Synaptic Plasticity and the NMDA Receptor

Computational Models of Neural Systems

Lecture 4.2
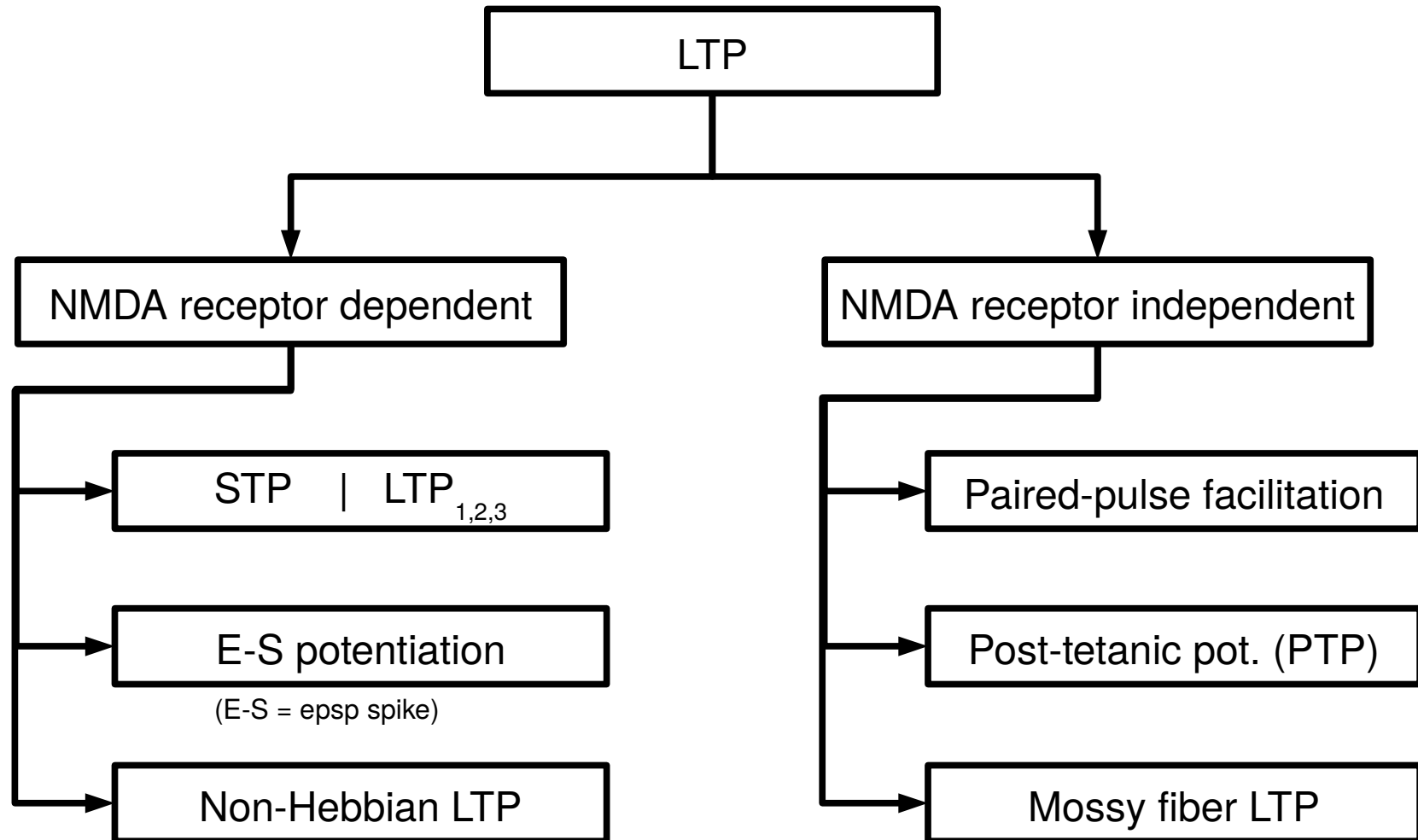
David S. Touretzky

November, 2021

Synaptic Plasticity Is A Major Research Area

- Long Term Potentiation (LTP)

- Reversal of LTP

- Long Term Depression (LTD)

- Reversal of LTD

- Short-Term Potentiation

- and more...

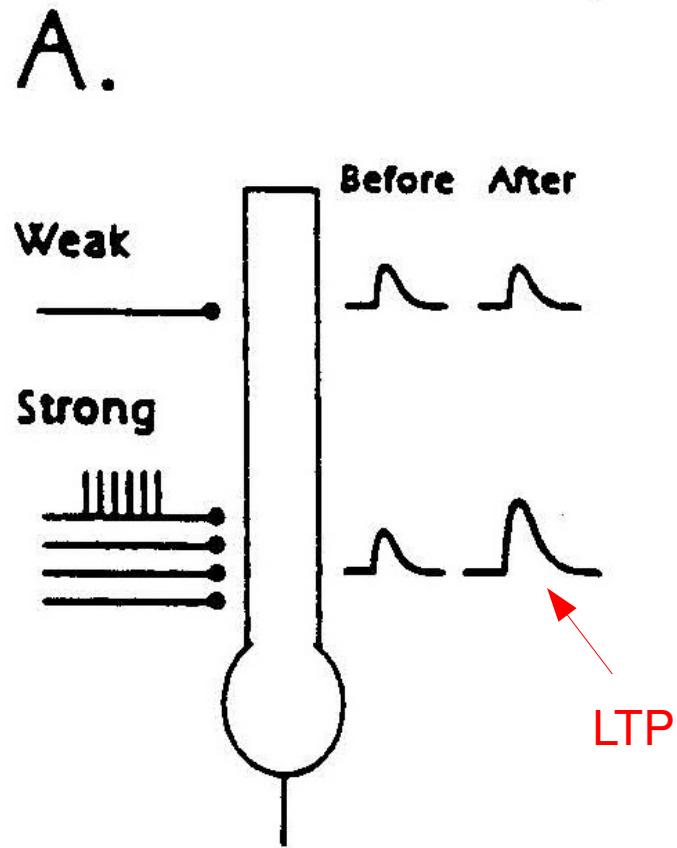Thousands of papers!

Types of Plasticity in Hippocampus

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                        ┌─────────────────────┐
                        │         LTP         │
                        └─────────────────────┘
                                   │
              ┌────────────────────┴────────────────────┐
              ▼                                          ▼
┌───────────────────────────┐          ┌───────────────────────────┐
│  NMDA receptor dependent  │          │ NMDA receptor independent │
└───────────────────────────┘          └───────────────────────────┘
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NMDA receptor dependent	NMDA receptor independent
STP | LTP$_{1,2,3}$	Paired-pulse facilitation
E-S potentiation (E-S = epsp spike)	Post-tetanic pot. (PTP)
Non-Hebbian LTP	Mossy fiber LTP

Bliss & Collingridge 1993

Short-Term Plasticity

- Could serve a spike filtering function.

- Synapses with <u>low</u> probability of transmitter release are more likely to show facilitation.

  - Acts as a high pass filter: high frequency spike trains will be transmitted more effectively.

- Synapses with a <u>high</u> probability of transmitter release are more likely to show depression.

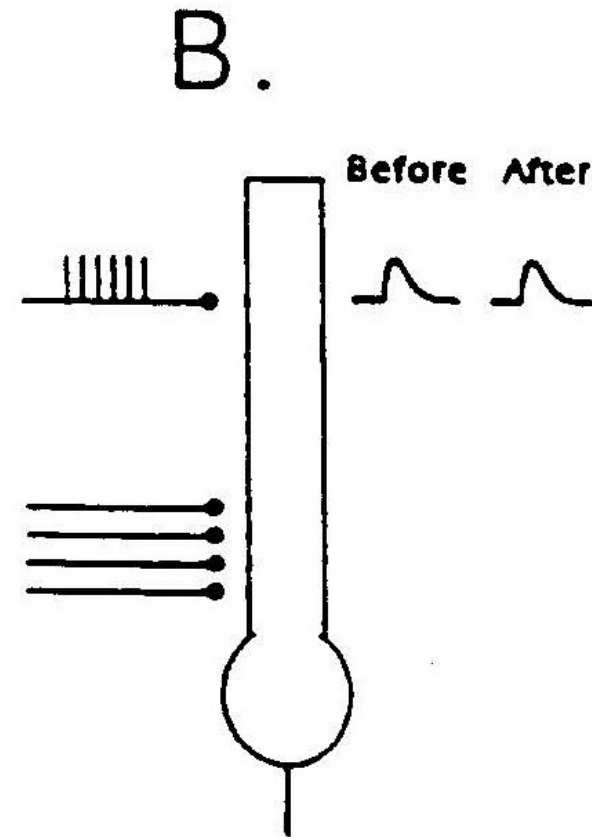 - Acts as a low pass filter: occasional spikes are transmitted without change, but high frequency spike trains are attenuated.

Properties of LTP

- Input specificity

    - Only active input pathways potentiate.

- Associativity

    - A strong stimulus on one pathway can enable LTP at another pathway receiving only a weak stimulus.

    - Baxter & Byrne called this "heterosynaptic" LTP

- Cooperativity

    - Simultaneous weak stimulation of many pathways can induce LTP.

- Rapid induction

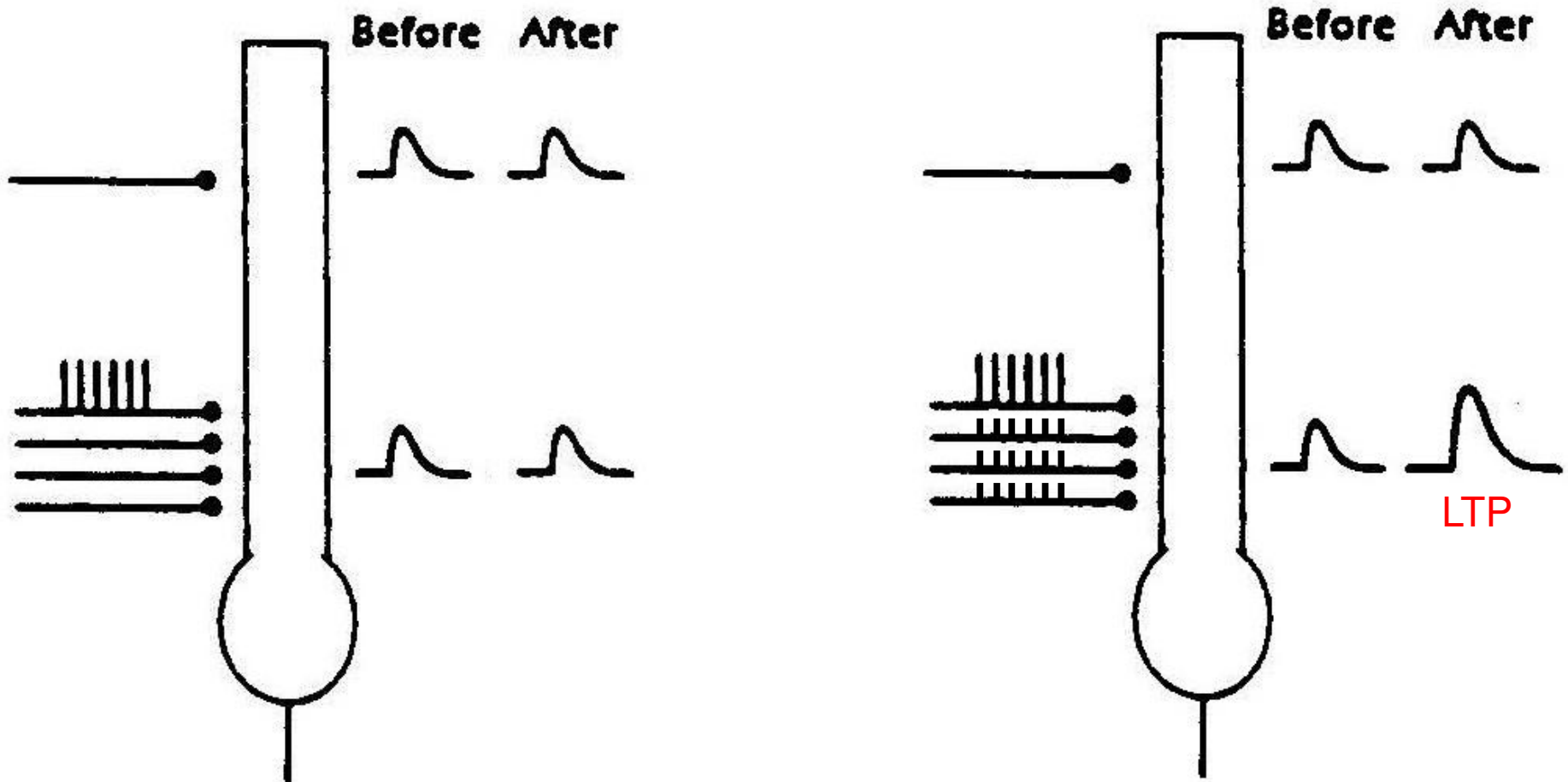   - Brief high-frequency stimuli can quickly potentiate a synapse.
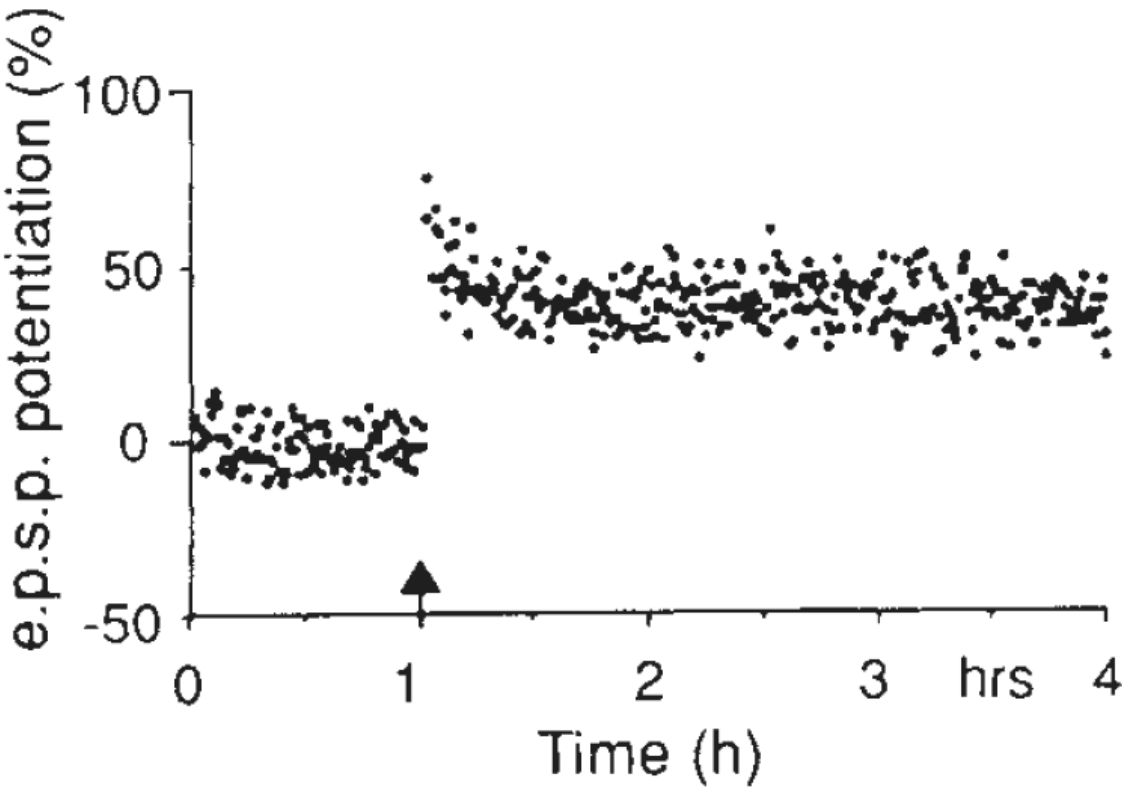
Input Specificity　　Threshold Effect

