# Synaptic Plasticity and the NMDA Receptor

Computational Models of Neural Systems

Lecture 4.2

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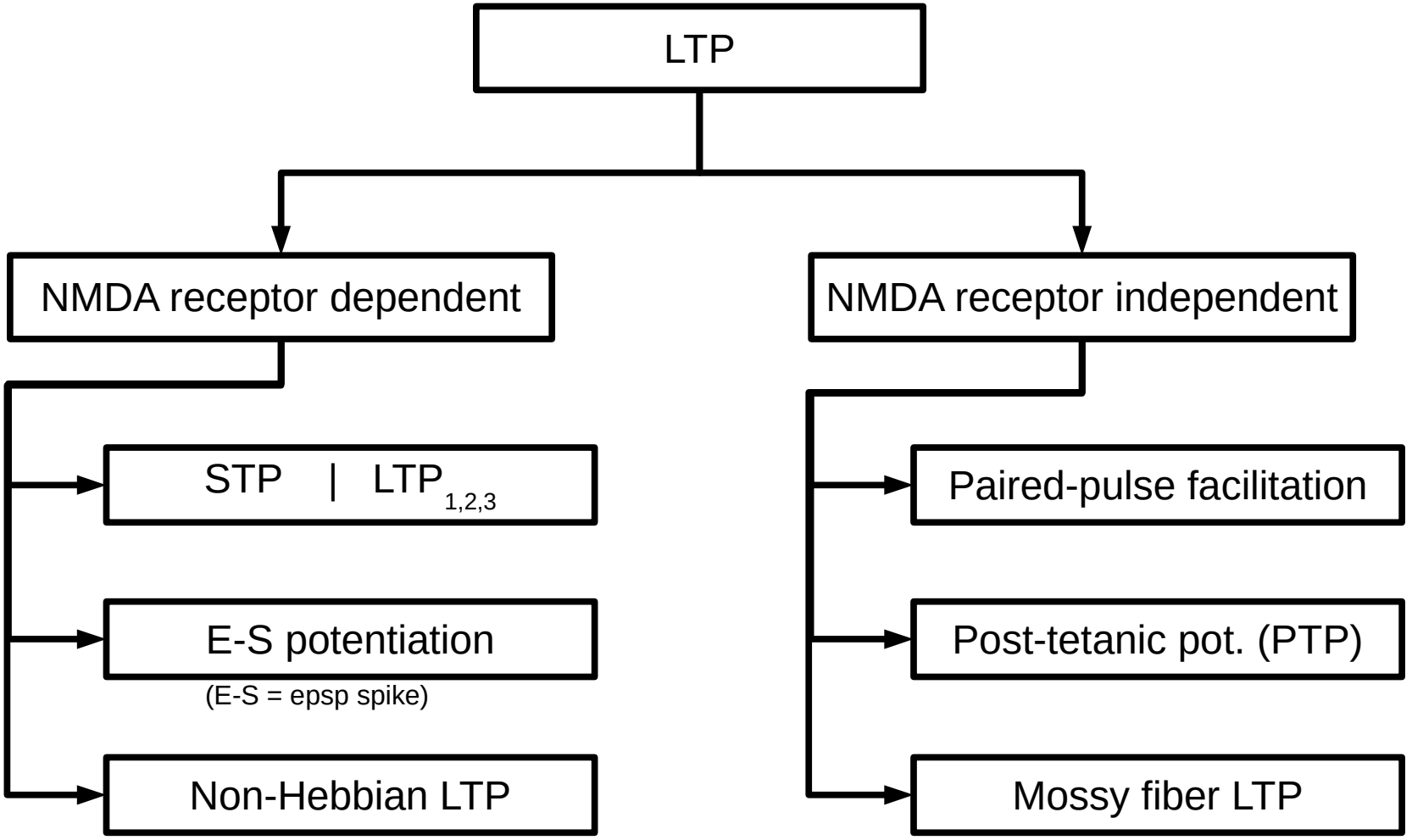
# Synaptic Plasticity Is A Major Research Area

