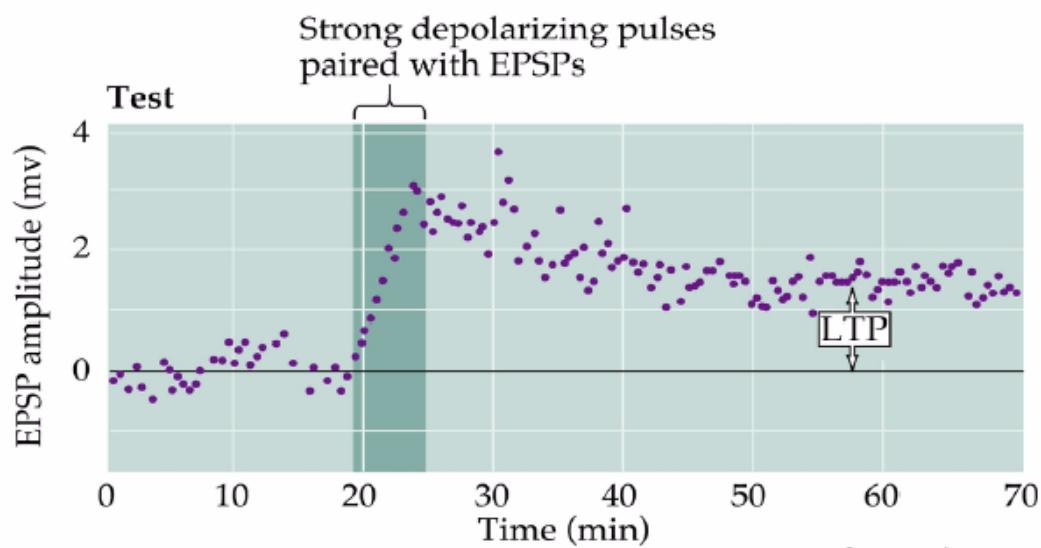
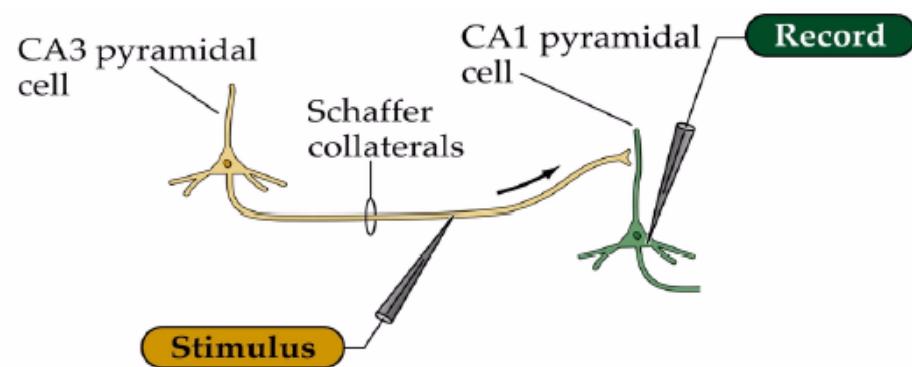


NMDA receptor confers associativity



NMDA receptor is the “coincidence detector”

Pairing-induced LTP



© 2001 Sinauer Associates, Inc.

LTP may be induced by:

synaptic tetani

pairing low frequency stimulation with
postsynaptic depolarization

LTP induction is blocked by:

postsynaptic hyperpolarization

NMDA-R antagonists

pairing with depolarization to E_{Ca}

LTP may be induced by:

photolysis of caged Ca

postsynaptic injection of constitutively active
Ca-calmodulin-dependent protein kinase II

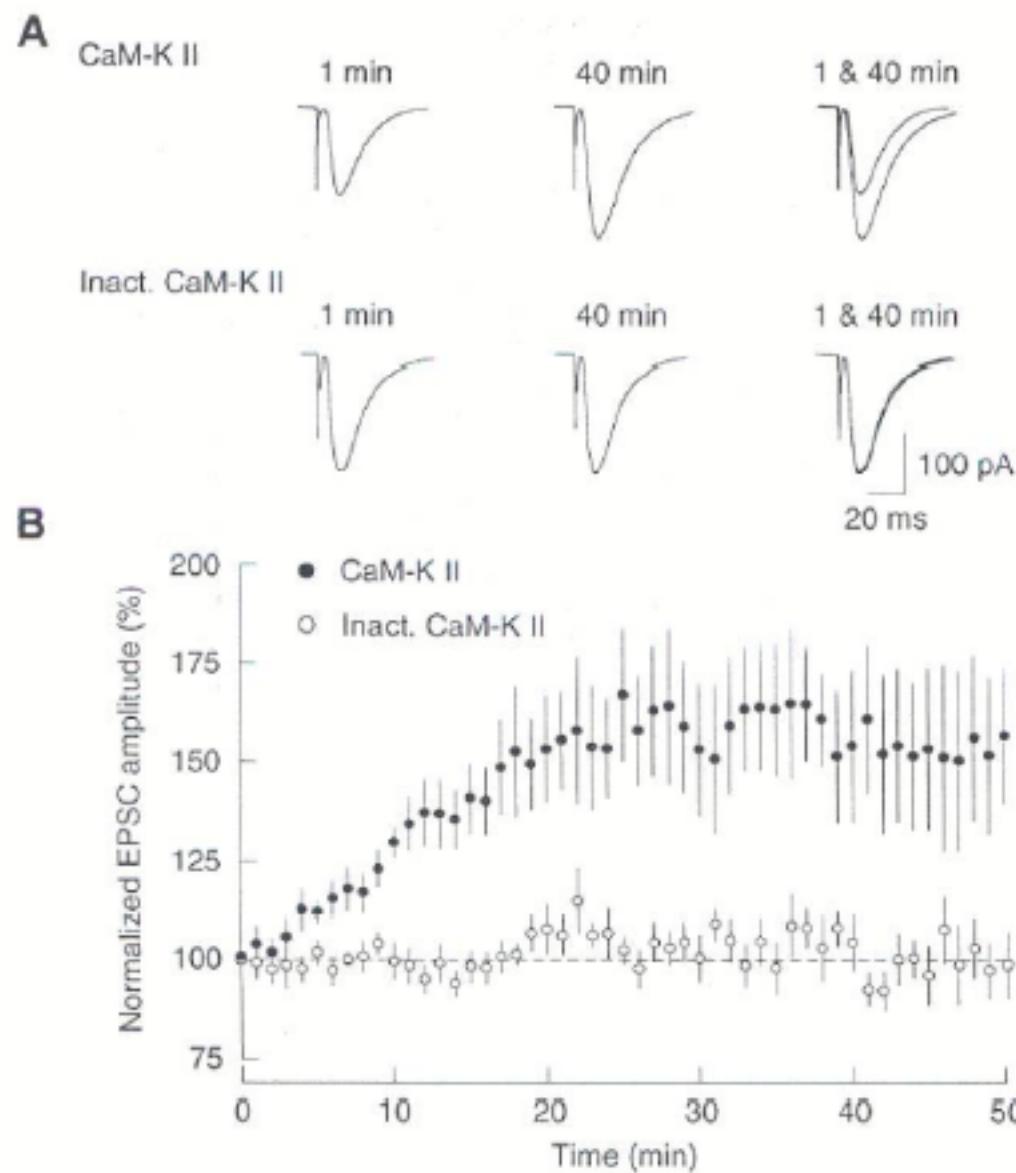
LTP induction is blocked by:

strong Ca chelators (BAPTA)

inhibitors of CaMK II

mutant mice which lack CaMKII activity

Postsynaptic Active CaMKII causes an LTP-like effect



Expression

Mechanisms that increase or decrease synaptic strength.

How to make a synapse stronger?

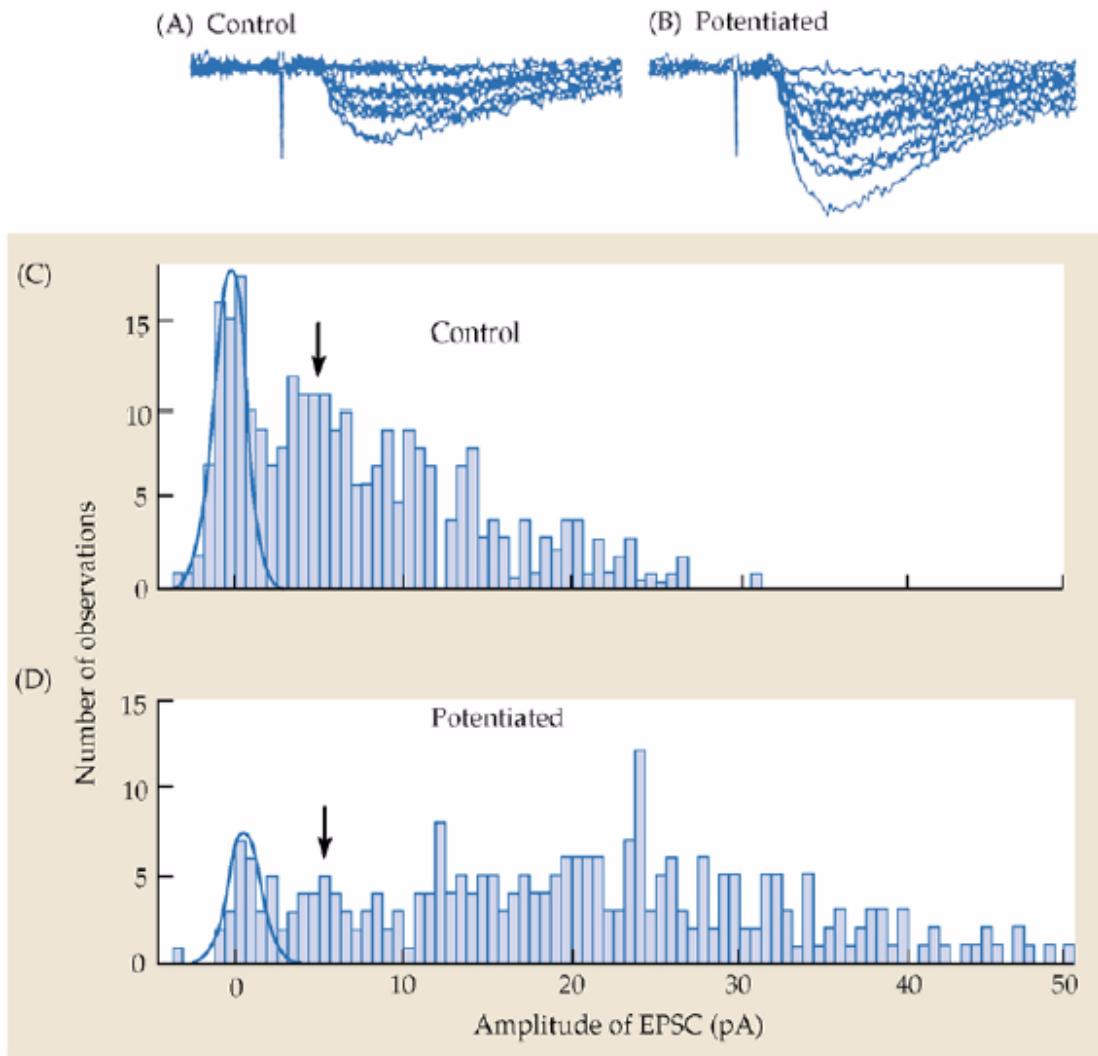
Presynaptic:

- Increase probability of release
- Increase amount of transmitter-vesicle

Postsynaptic:

- More receptors
- Increased unitary conductance
- Increased agonist affinity
- Altered kinetics
- Increased conduction from synapse to recording site

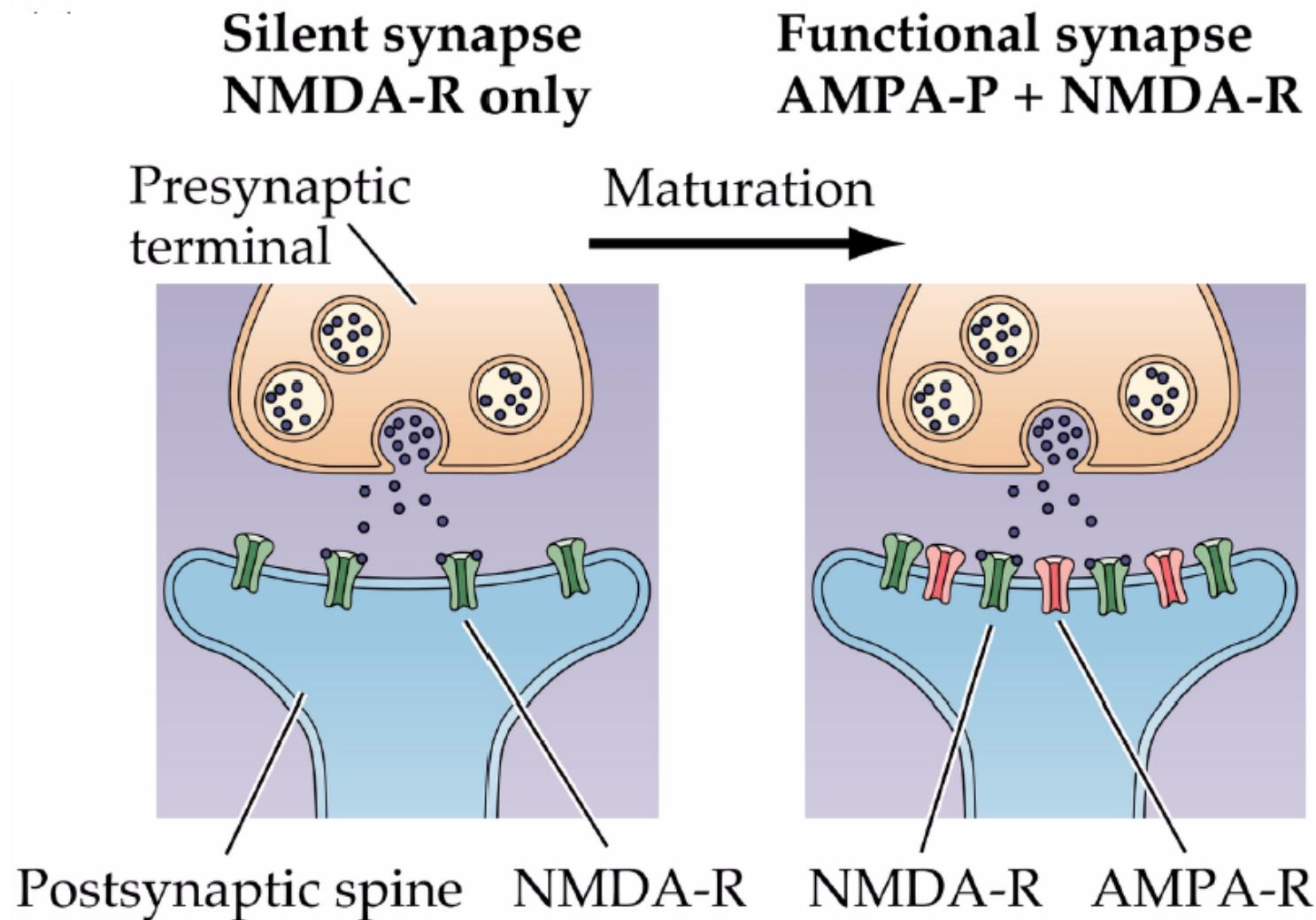
Lower synaptic failure rate after LTP



© 2001 Sinauer Associates, Inc.