Associativity

Computational Models of Neural Systems

Cooperativity

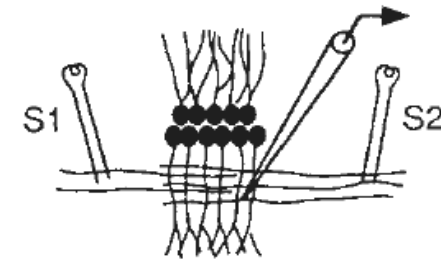Computational Models of Neural Systems
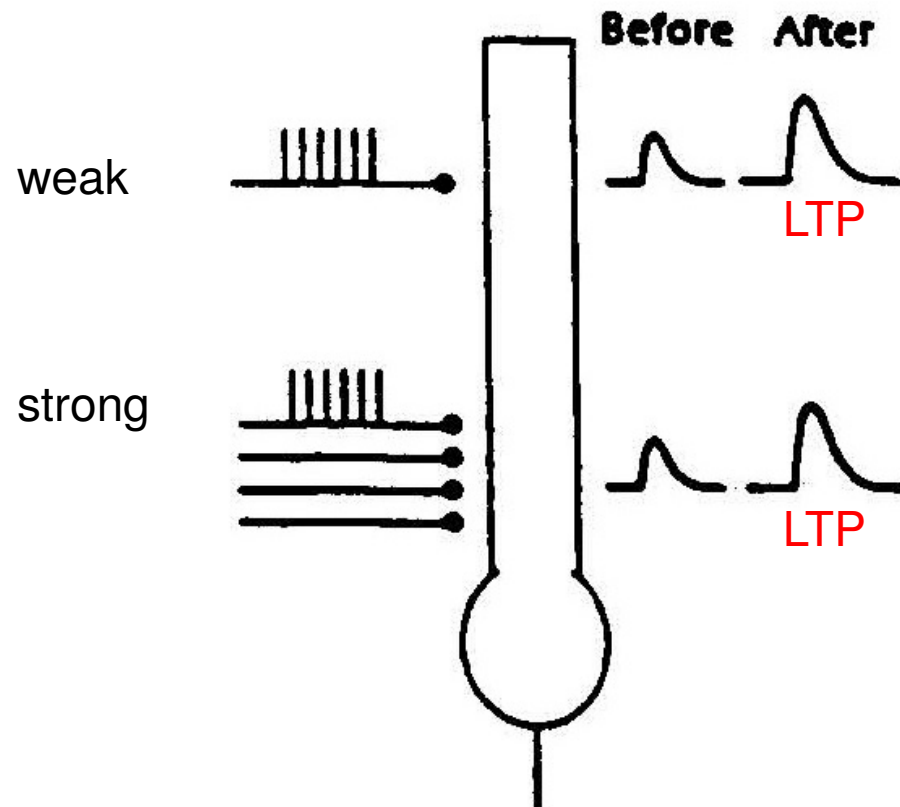
LTP in the Perforant Path of Hippocampus
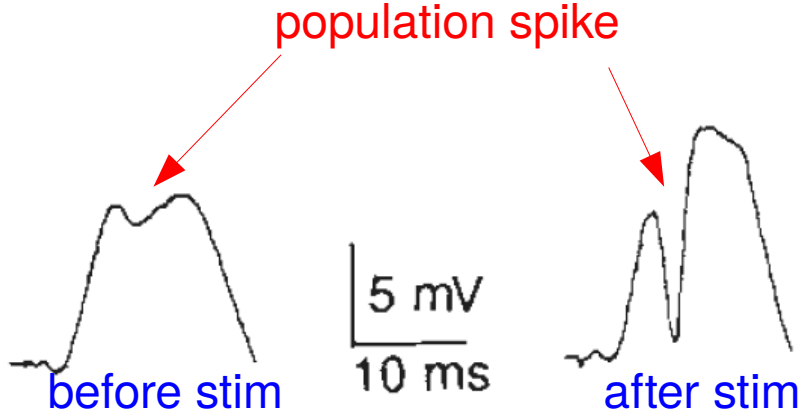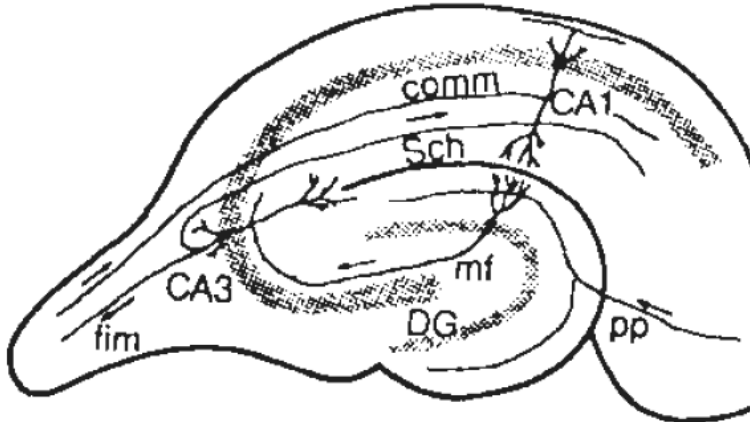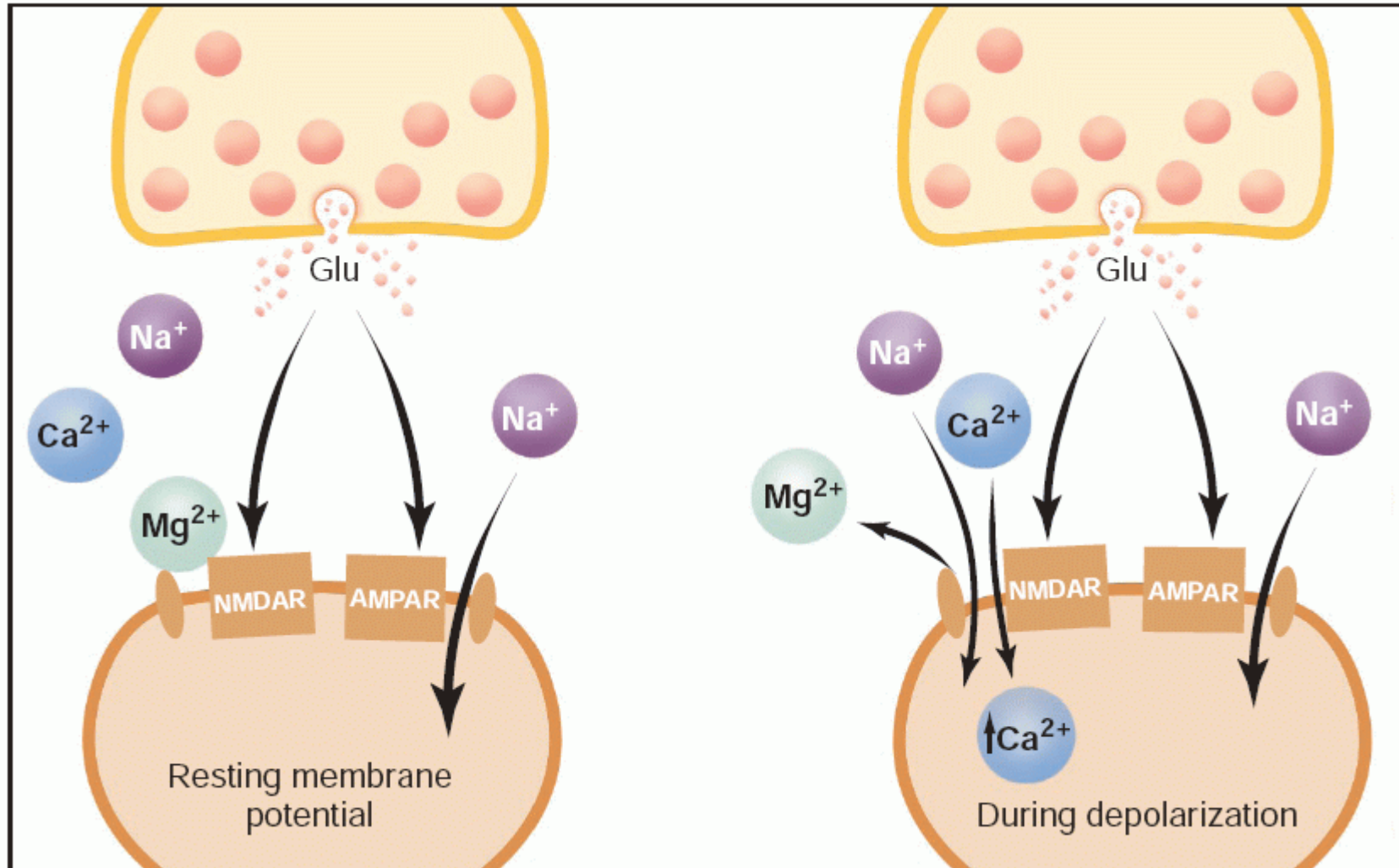
Specificity and Associativity

- Electrodes placed so that S1 activates fewer fibers than S2.

- Weak input S1 alone:
  - PTP, but no LTP

- Strong input S2 alone:
  - LTP only on strong pathway

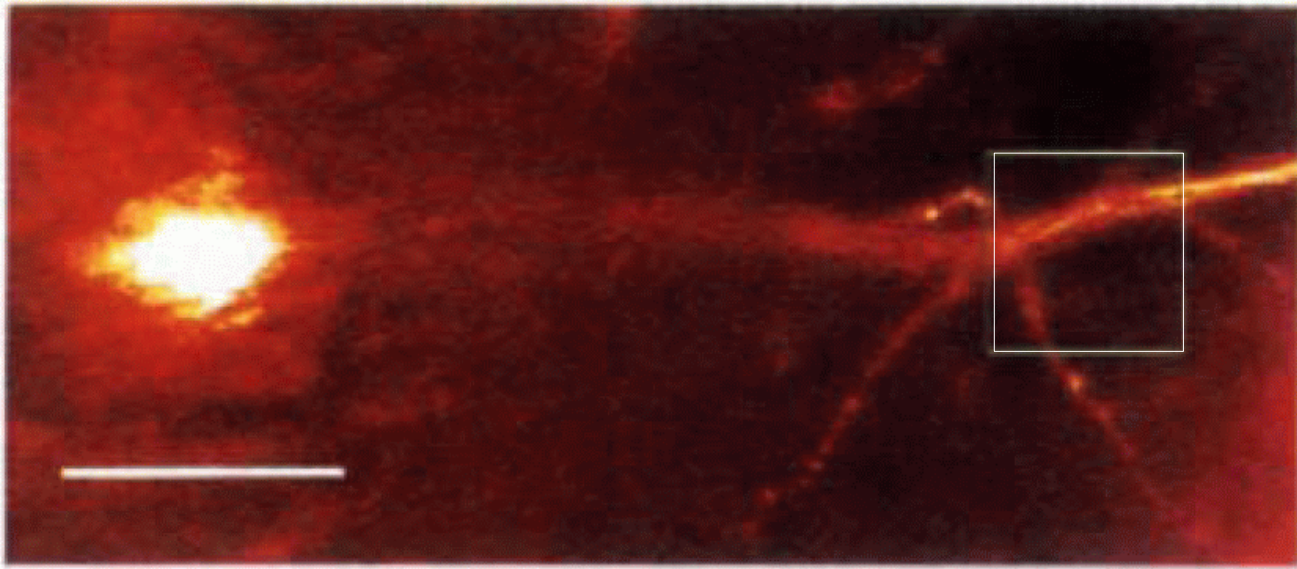- Weak + Strong together:
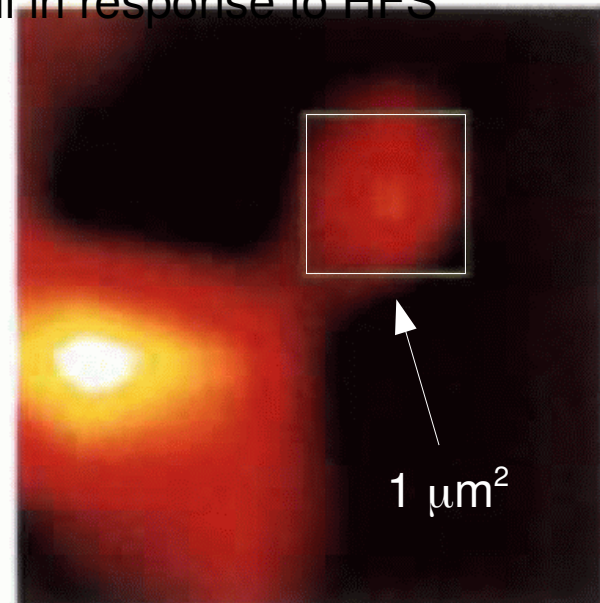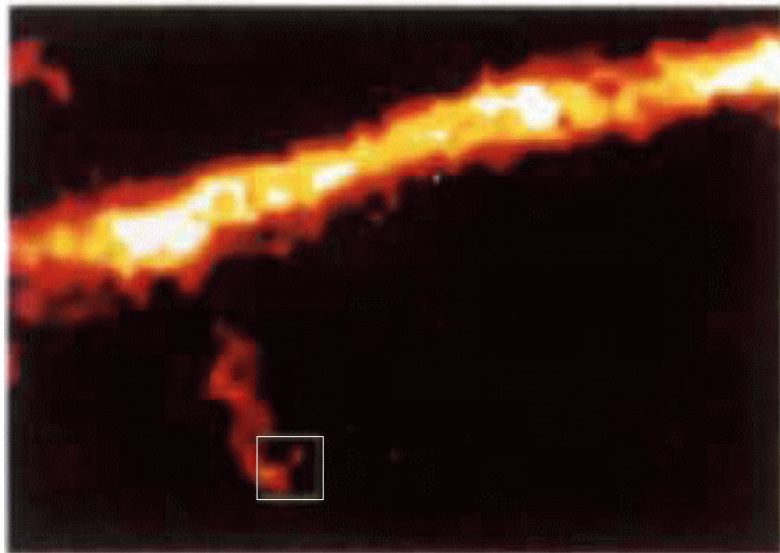 - LTP at both pathways
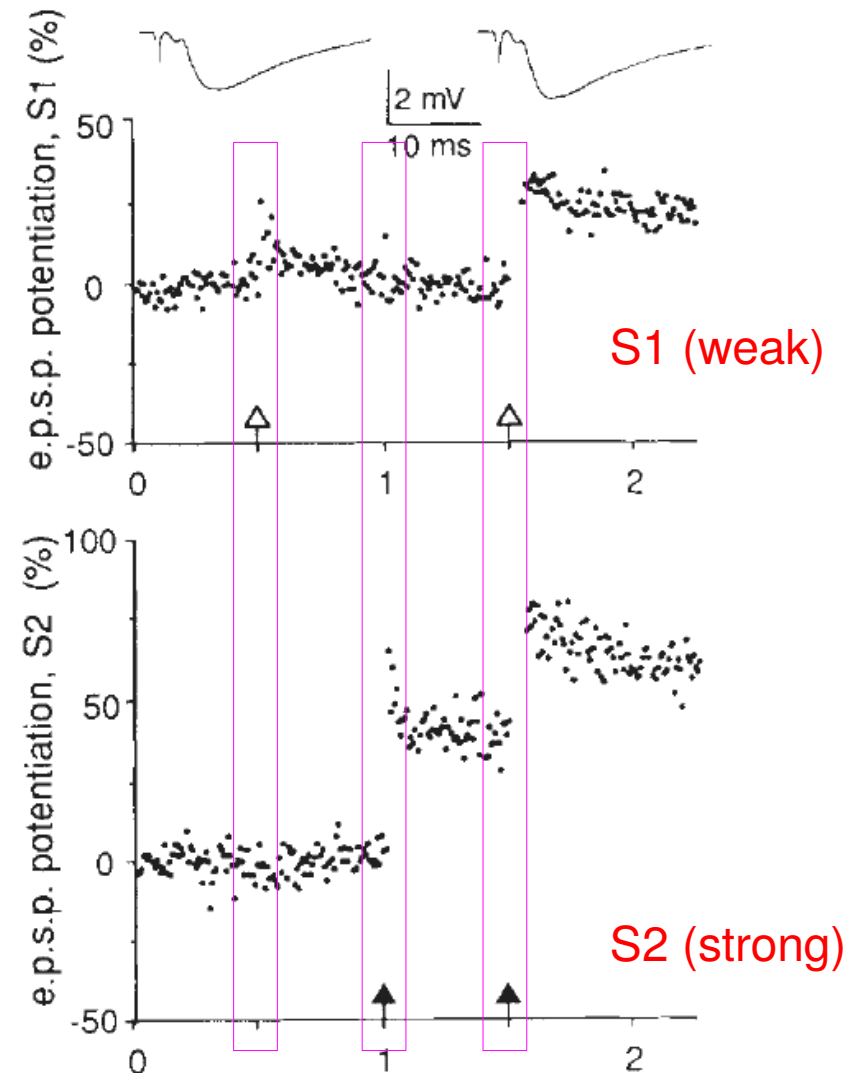
The NMDA Receptor
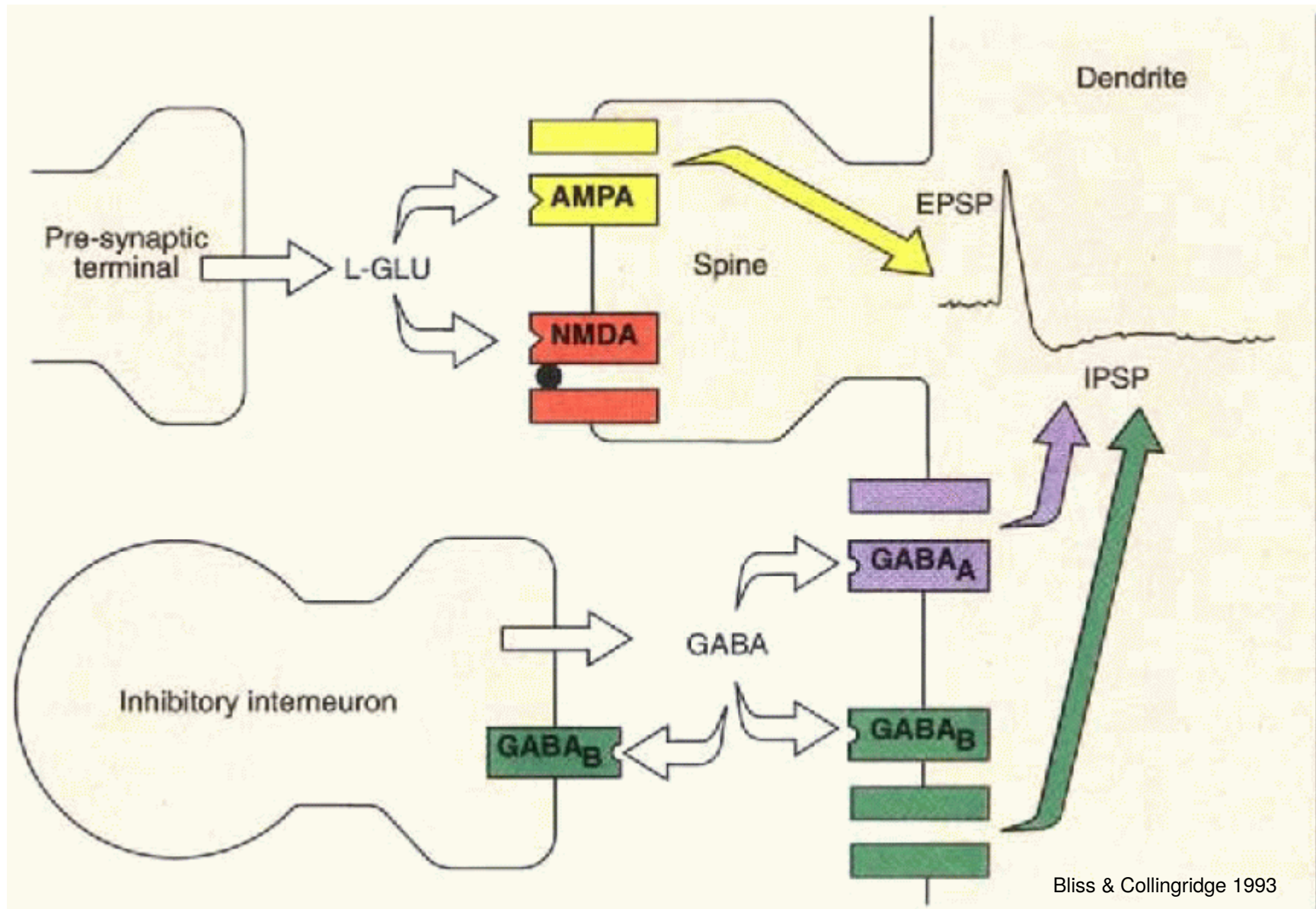