- 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




Bliss & Collingridge 1993

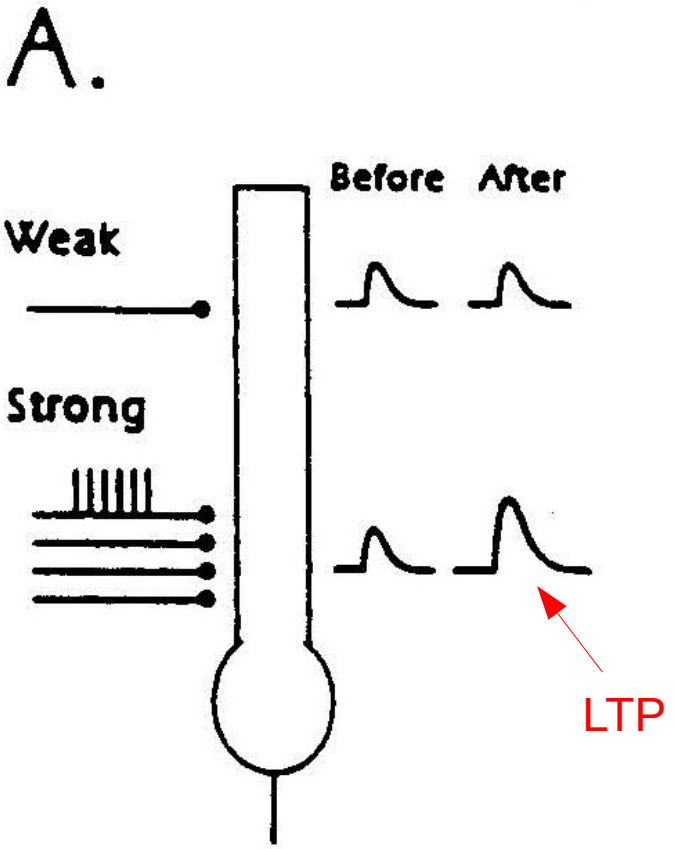
# Short-Term Plasticity

- Could serve a spike filtering function.
- Synapses with low 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 high probability of transmitter release are more like to show depression.
  - Acts as a low pass filter: occasional spikes are transmitted without change, but high frequency spike trains are attenuated.

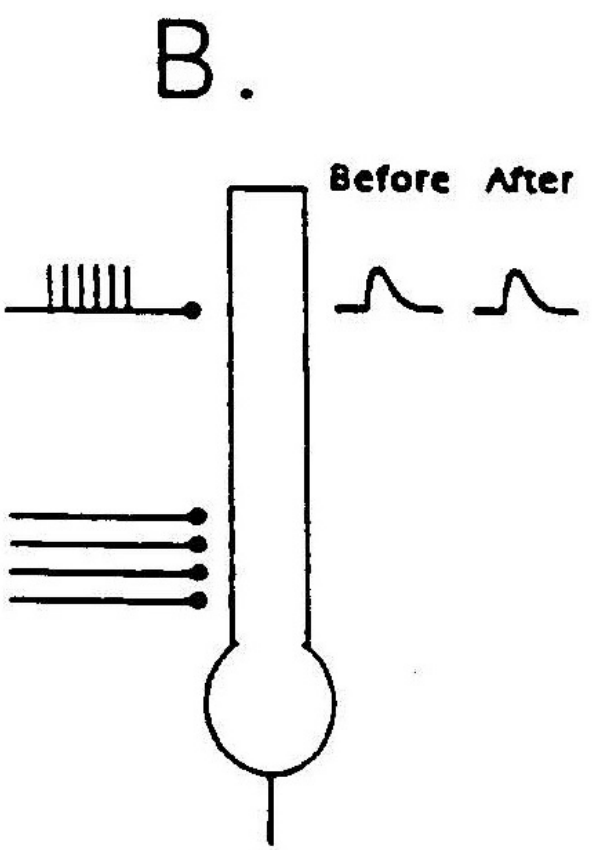
# Properties of LTP

- 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.