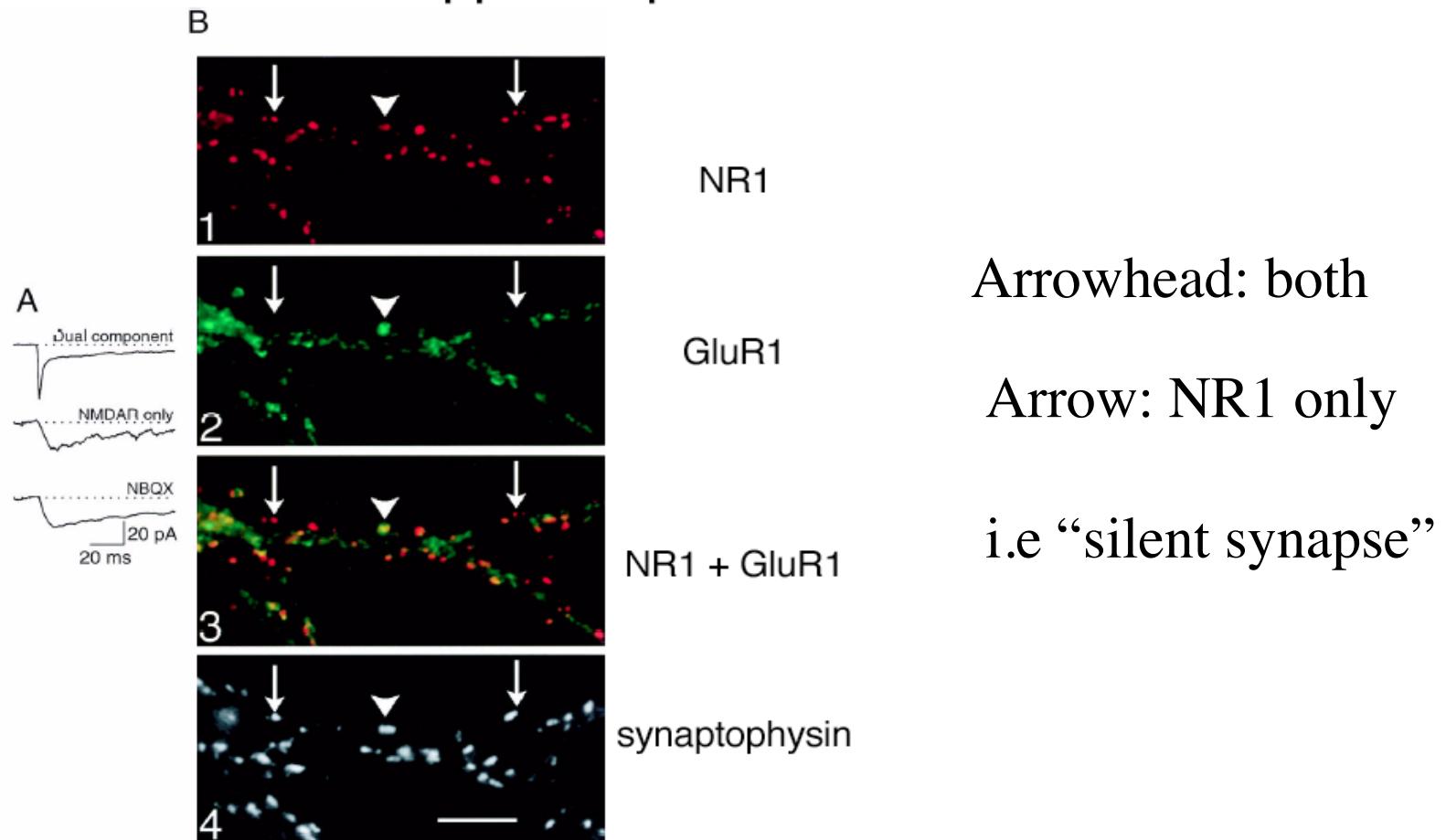
Recordings made with “minimal stimulation”

The “silent synapse” model



Evidence for silent synapses: Immunocytochemistry in cultures cells

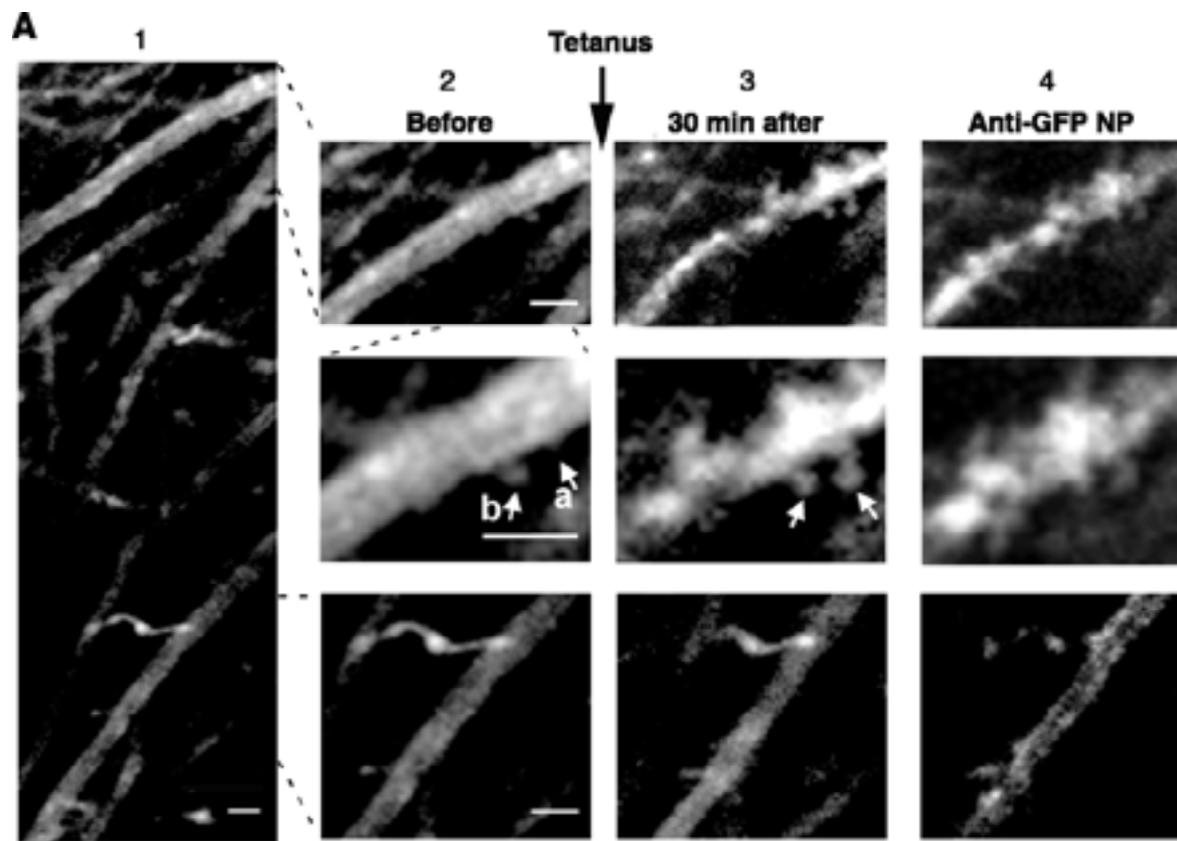
NMDA-only mEPSCs and NR1-only puncta In cultured hippocampal neurons



Evidence for silent synapses: live TPM imaging

Rapid spine delivery and redistribution of AMPA receptors after synaptic NMDA receptor activation.