Magnesium block: very
little NMDA current

Malenka 1999

Fluorescence Imaging of Calcium in Dendritic Spine

Calcium influx in a CA1 pyramidal cell in response to HFS

1 μm^2

Response to Single Stimulus

Bliss & Collingridge 1993

Response to High Frequency Spike Train
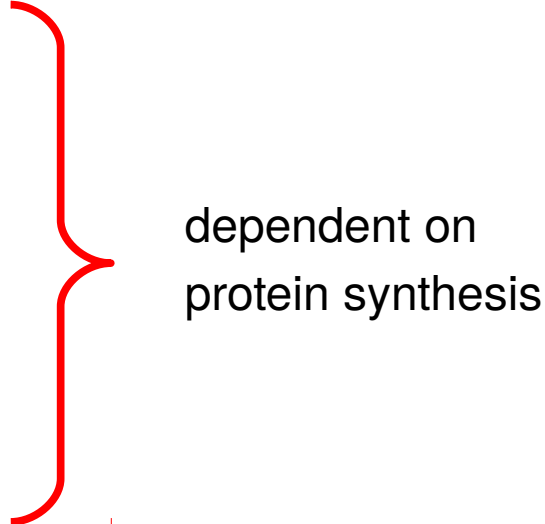

Bliss & Collingridge 1993
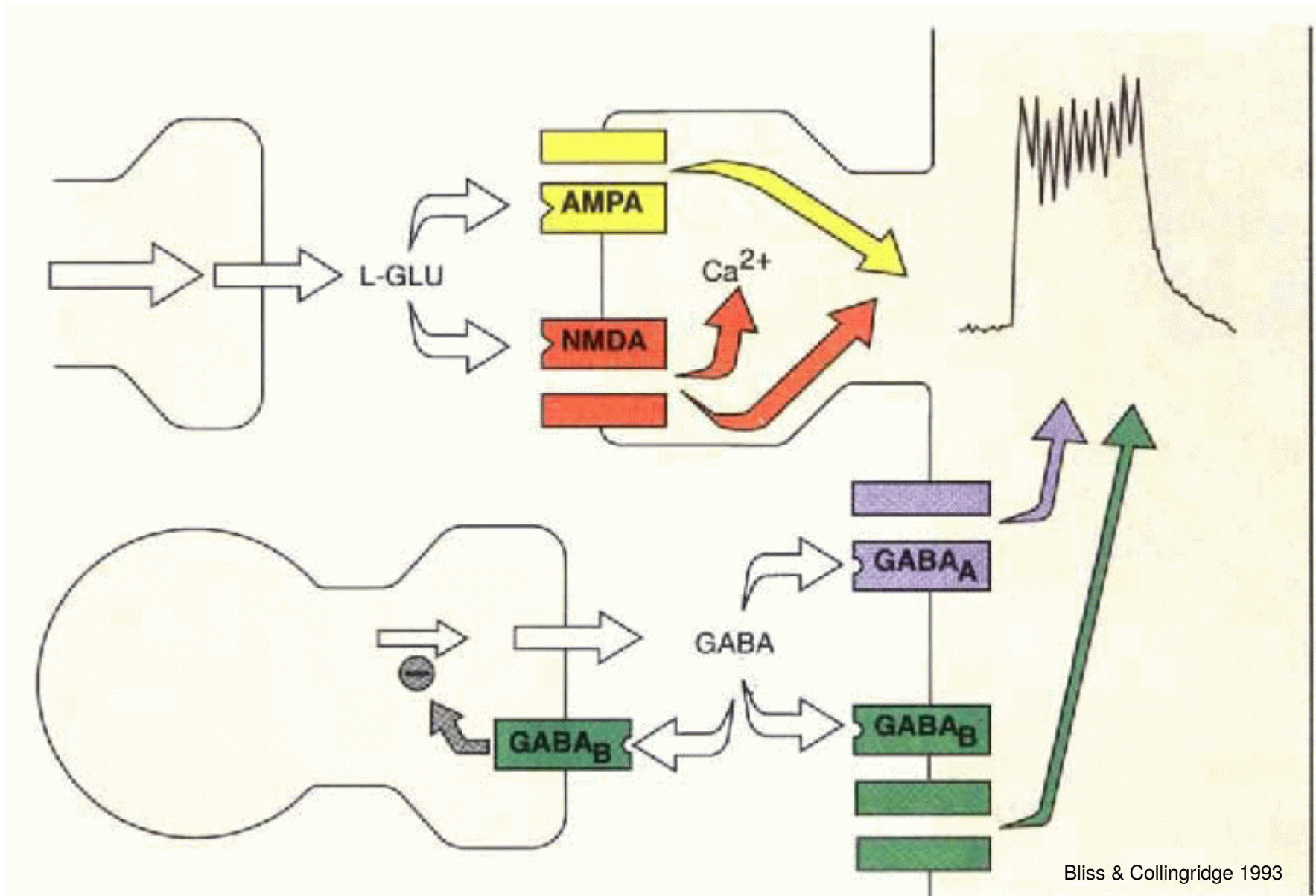
Evidence that NMDA Receptor Contributes to LTP

- Blocking NMDA receptors blocks LTP even though the cell is firing.

- Activation of NMDA receptors causes Ca^{2+} to accumulate in dendritic spines.

- Buffering Ca^{2+} using calcium chelators inhibits LTP.

- Adding Ca^{2+} directly to the cell enhances synaptic efficacy, mimicking LTP.

- But stability of LTP may depend on other mechanisms (mGluR; 2nd messenger).
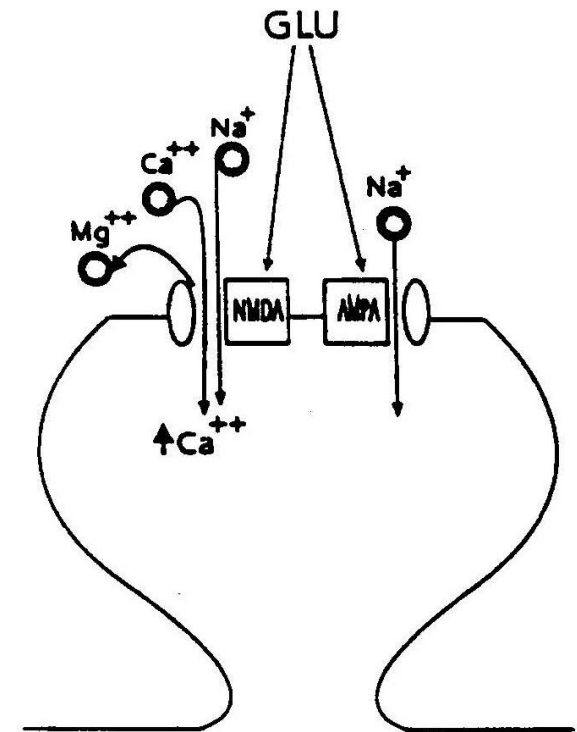
Phases of LTP

- Short Term Potentiation (STP): 10–60 minutes

- Early stage LTP (LTP1): 1–3 hours

  – blocked by kinase inhibitors but not protein synthesis inhibitors

- Late stage LTP2: several days

  – blocked by translational inhibitors but independent of gene expression

- Late stage LTP3: several weeks

  – involves expression of Immediate Early Genes (IEGs)