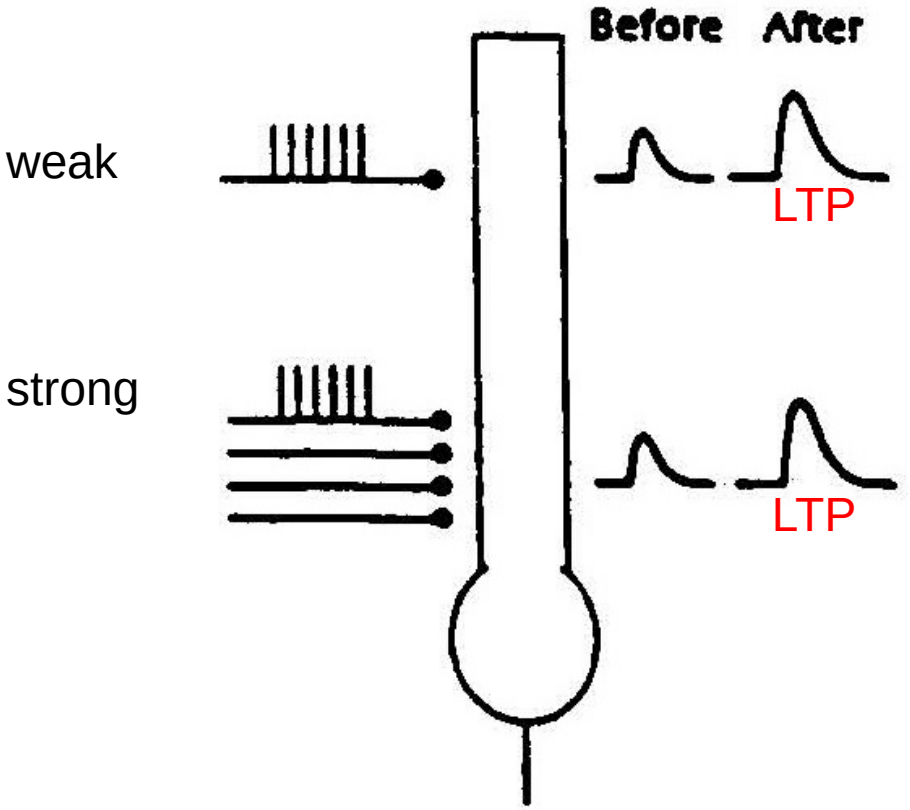
# Input Specificity



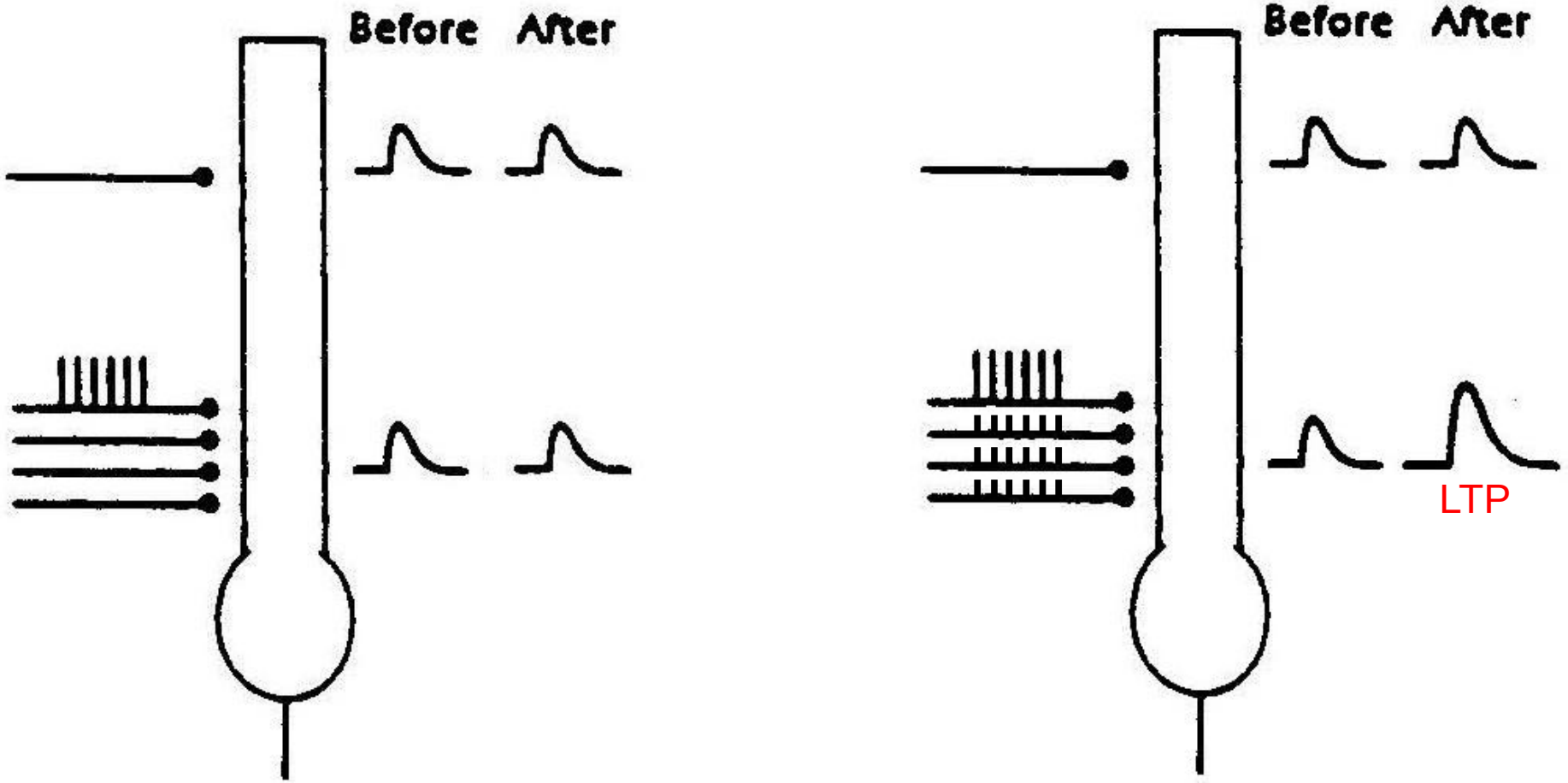