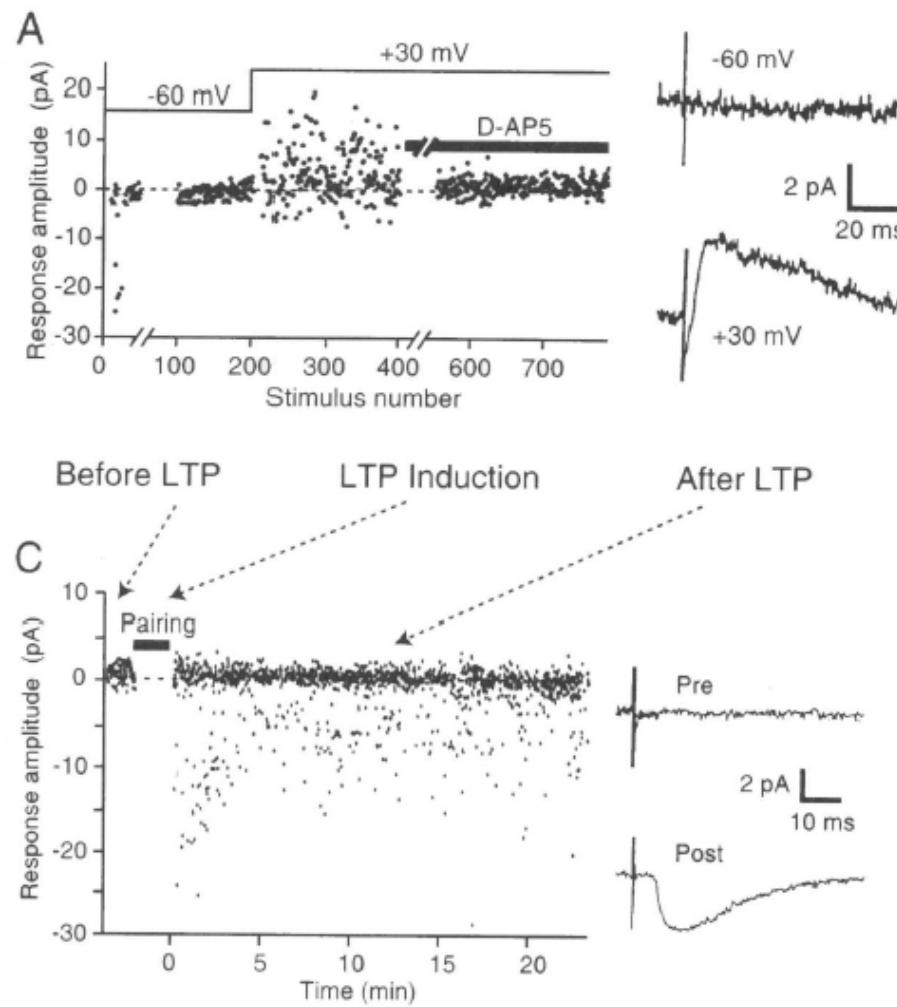
By Shi et al. (1999) Science 284: 1811-1816.



Cultured slices -viral infection with GluR1-GFP gene

Look at the arrows

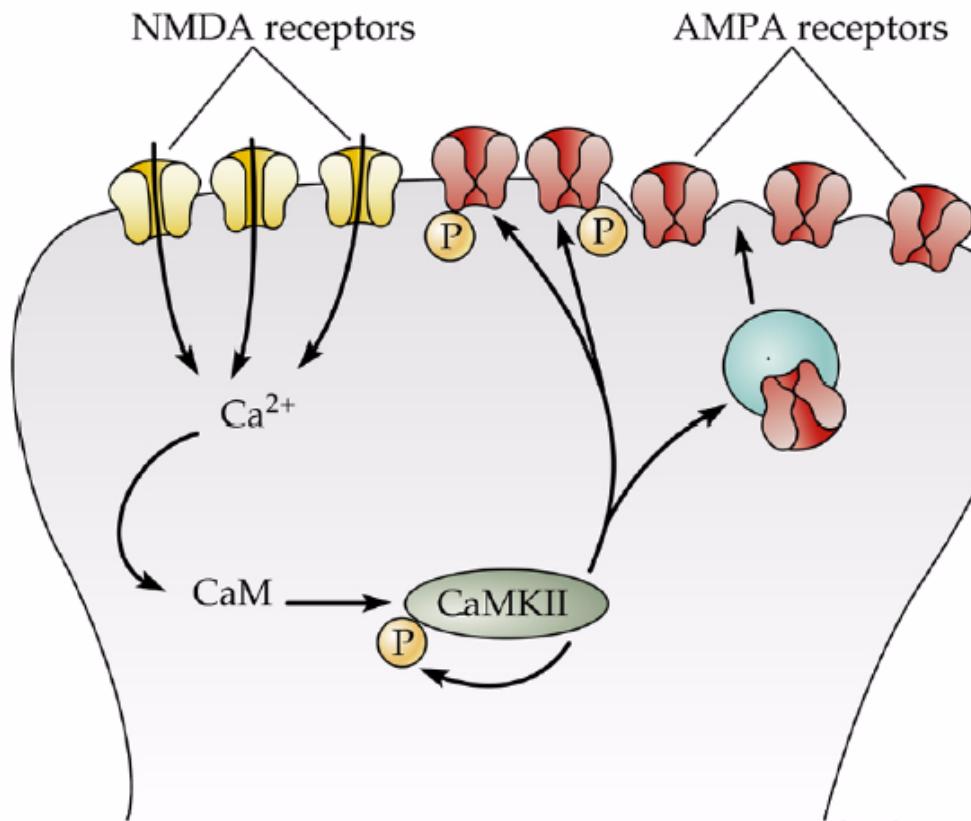
Electrophysiological evidence for silent synapses: the “free lunch”: experiment -->



Synapse that contain Only NMDAR's: no response at negative potential.