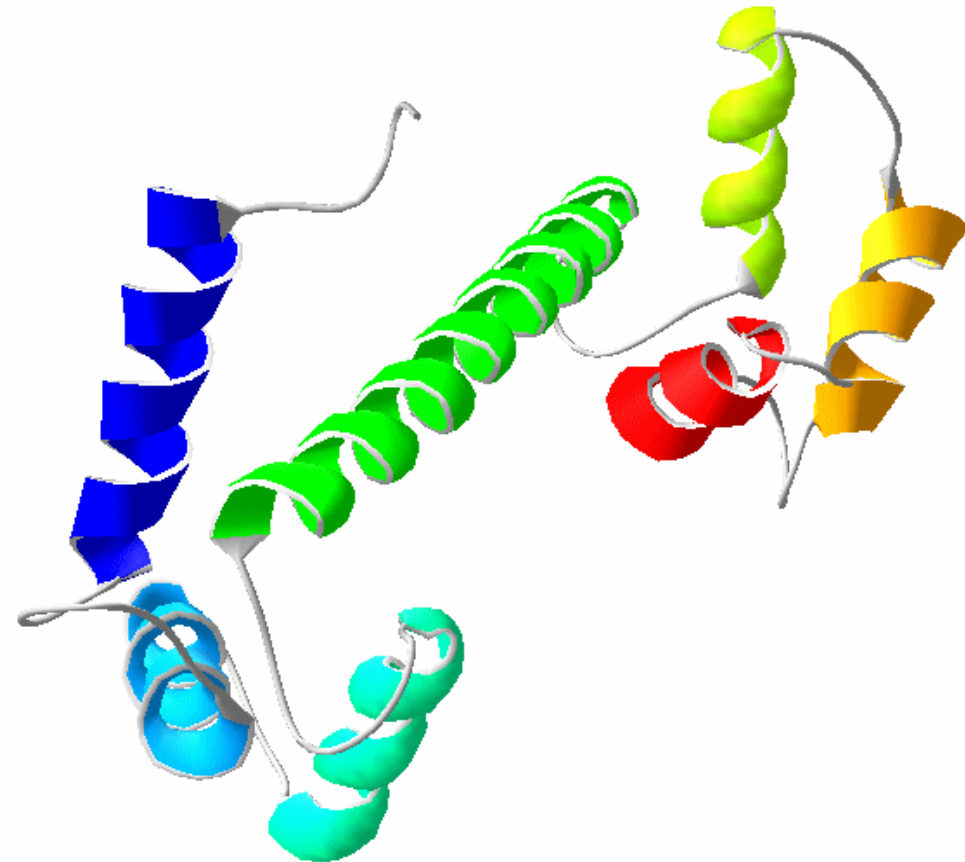dependent on protein synthesis

Early Phase LTP
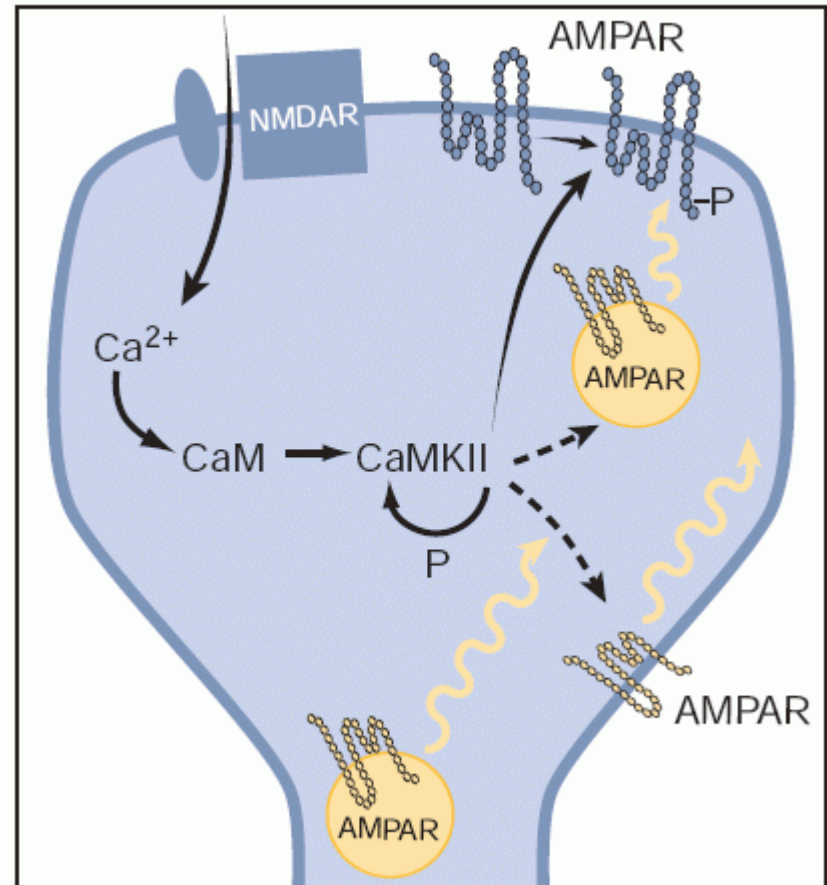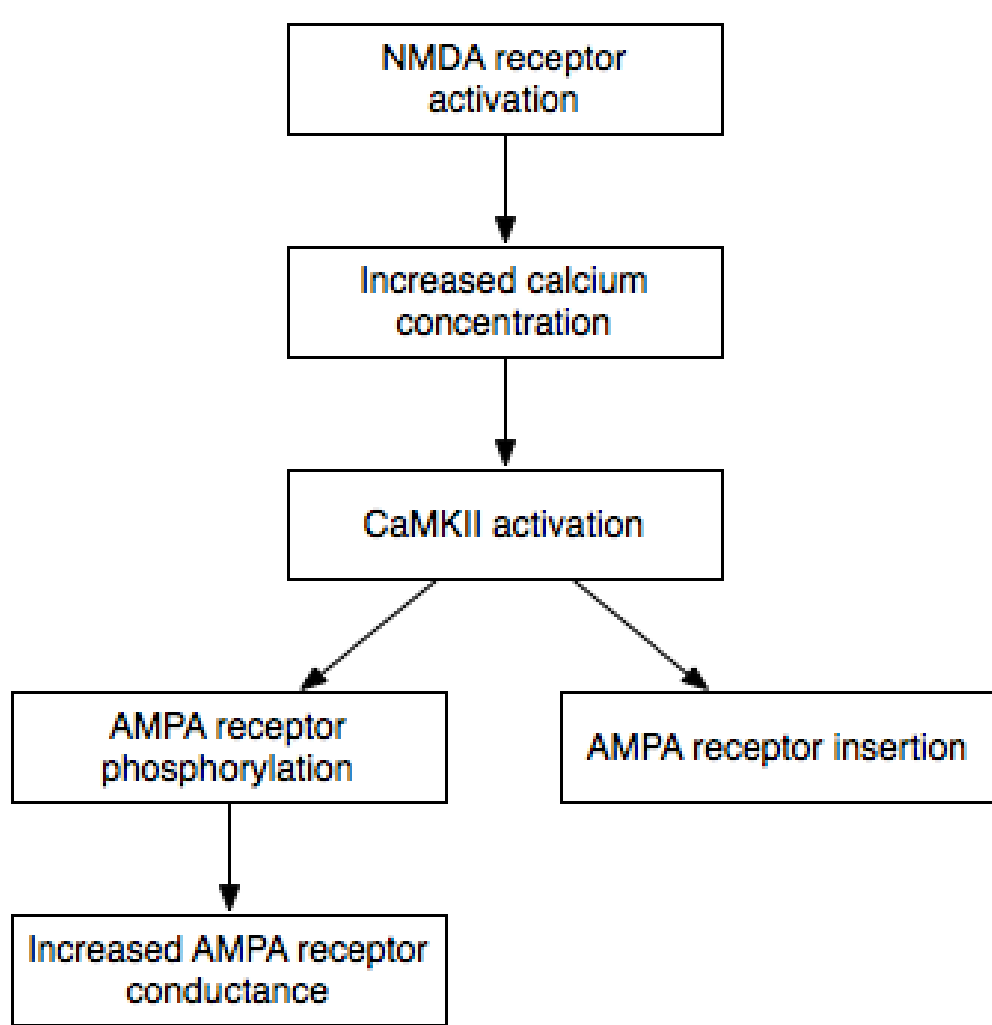
AMPA Receptor trafficking
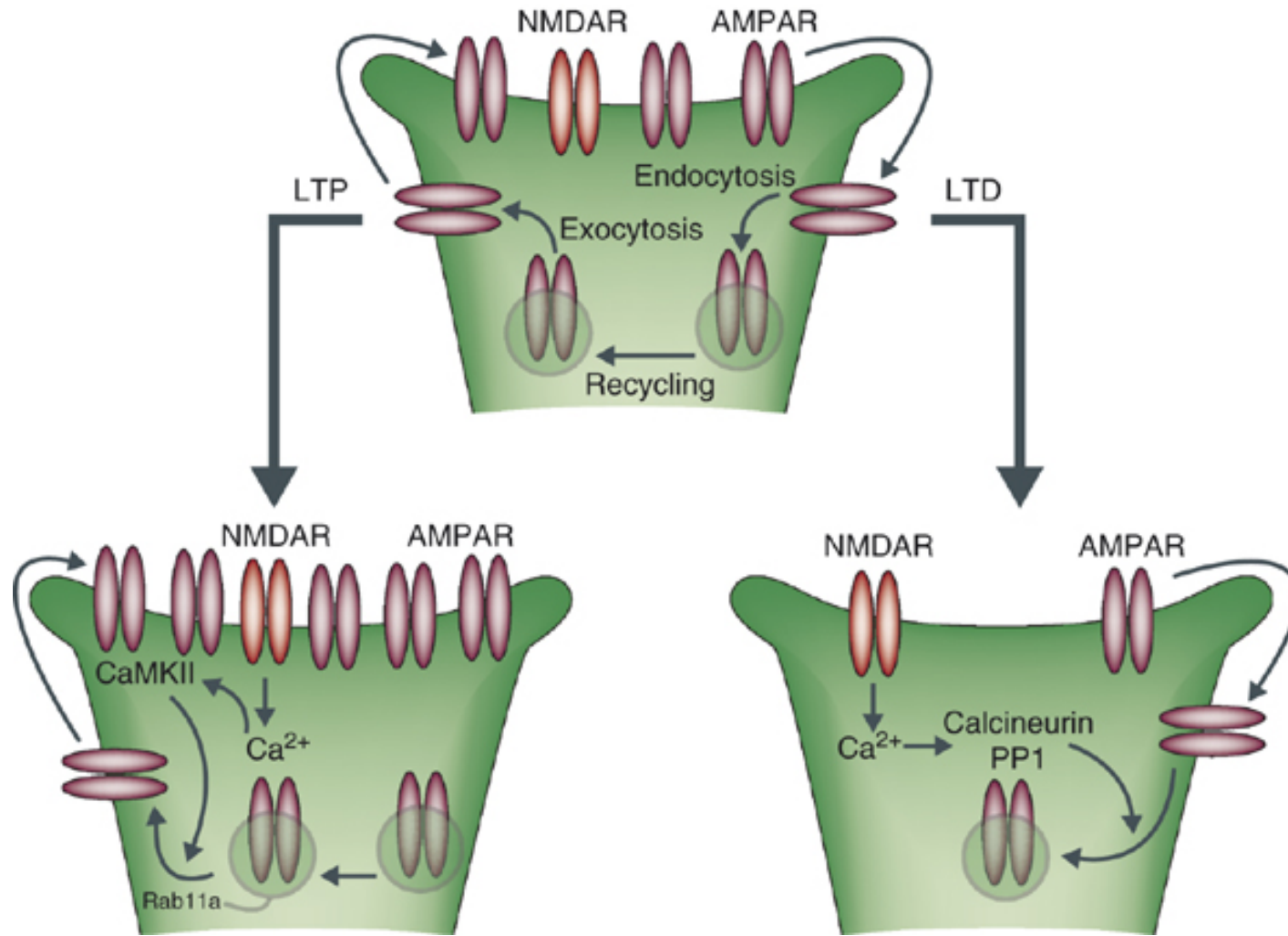
Citria & Malenka (2008)

Calmodulin

- Calcium-binding protein involved in many metabolic processes

- Small: approx. 148 amino acids

- Can bind up to 4 calcium atoms

- Ca^{2+} could come from NMDA current or release from internal stores

- The Ca^{2+}/calmodulin complex activates CamKII

CaMKII

- Calcium/calmodulin-dependent protein kinase II: 2 rings of 6 subunits; accounts for 1-2% of protein in the brain

- Activated by binding Ca^{2+}/calmodulin complex.

- Must be phosphorylated to induce LTP.

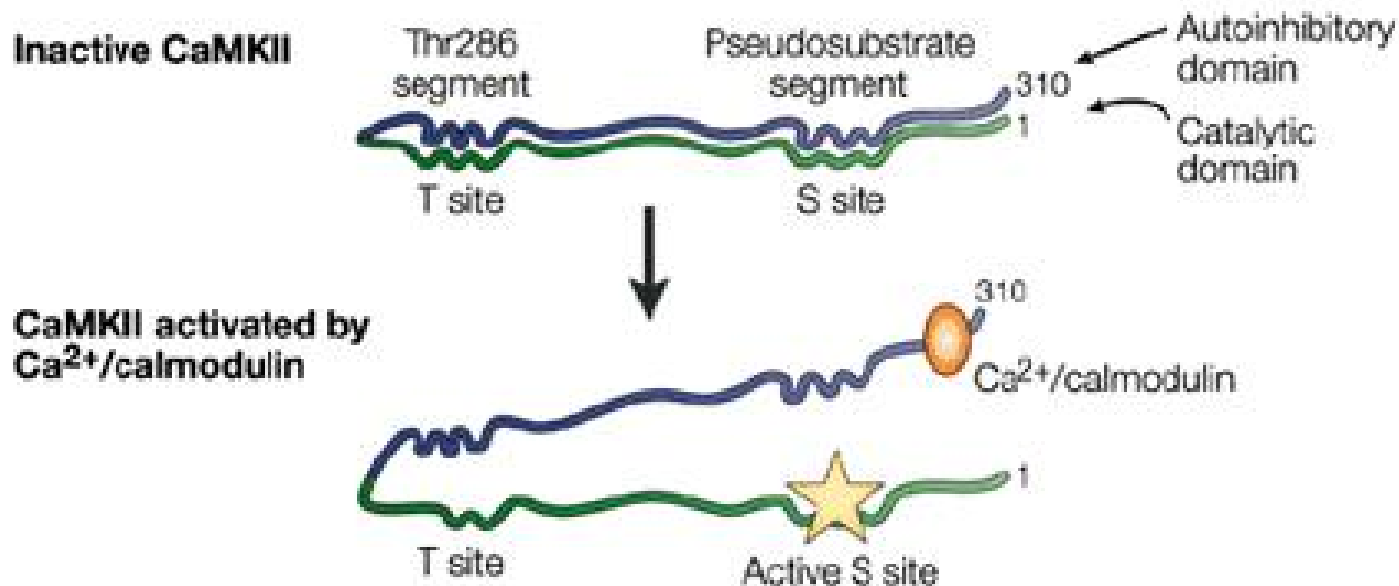- Acts on AMPA receptors & many other things.

Inactive CaMKII

Thr286 segment — T site

Pseudosubstrate segment — S site

Autoinhibitory domain

Catalytic domain

310
1

CaMKII activated by Ca^{2+}/calmodulin
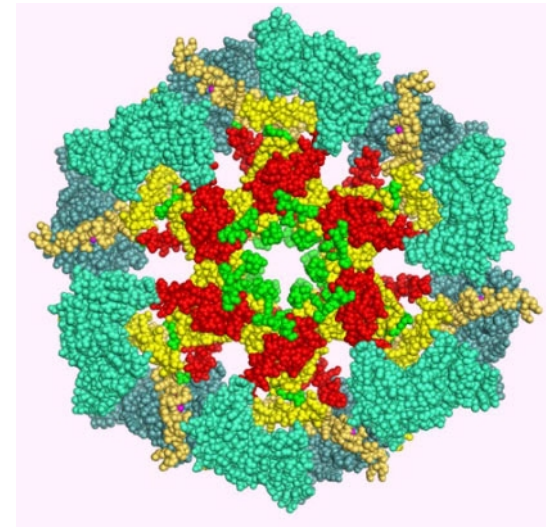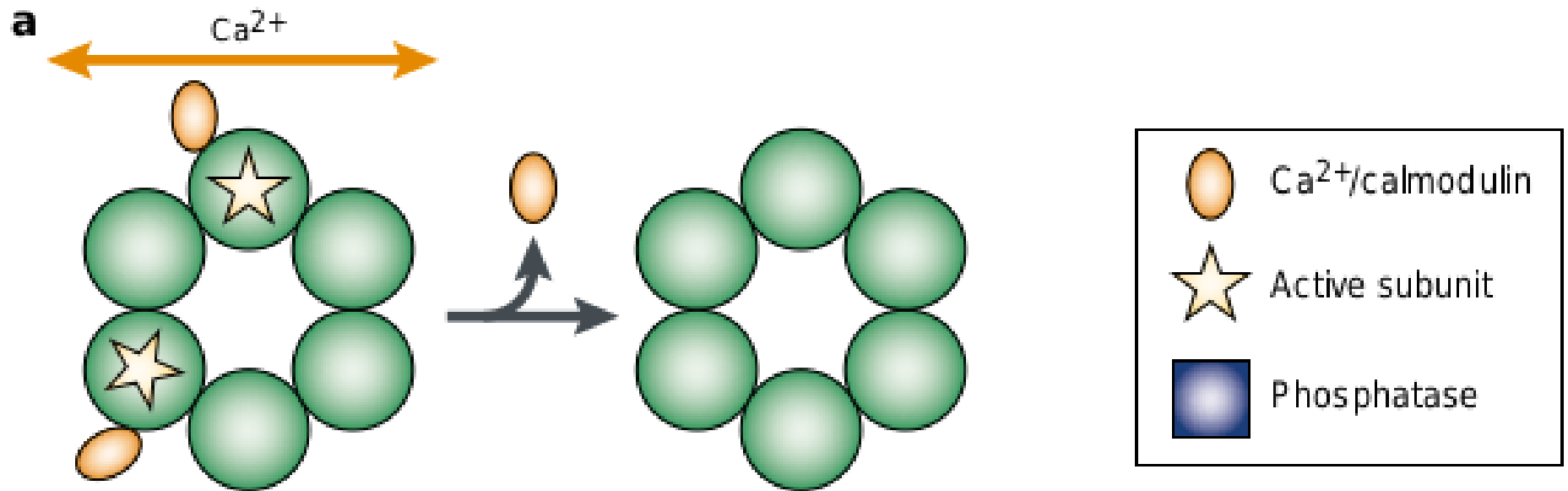
T site

310 — Ca^{2+}/calmodulin

1

Active S site

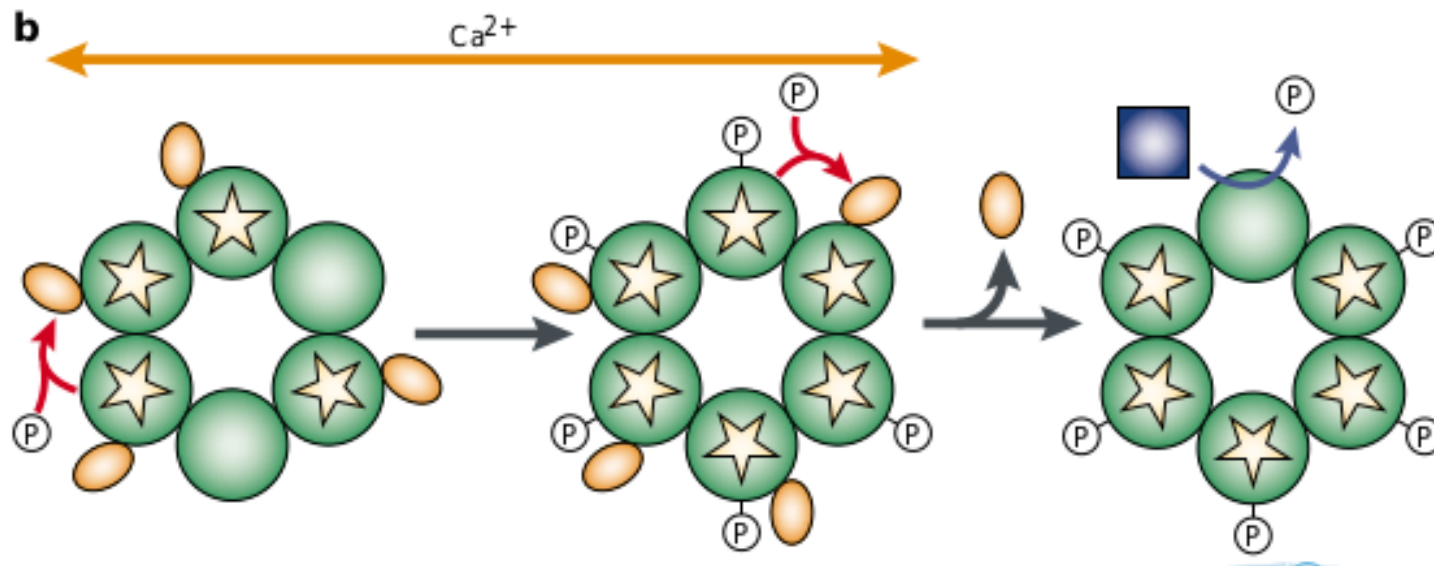Figure 2. Regulation of CaMKII. John Lisman et al. Nature 2002; 3: 179-190
At basal Calcium ion concentrations, the kinase will be blocked, because the autoinhibitory domain stays bound to the catalytic domain. Ca^{2+}/Calmodulin binding will activate the kinase [2].