# Threshold Effect



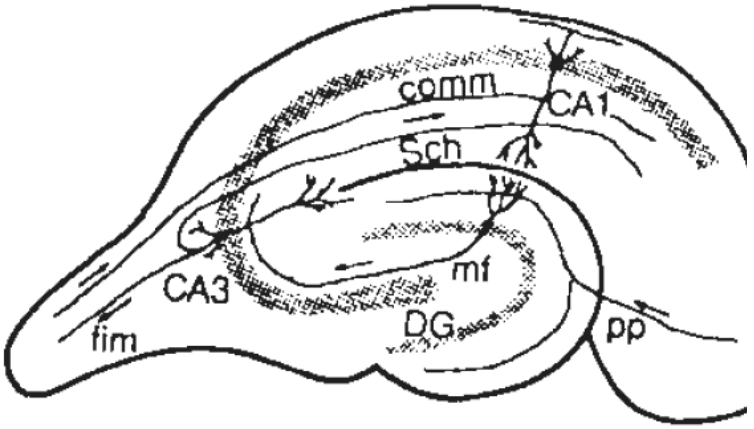
# Associativity

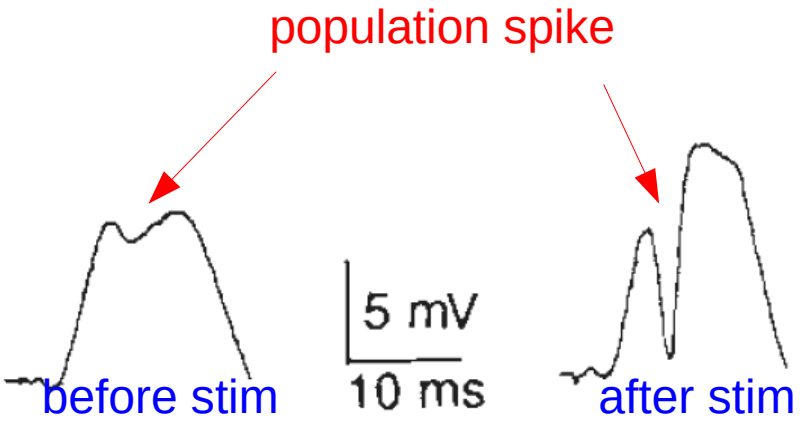


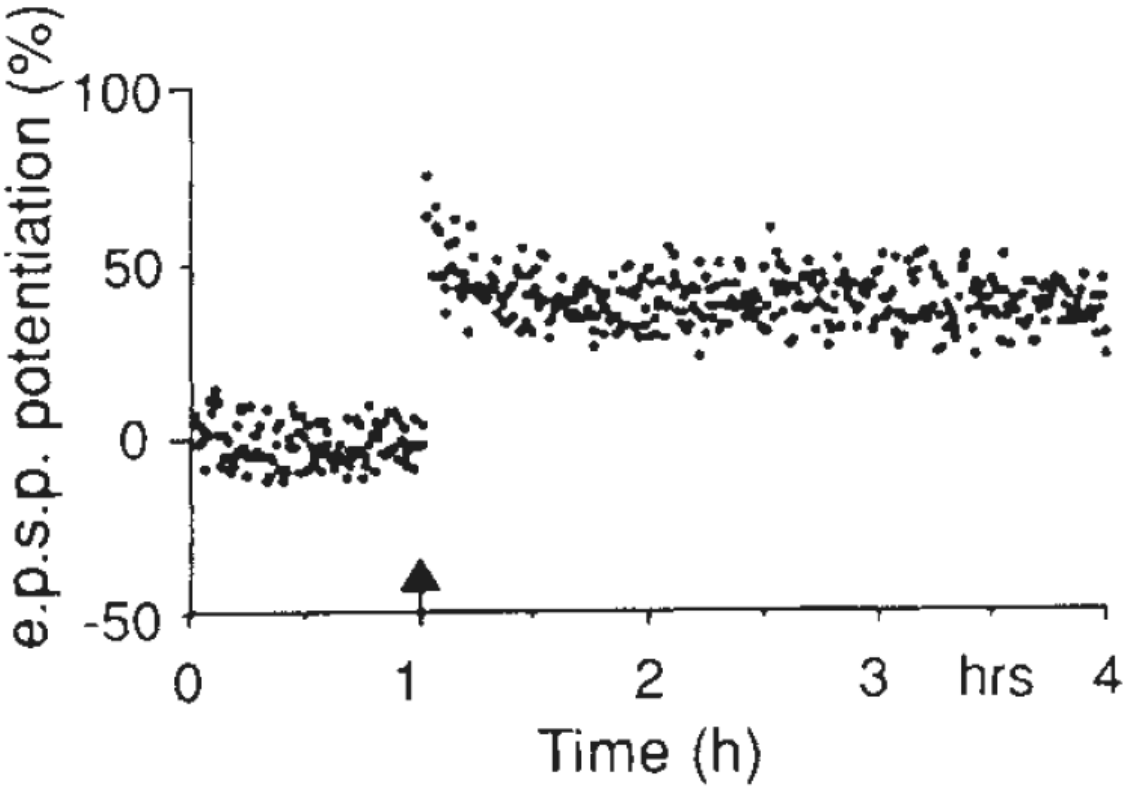
# Cooperativity



# LTP in the Perforant