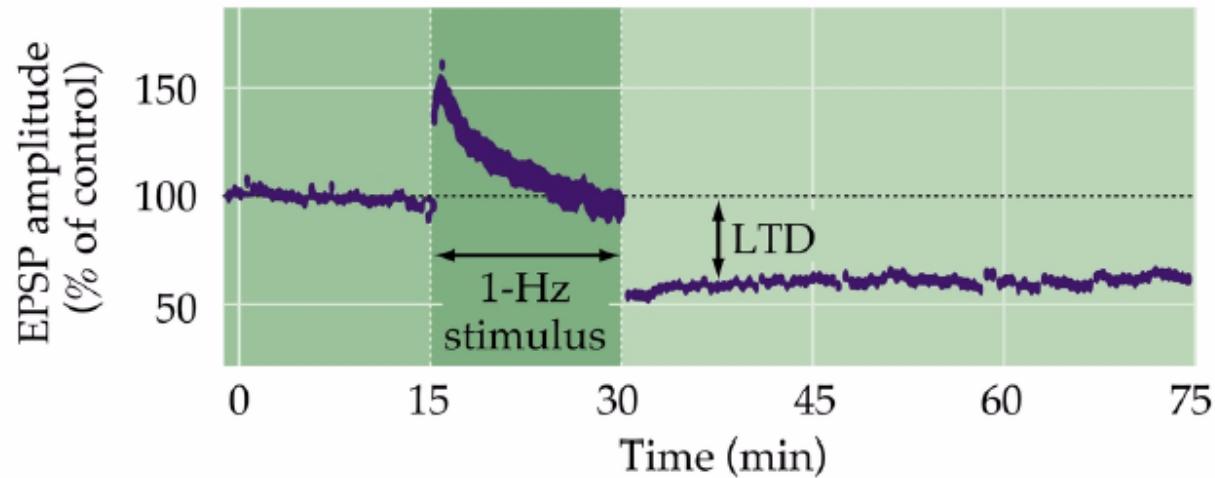
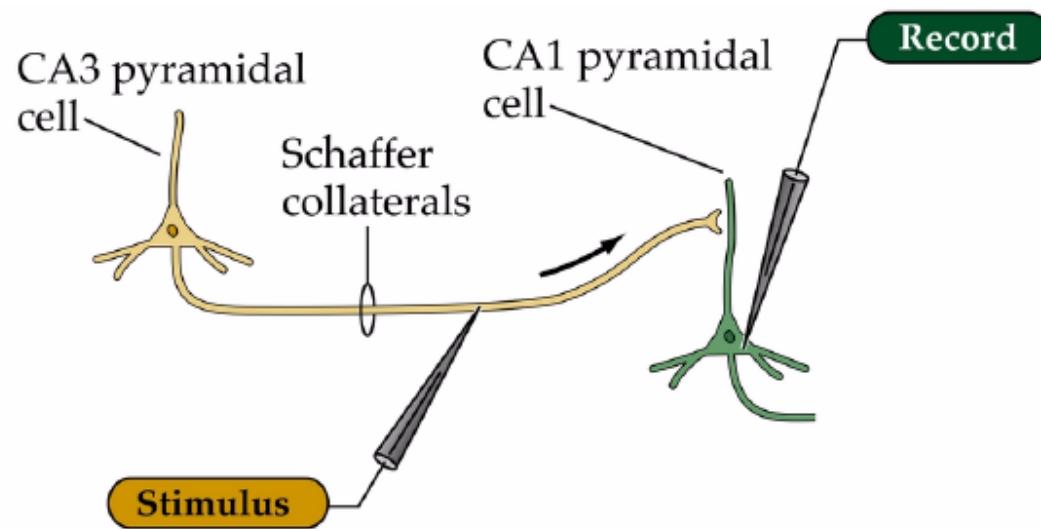
After pairing:
response at negative potential.

The Malinow/Nicoll/Malenka model of LTP expression



© 2001 Sinauer Associates, Inc.