CaMKII Activation by Calmodulin

Short-Term CaMKII Auto-Phosphorylation

- If intracellular concentration of Ca^{2+} is higher and Ca^{2+}/calmodulin binds to two adjacent subunits, one can phosphorylate the other. Lasts several minutes.

Long-Term CaMKII Auto-Phosphorylation Can Persist Independent of Calcium If Auto-Phosphorylation Rate is High Enough
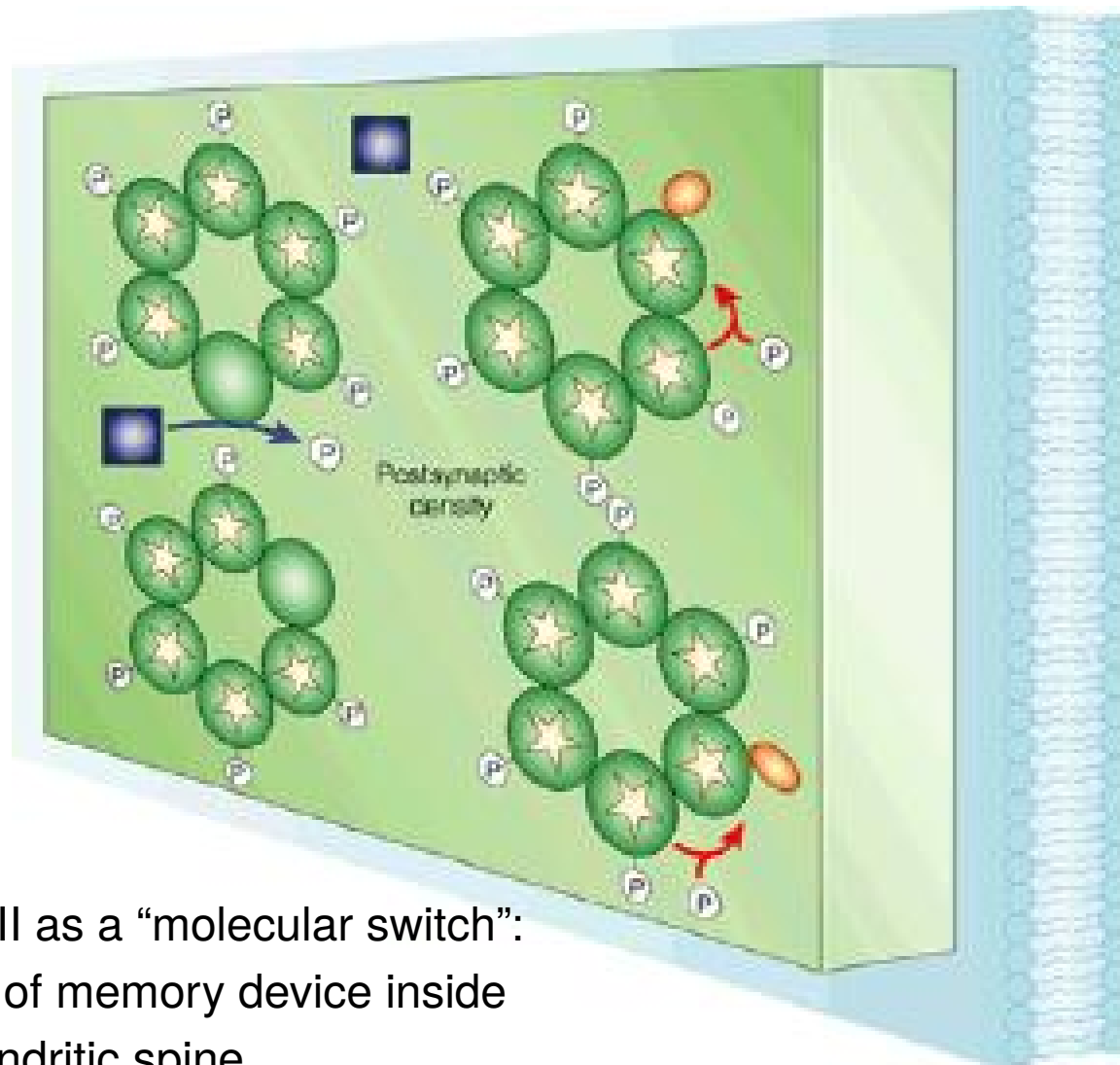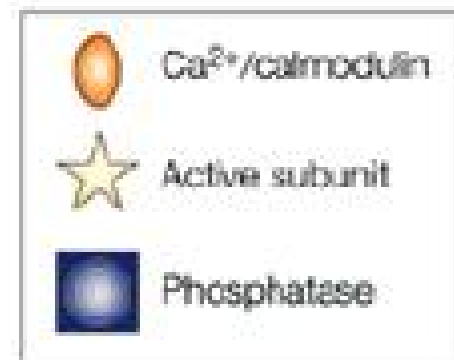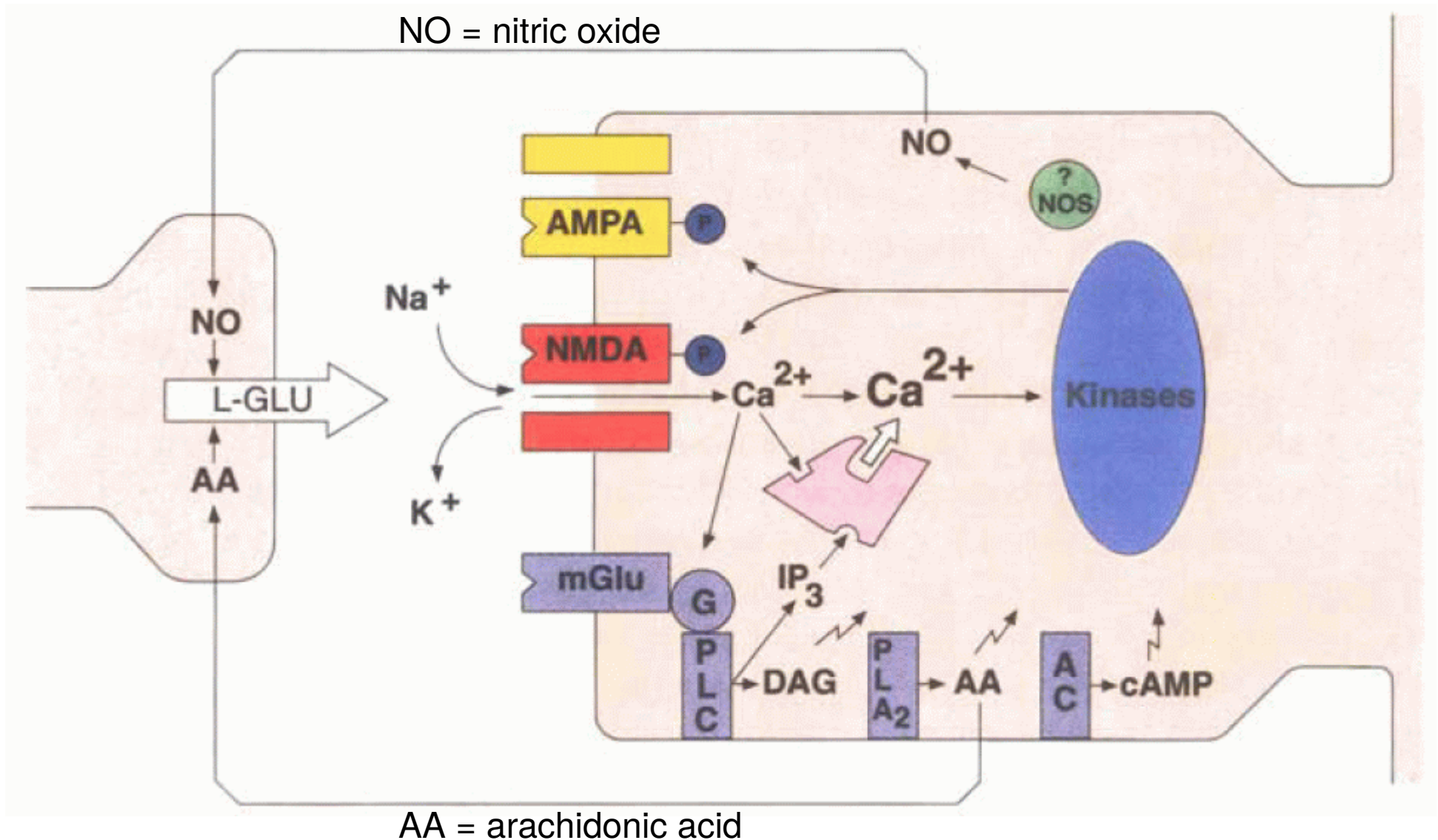

Figure 4. Long-term persistent Autophosphorylation of CaMKII. John Lisman et al. Nature 2002; 3: 179-190 The autophosphorylation rate exceeds the rate of dephosphorylation [2].
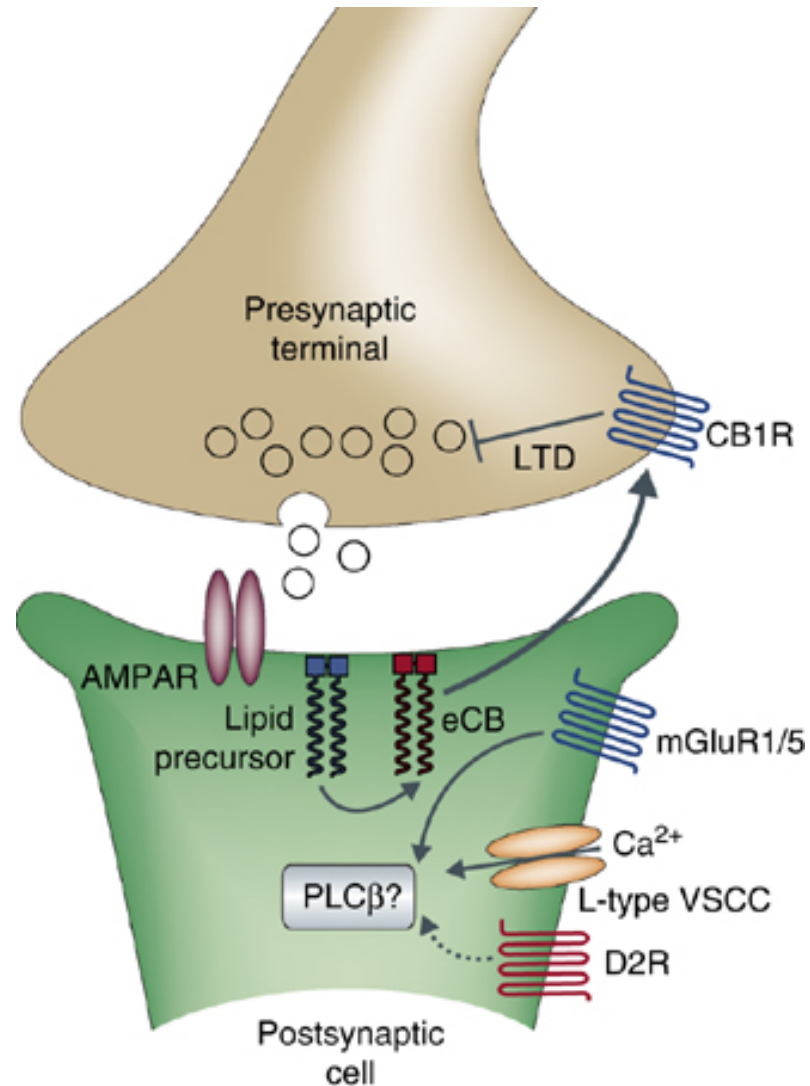
CaMKII as a "molecular switch": a kind of memory device inside the dendritic spine.