Hippocampal LTD



Hippocampal LTD

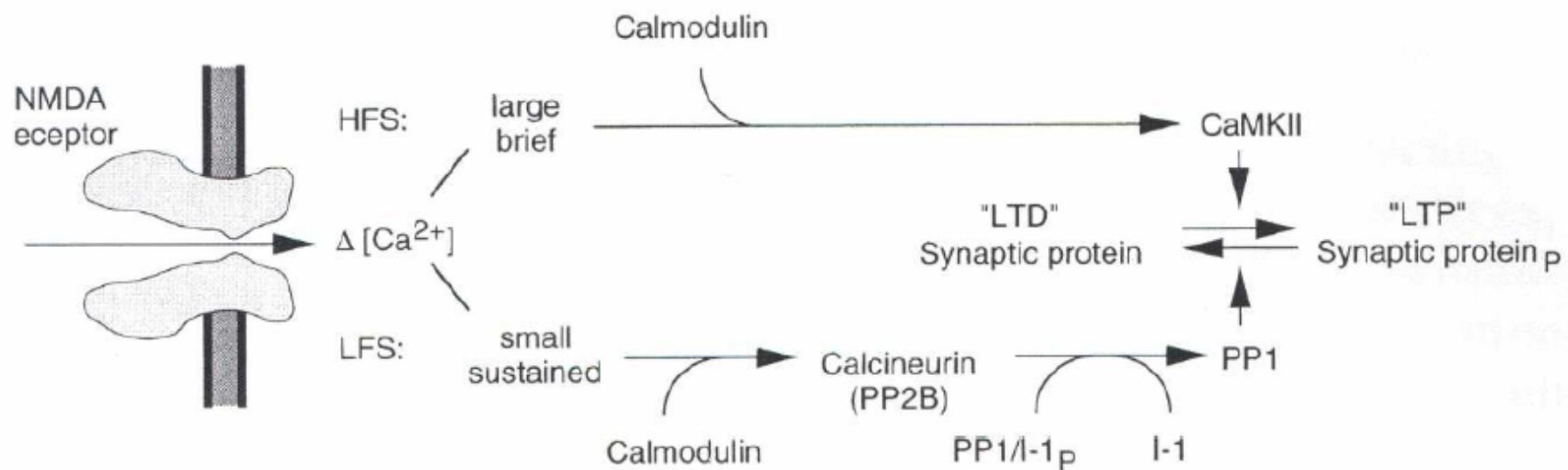
May be produced by:

prolonged low-frequency stimulation
bath-applied glutamate
pairing with depolarization to -40 mV

Is blocked by:

NMDA-R antagonists
postsynaptic Ca chelators
postsynaptic calcineurin/PP-1 inhibitors
mutants which lack calcineurin activity

How can Ca influx through NMDA-Rs trigger both LTP and LTD?



There are several other forms of LTP and LTD that do not require activation of postsynaptic NMDA-Rs:

LTP at the hippocampal mossy fiber-CA3 and cerebellar parallel fiber-Purkinje cell synapses utilizes a cascade involving presynaptic Ca flux via voltage-gate channels/activation of Ca-sensitive adenylyl cyclase type I/PKA activation/phosphorylation of RIM1 ser-413/increased transmitter release

LTD at the cerebellar parallel fiber-Purkinje cell synapse involves activation of postsynaptic mGluR1/diacylglycerol production and Ca transients/PKC activation/phosphorylation of GluR2 ser-880/PICK1 binding to GluR2/clathrin-mediated endocytosis of postsynaptic AMPA-Rs.

The million dollar question:

Are LTP/D involved in memory?

-Blocking LTP/D blocks the formation of memories
APV-Morris maze- mutants

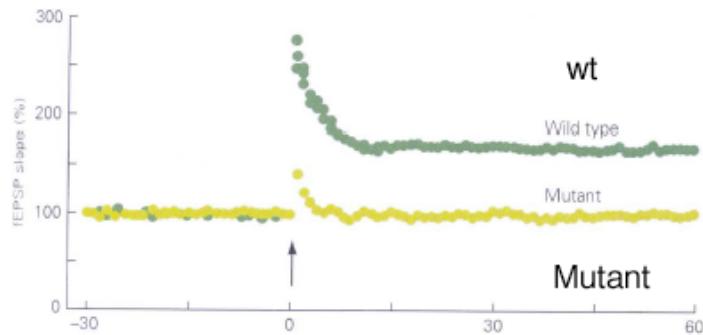
-Saturation of LTP erases memories
Limited by the proportion of synapses altered. Difficult to do in a large distributed network

The formation of memories increases the responses

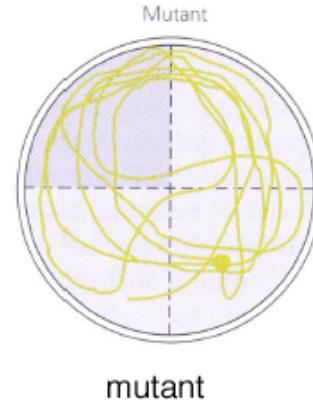
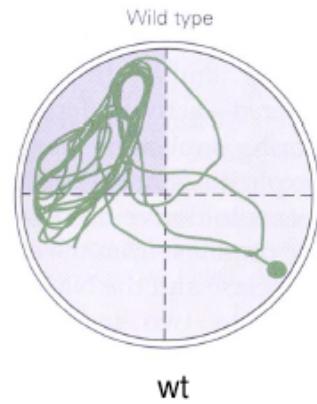
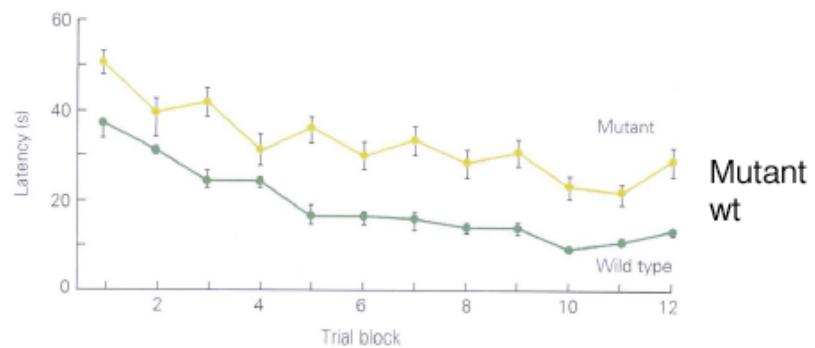
Firs trial was dissapointing. It was just the heat
Memories saturate LTP

LTP and watermaze learning deficits in CA1-restricted NR1 null mouse (will lack LTP and LTD)