Retrograde Messengers as a Pre-Synaptic Mechanism for LTP

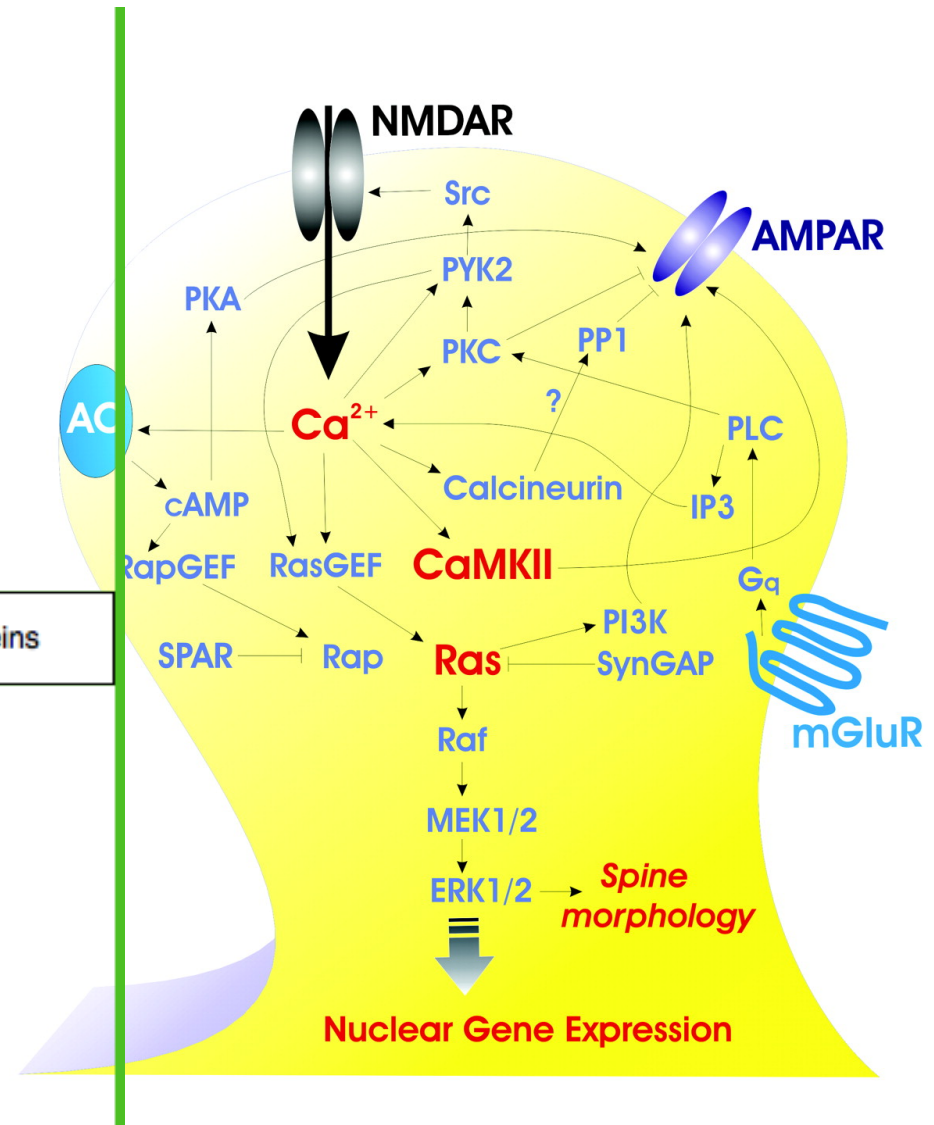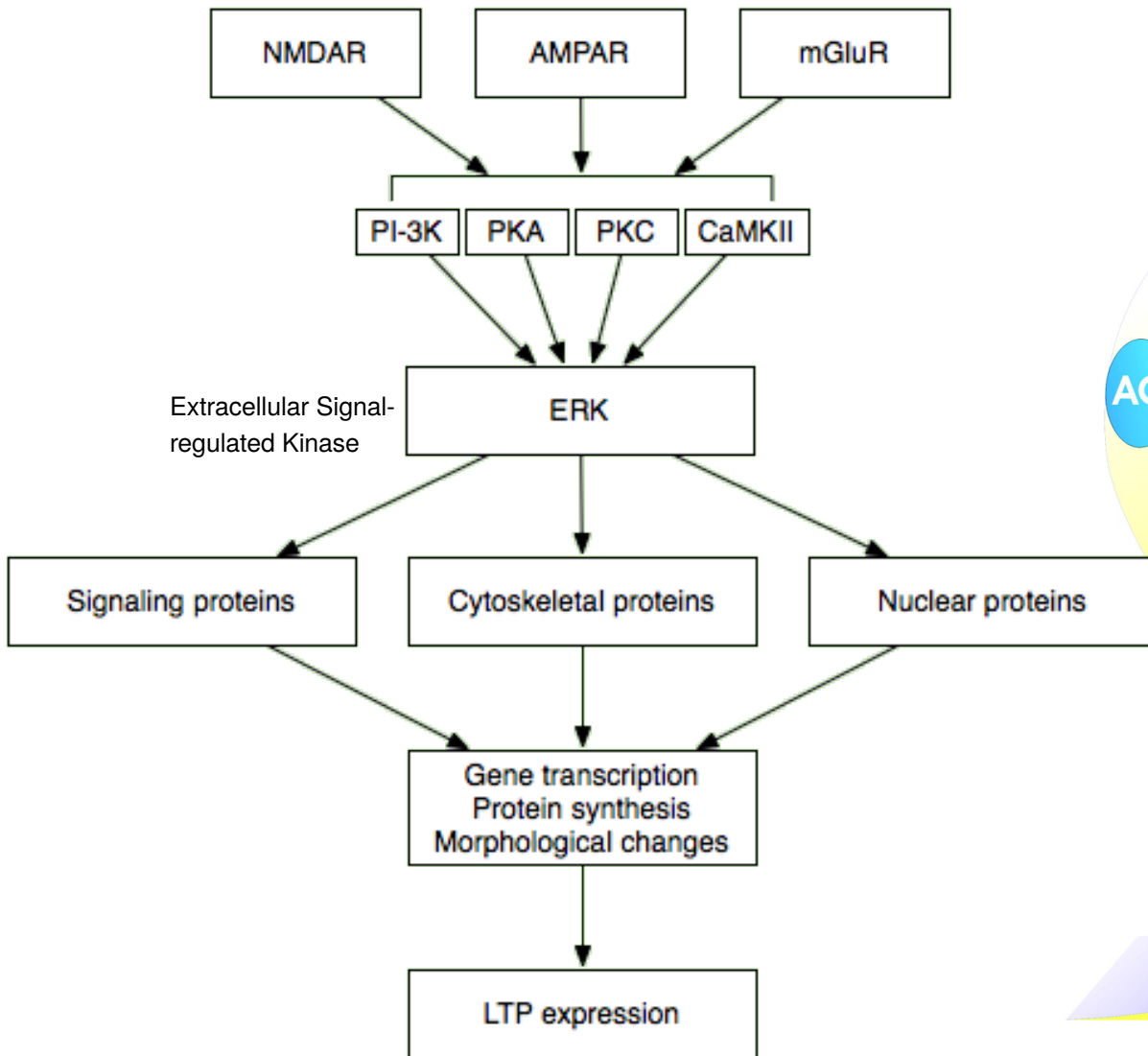NO = nitric oxide

AA = arachidonic acid

Retrograde Transmission of Endocannabinoids

LTD of excitatory synapses onto medium spiny cells in striatum resulting from retrograde transmission of an endocannabinoid signal.
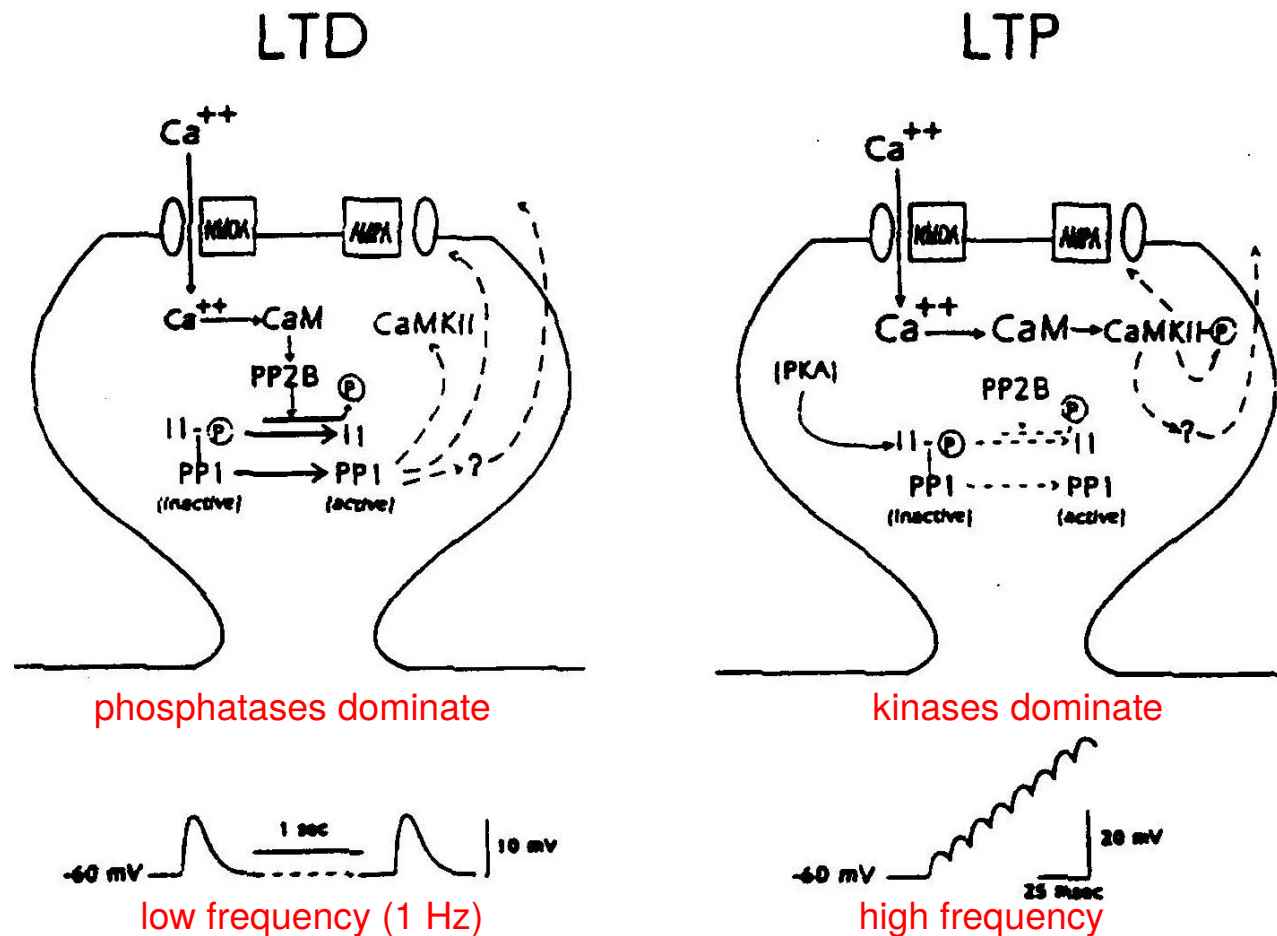
Late Phase LTP

LTP and LTD

- Most synapses that exhibit LTP also show LTD.

- Hypothesis: the balance between phosphatases and kinases determines potentiation vs. depression.

LTD — phosphatases dominate — low frequency (1 Hz)

LTP — kinases dominate — high frequency

# Ocular Dominance Formation in Area 17 (V1)

- Most neurons in area 17 show some ocular dominance (OD)

- Critical period for OD formation in kittens: up to 3 months

- OD column formation depends on activity of visual receptors

    - Demonstrated through ocular deprivation experiments

- Also depends on postsynaptic activity; NMDA-dependent
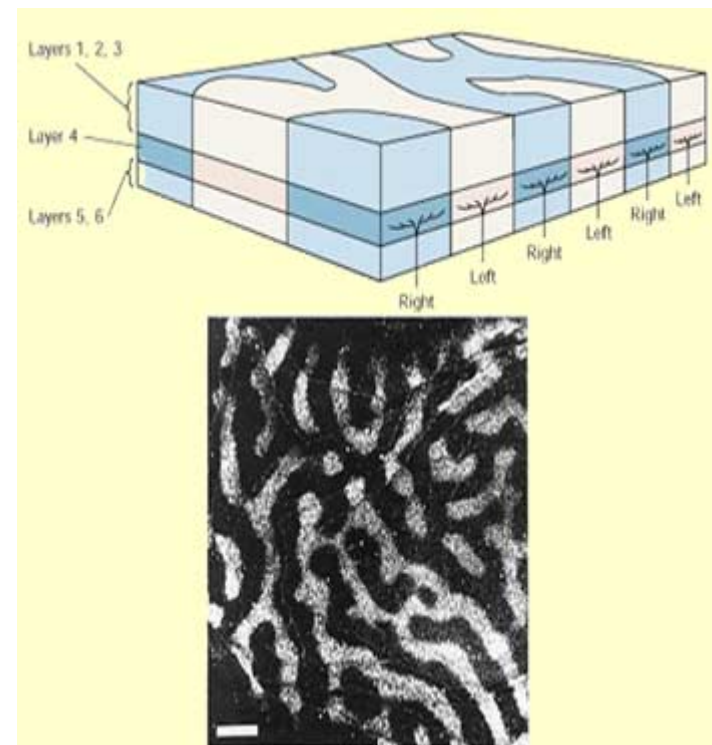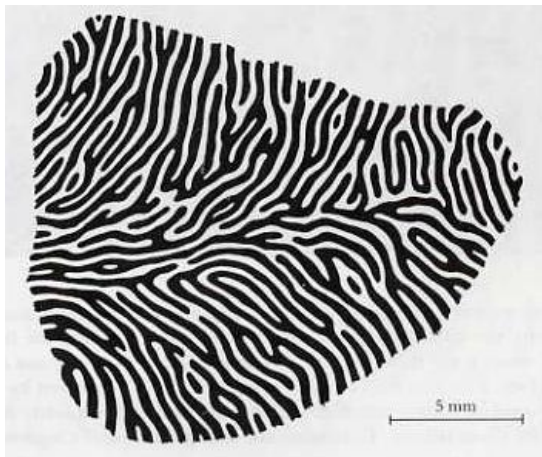
# BCM Rule and Ocular Dominance in Area 17 (V1)

- Monocular deprivation experiments:

    - Brief period of MD shifts dominance to the open eye

    - OD changes take only a few hours to start

    - Deprived eye responses can be restored withing minutes by bicucculine (GABA blocker)
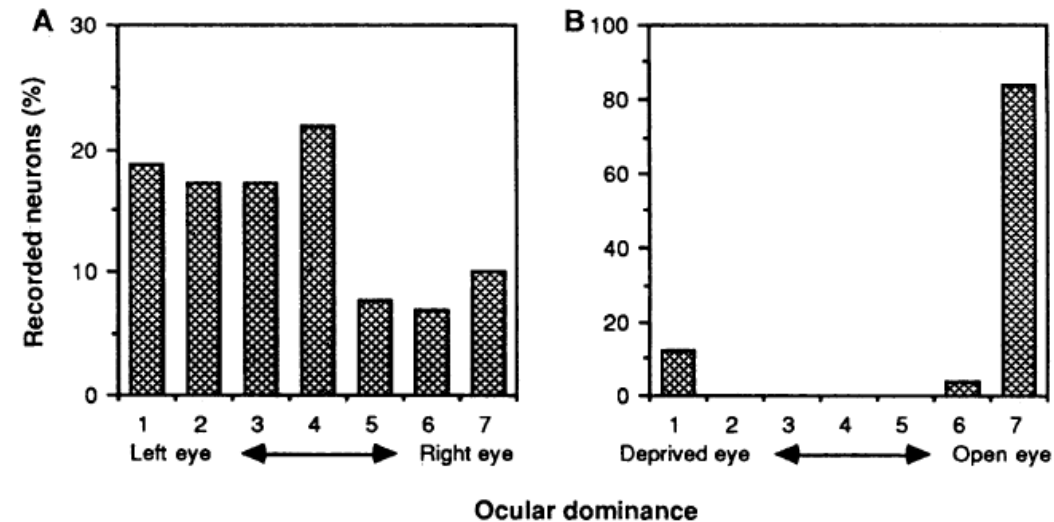
- Binocular deprivation (BD) does <u>not</u> decrease synaptic efficacy in 2 month old kittens.

# Bear et al. Model of Synaptic Plasticity in Area 17
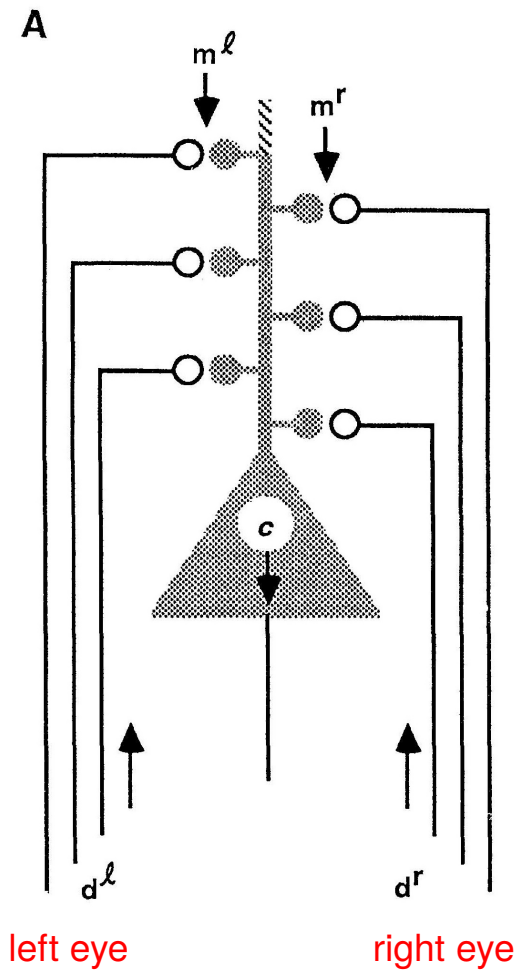
$$c = m^l \cdot d^l + m^r \cdot d^r$$

c = cortical cell activity
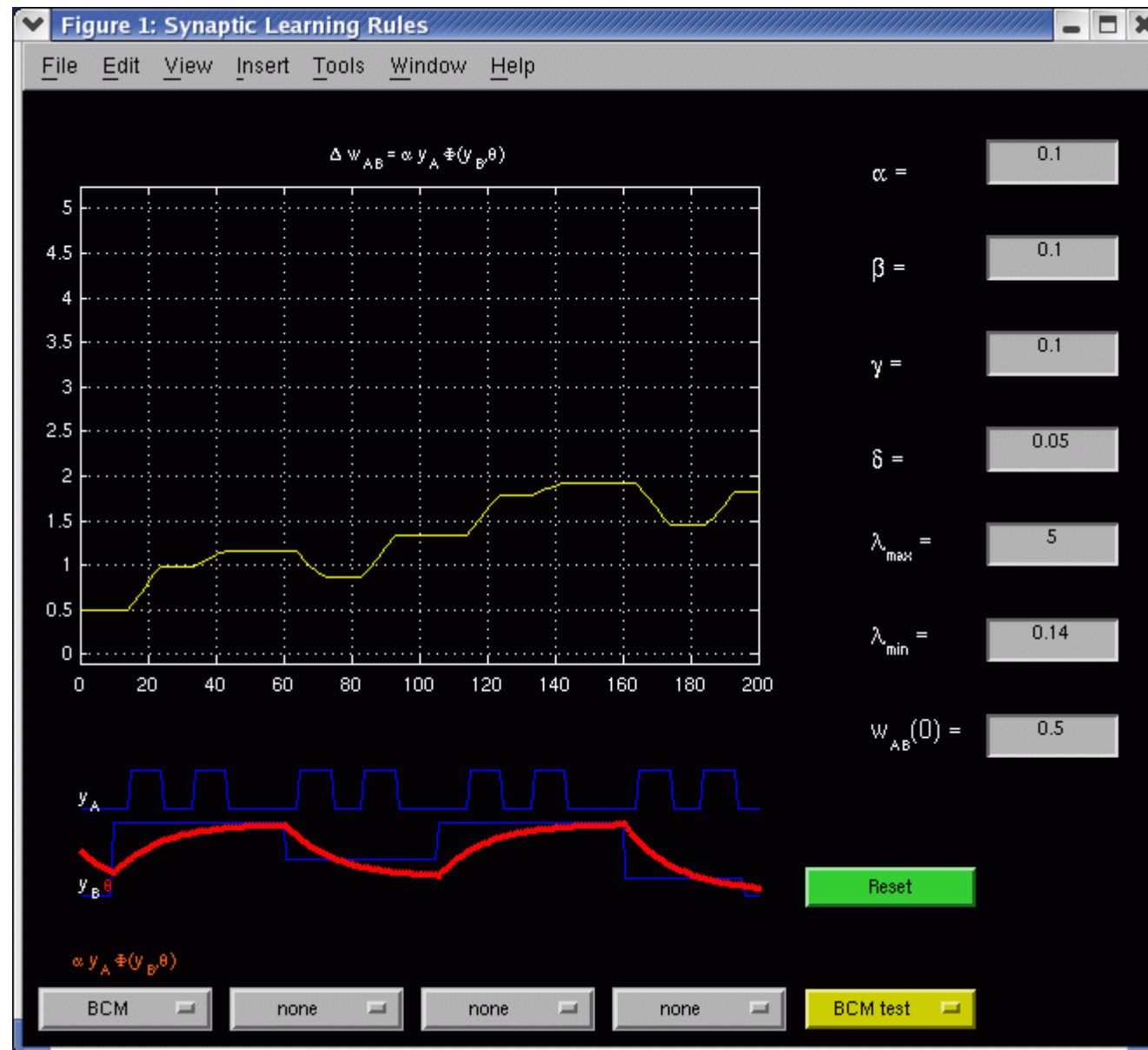m = synaptic weights
d = presynaptic activty

$$\frac{dm}{dt} = \Phi(c, \bar{c})$$
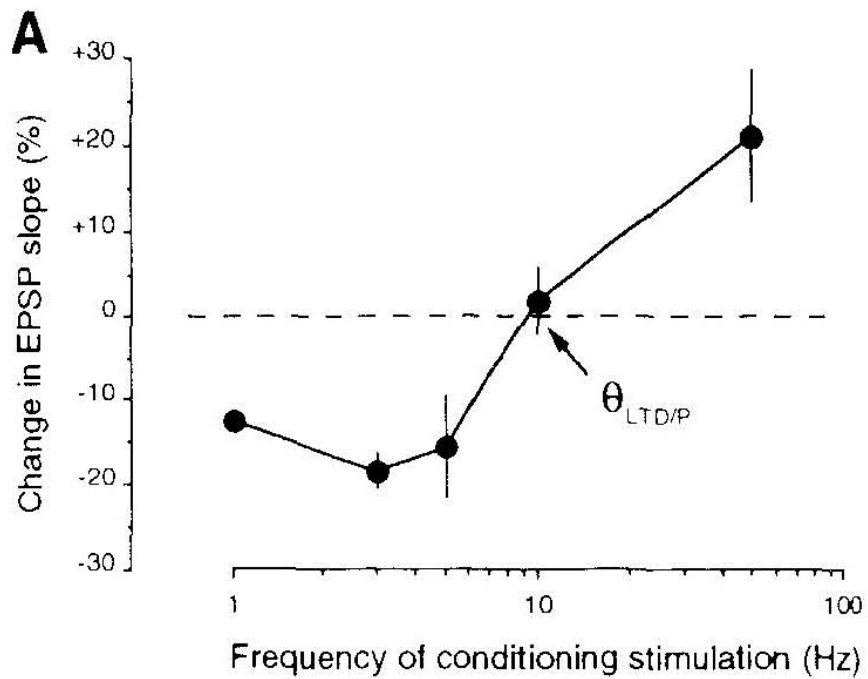
Sliding Threshold

- When closed eye reopened, OD distribution quickly restored.

- Hypothesis: sliding threshold for synaptic modification.

- $\theta_M = \langle c^2 \rangle$

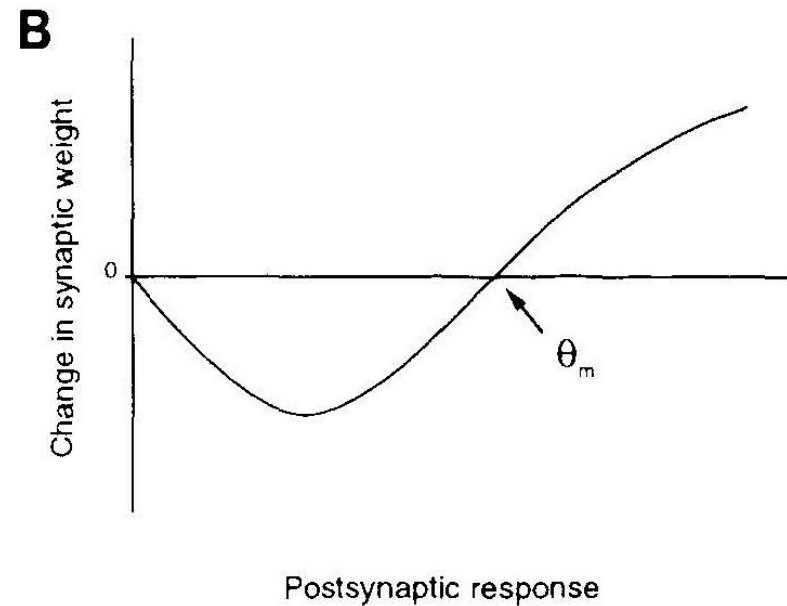- Sign of weight change depends on level of postsynaptic activity.

BCM Rule

Computational Models of Neural Systems
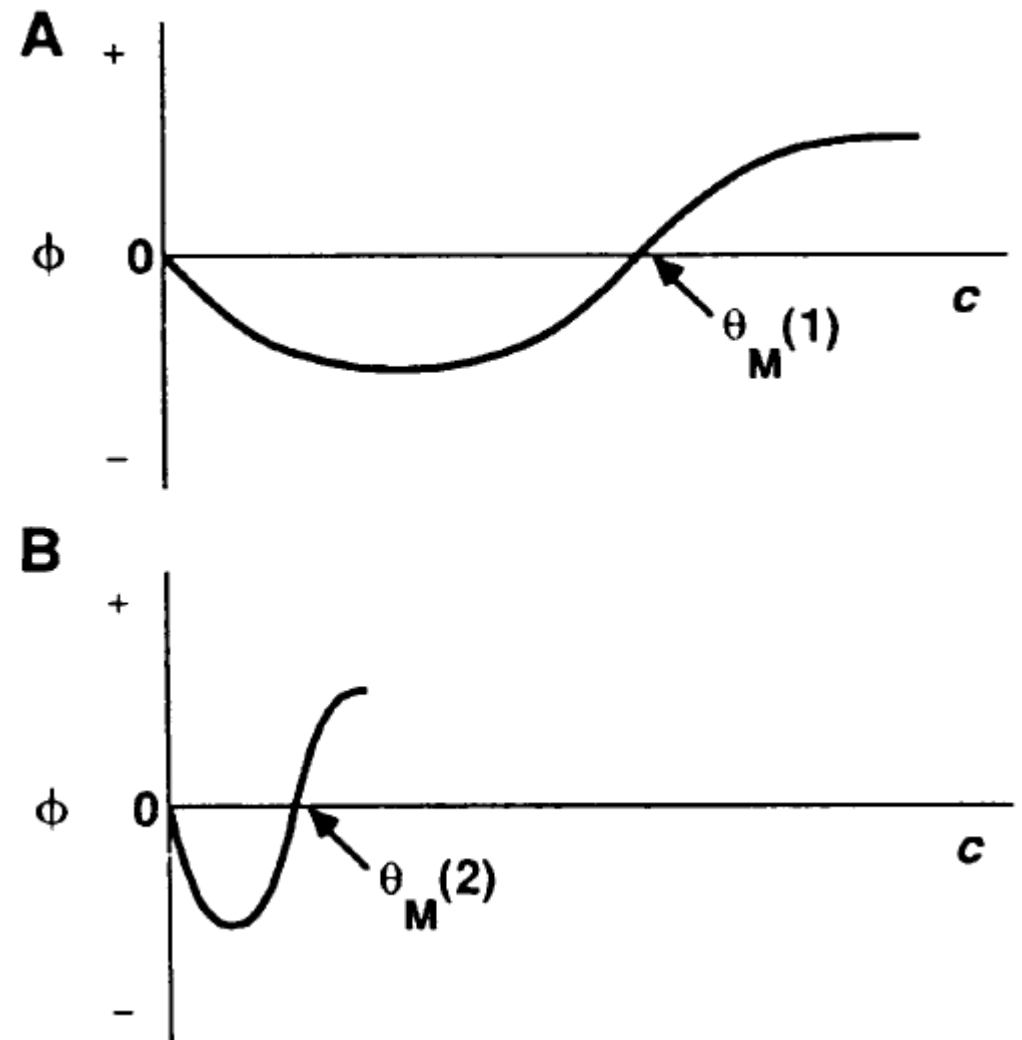
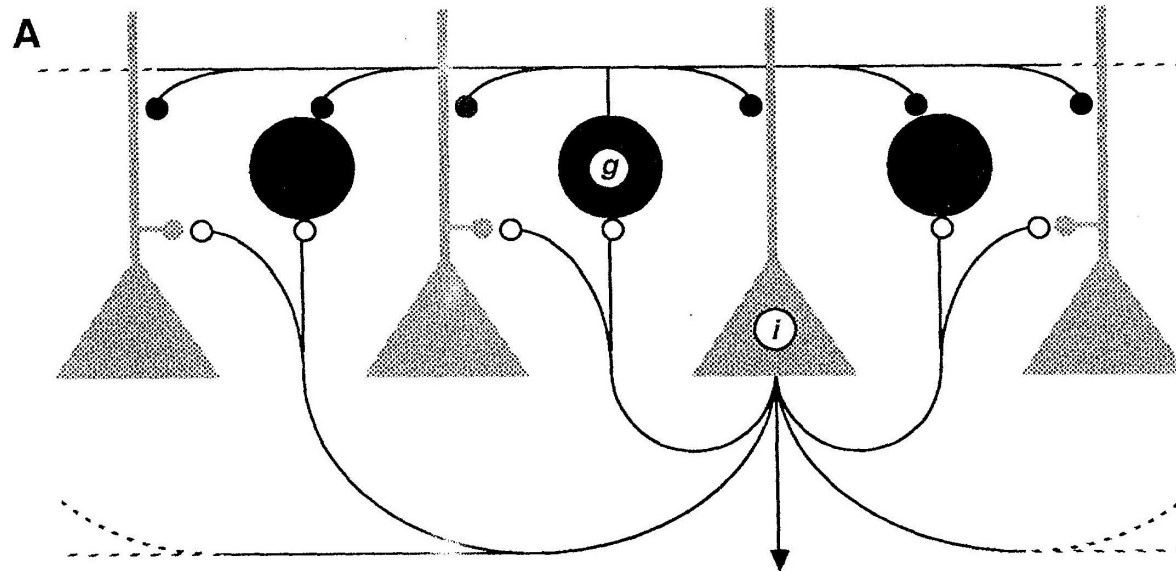# BCM Rule Can Cause Increase or Decrease

900 pulses delivered
at the frequencies shown

Need for Inhibitory Inputs

- Absence of presynaptic activity from deprived eye would cause weights to go to 0; how could they ever grow again?

- Solution: inhibition from interneurons makes it appear that the weights are zero, but in reality they're just small.


$$c = m^l \cdot d^l + m^r \cdot d^r + \sum L_{ij} c_j$$

What Does This Model Explain?

- Binocular deprivation (BD) doesn't reduce synaptic efficacy because the cortical cells aren't firing.

  - Explanation: BCM learning requires at least some postsynaptic activity.

- Bicucculine (GABA blocker) restores deprived eye responses in minutes.

  - Explanation: synaptic strengths for deprived eye need not decrease to zero. Just need to get low enough to be balanced by cortical inhibition. Bicucculine shuts off this inhibition.

How Might the Threshold θ be Altered?

- Could level of CaMKII auto-phosphorylation determine the threshold θ_M?

- Auto-phosphorylation increases the affinity of CaMKII for calmodulin by 1000-fold.

  – Could act as a calmodulin buffer
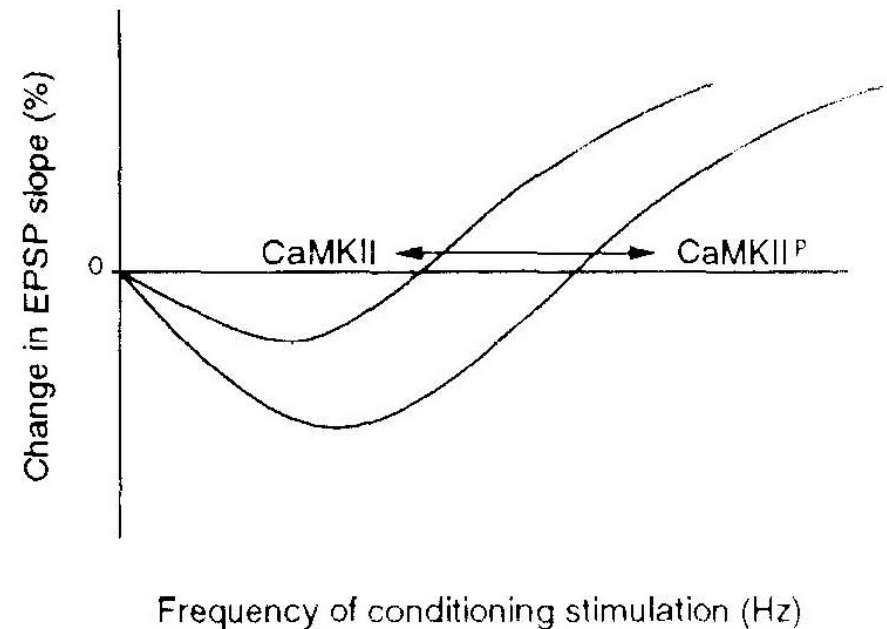
How Might the Threshold θ be Altered?