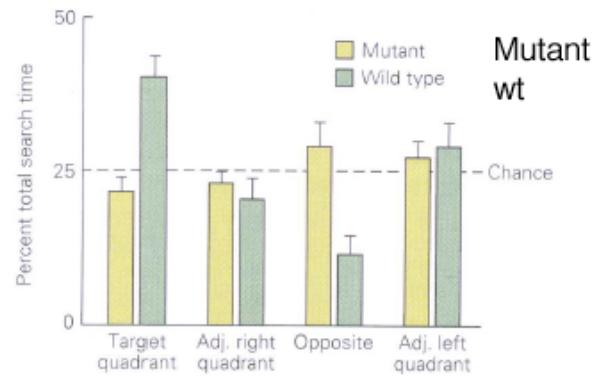
A LTP defect in the Schaffer collateral pathway



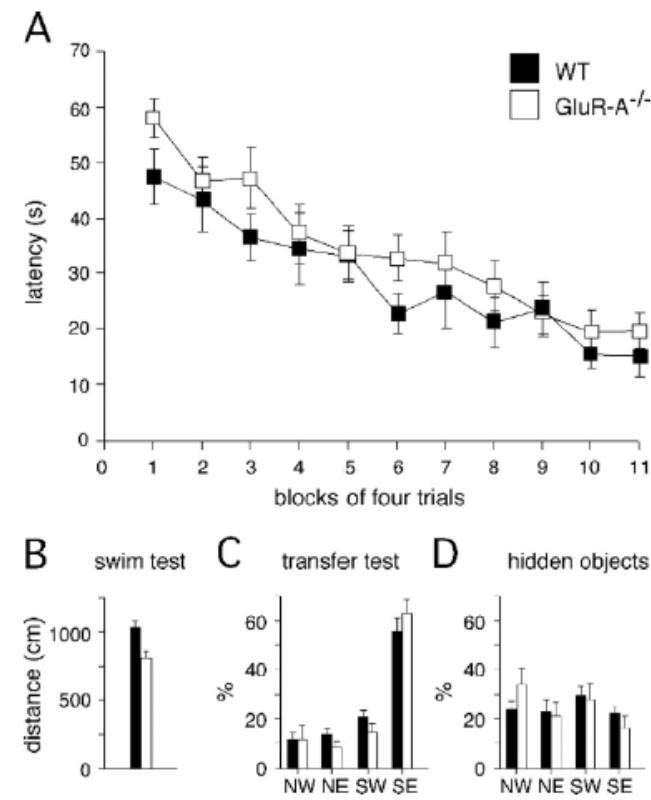
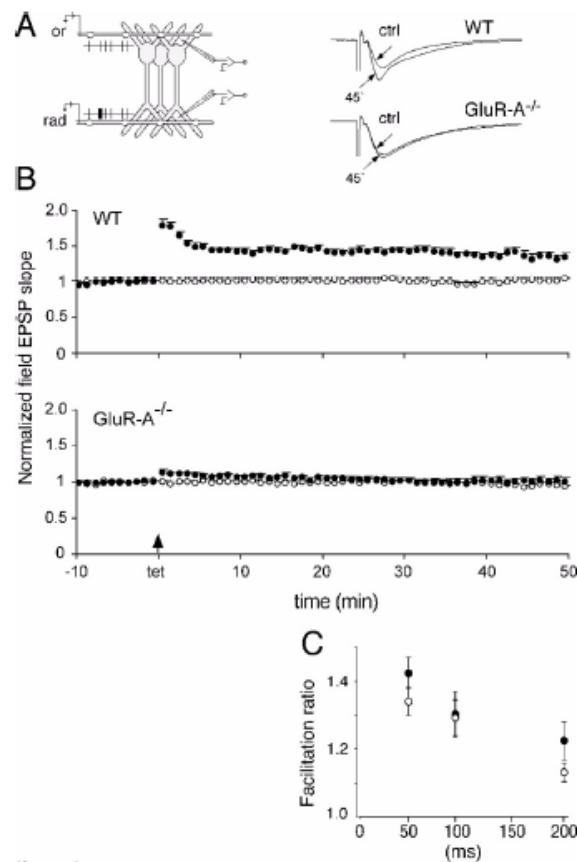
2 Escape latencies



b Search time



Impaired CA1 LTP but normal watermaze learning in GluR1 (GluRA) null mice



Caveat: later work showed that pairing-induced LTP was intact in the GluR1 null mouse. Moral of story: do a big walk in parameter space.

What will take to really test the hypothesis that LTP/LTD underlies certain forms of learning?

First, it will take a model system where there is a circuit level understanding of how making synapses weaker or stronger constitutes real behavioral memory.

Second it will take very specific and subtle molecular manipulations of LTP/LTD. Deletion of receptors or kinases/phosphatases has too many side-effects. Perhaps phosphorylation-site mutant knock-ins of the relevant kinase substrates will be the way to go.

Main points to take away from this lecture:

- 1) Synaptic plasticity is only one possible way to store information in the brain.
- 2) Hippocampal LTP is compelling as a model for memory not only because it is long-lasting, but also because it is input-specific and associative.
- 3) The biophysical properties of the NMDA-R (voltage-dependent Mg block and Ca permeability) confer associative LTP induction.
- 4) Hippocampal LTP requires a Ca/CaMKII cascade.
- 5) Hippocampal LTP is largely expressed postsynaptically, by insertion of functional AMPA-Rs.
- 6) Hippocampal LTD can reverse LTP.
- 7) Hippocampal LTD involves an NMDA-R/Ca/phosphatase cascade.
- 8) While the hypothesis that LTP/LTD underlie memory is attractive, it remains unproven.

A nice (very thorough) recent review:

Lynch MA. Long-term potentiation and memory.
Physiol Rev. 2004 84(1):87-136.