- θ_M is supposed to be a function of postsynaptic cell spike rate, not activity level local to the dendritic spine.

- So for this theory to be correct, spike rate information must propagate back to all spines. How does it do it?

Synaptic Tagging and Capture

How are synapses tagged for long term potentiation, which involves structural changes?
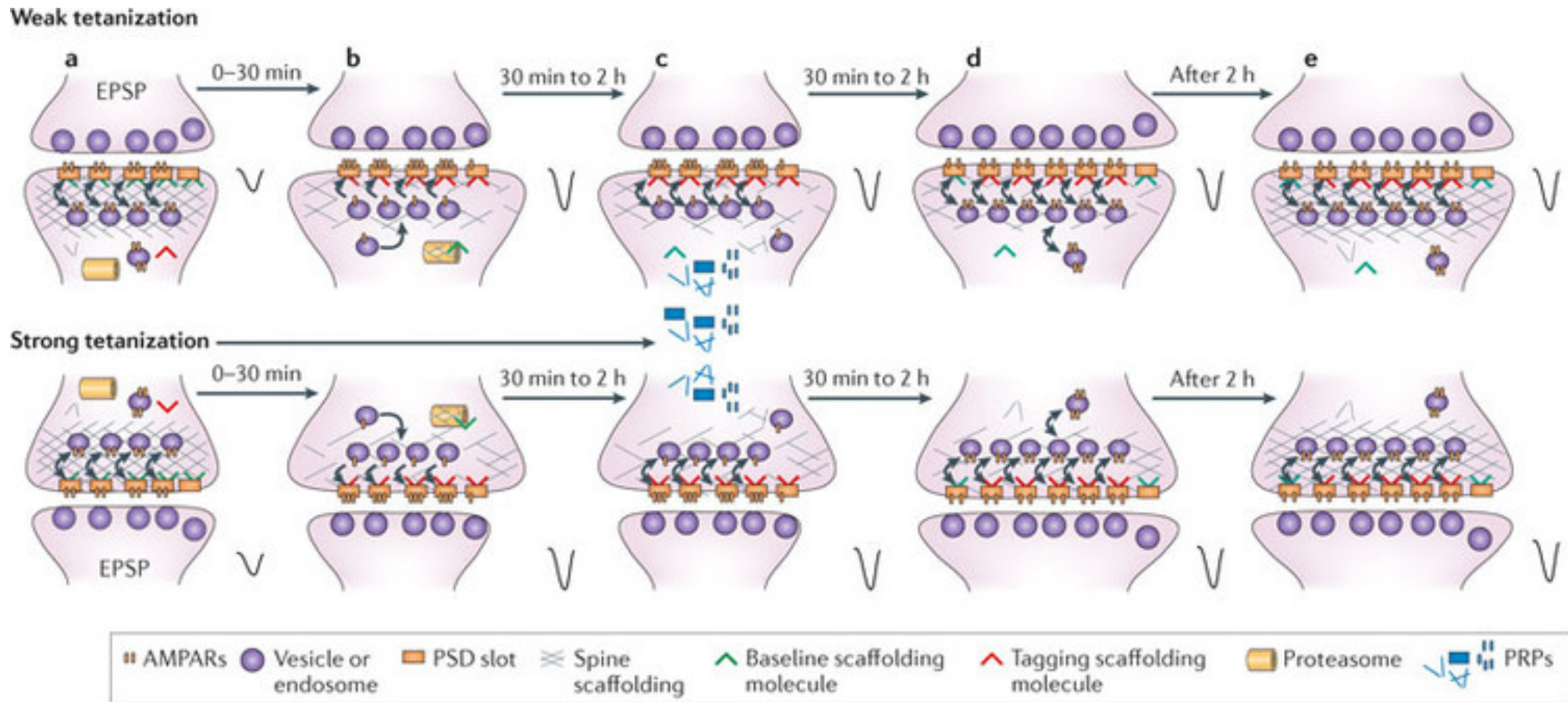

Nature Reviews | Neuroscience

Redondo & Morris (2011)
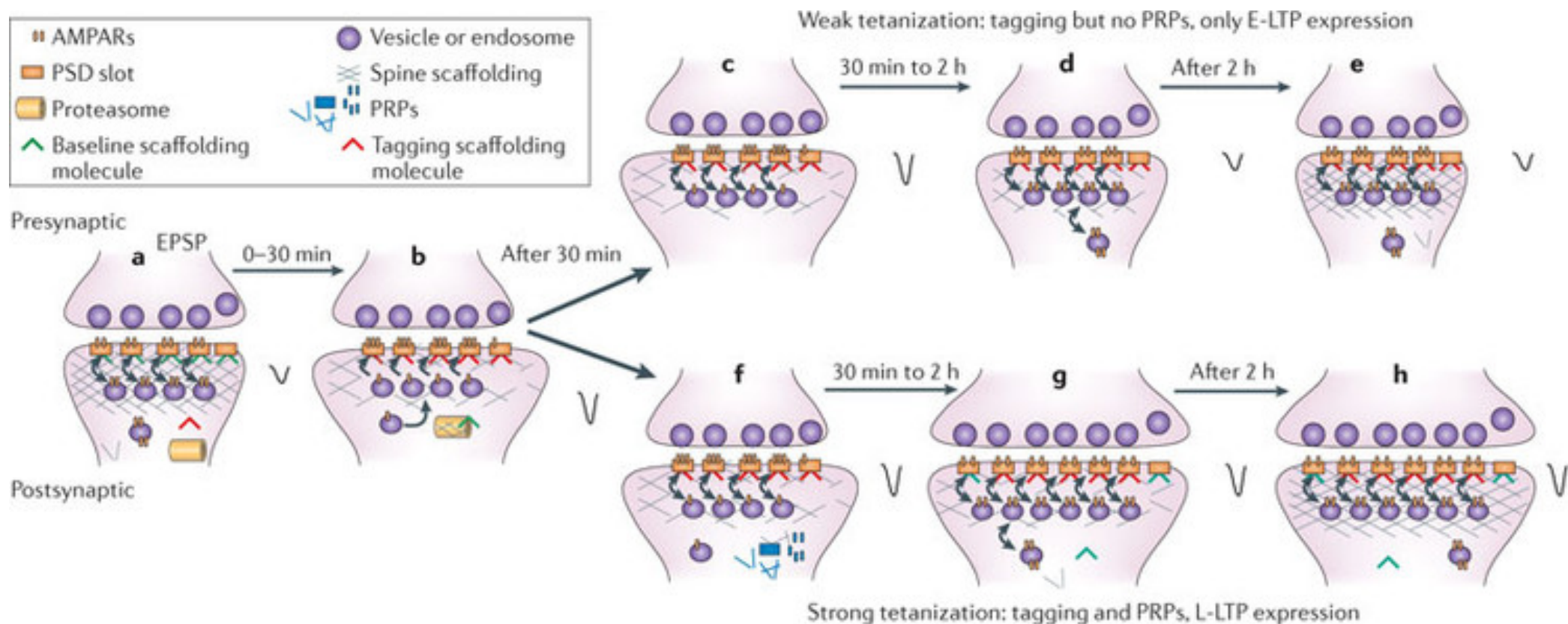
PRP = plasticity-related products
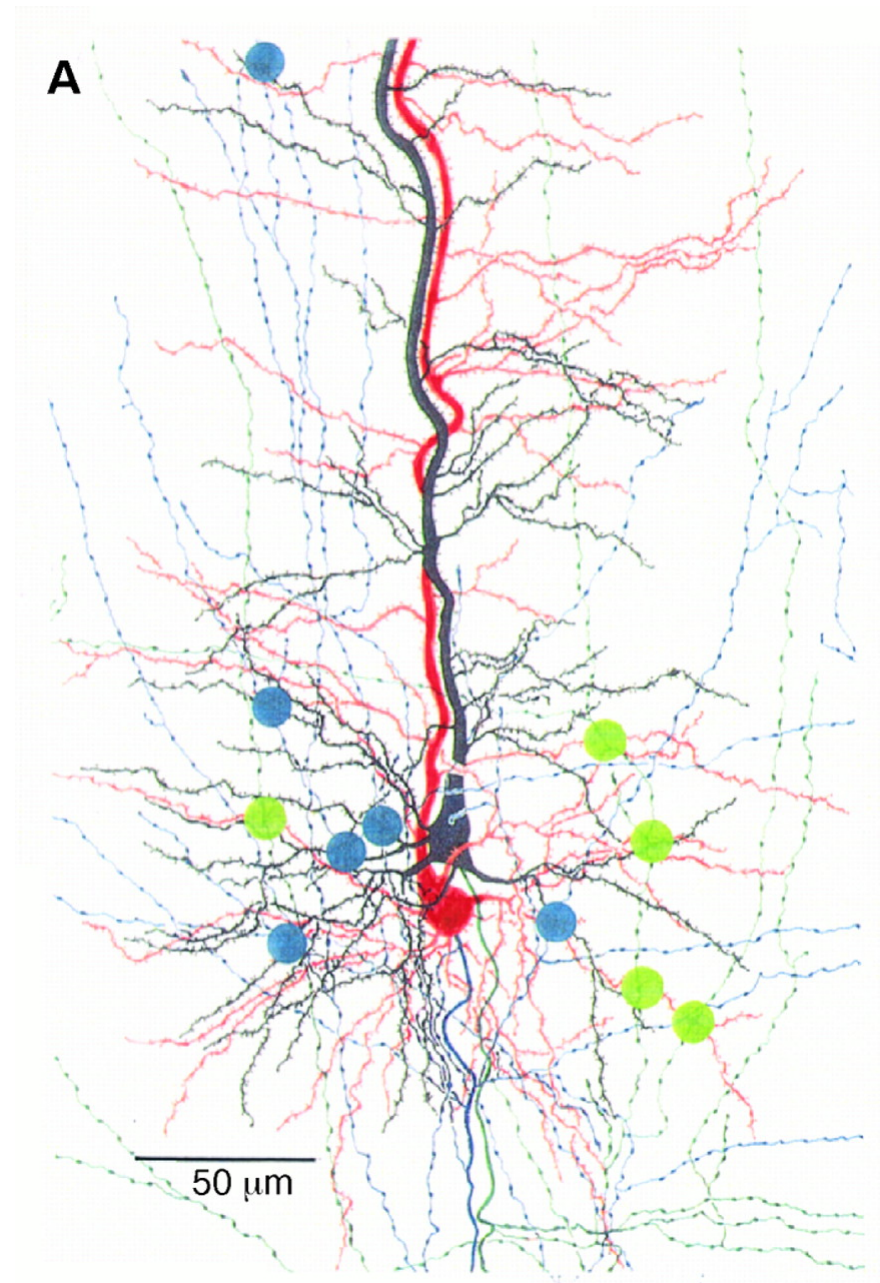E-LTP = early-stage LTP
L-LTP = late-stage LTP

Synaptic Tagging and Capture

Potentiation of a weakly-stimulated synapse can be rescued by PRPs transported cell-wide as a result of strong stimulation at other synapses.
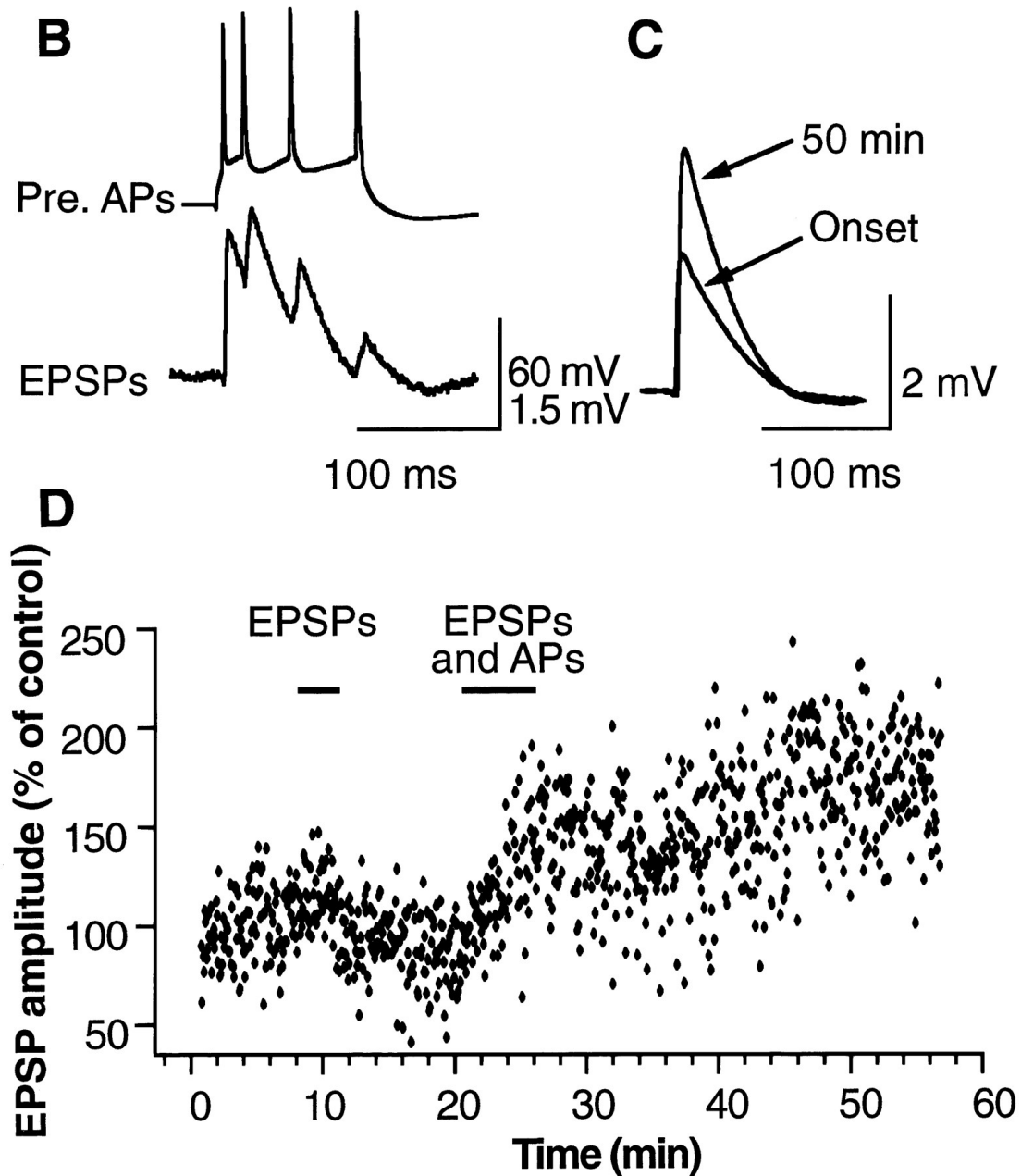

Nature Reviews | Neuroscience
Redondo & Morris (2011)

Spike-Timing-Dependent Synaptic Plasticity

- Markram et al., *Science,* 1997

- Pair of thick-tufted layer 5 pyramidal cells

- Synapses:

  - black to red (green dots)

  - red to black (blue dots)

- Paired pre- and postsynaptic spiking (5 spike pairs at 10 Hz, repeated 10 to 15 times spaced 4 seconds apart)

A

50 µm

Spike-Timing-Dependent Plasticity

Computational Models of Neural Systems

Timing Window for STDP

Computational Models of Neural Systems