Path of Hippocampus

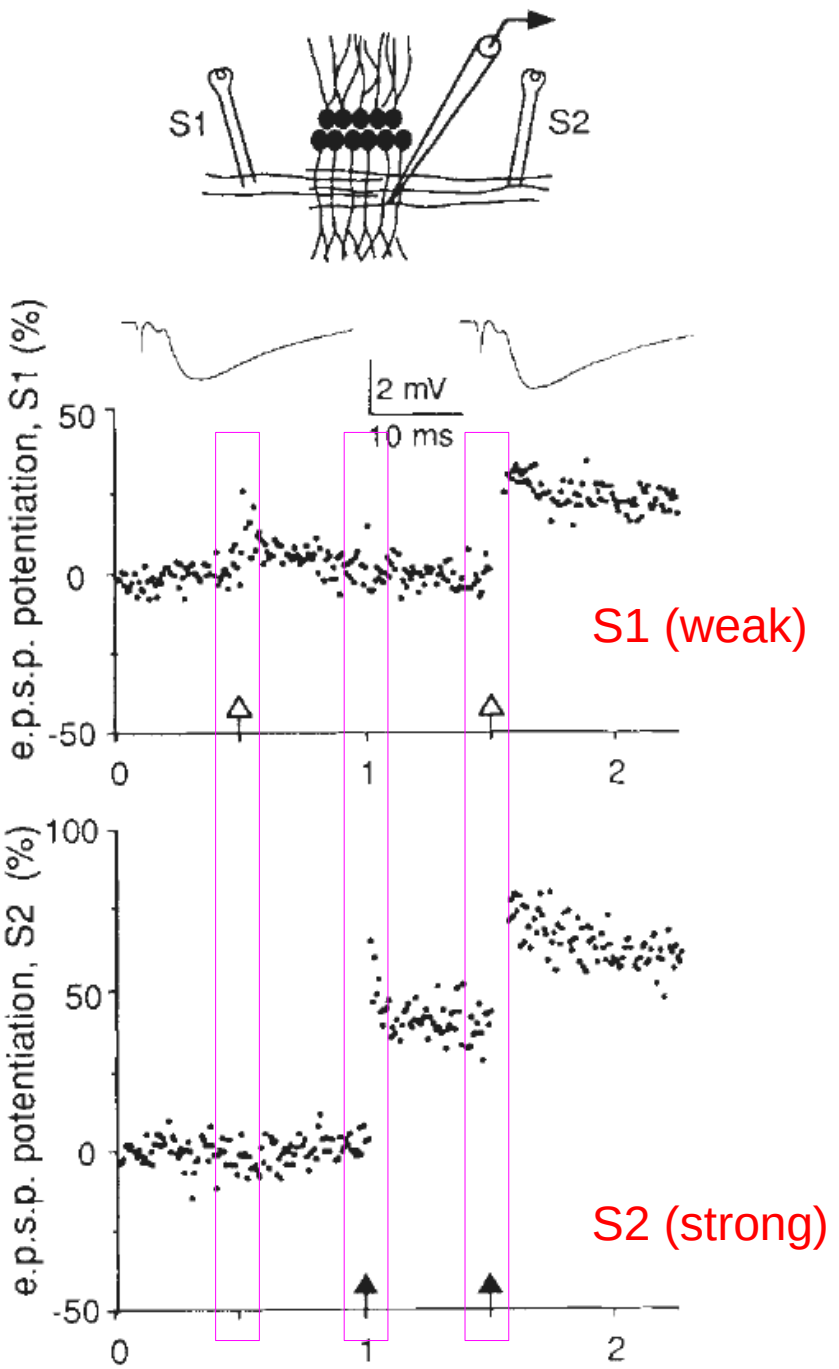


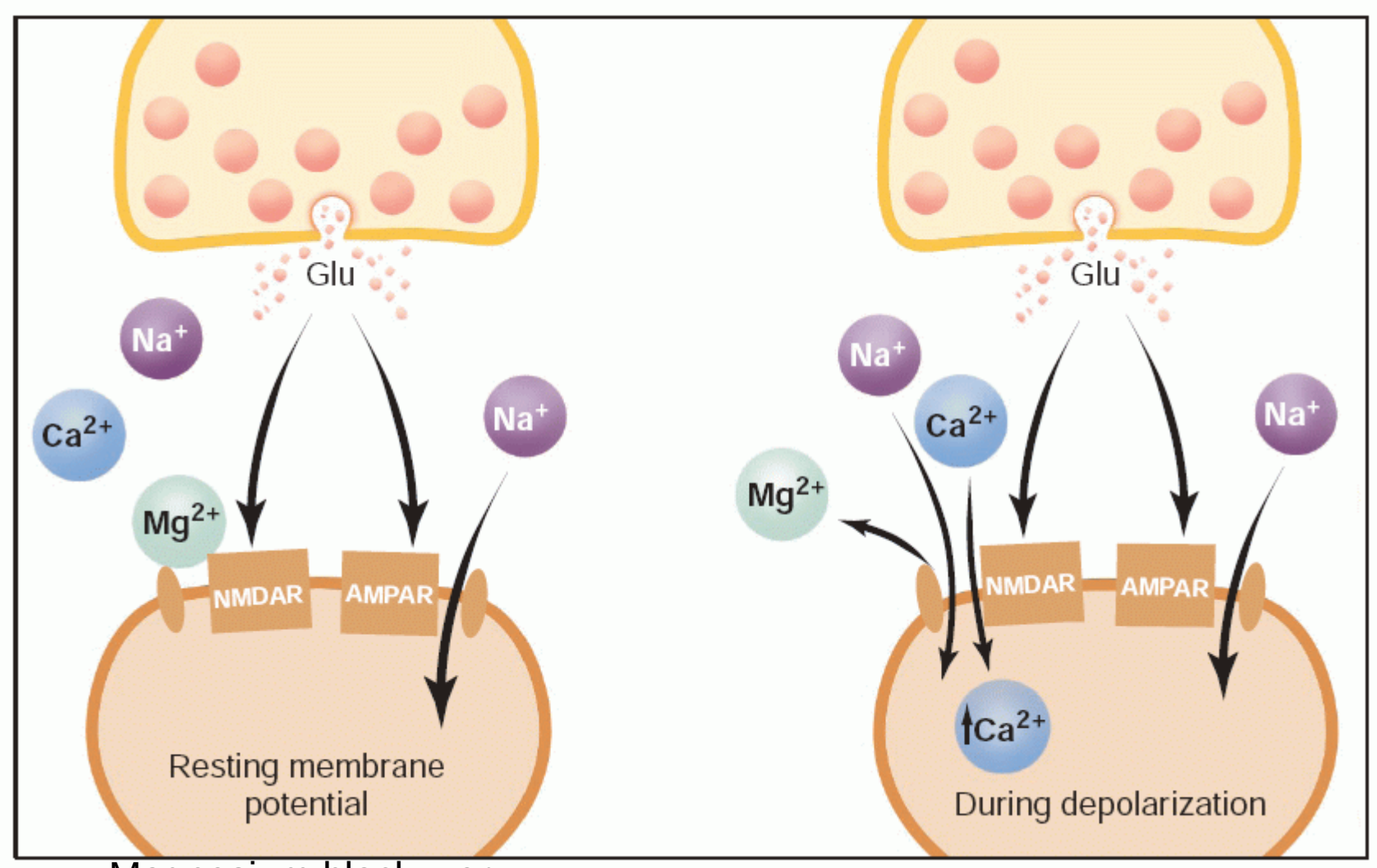



# Specificity and Associativity

- 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



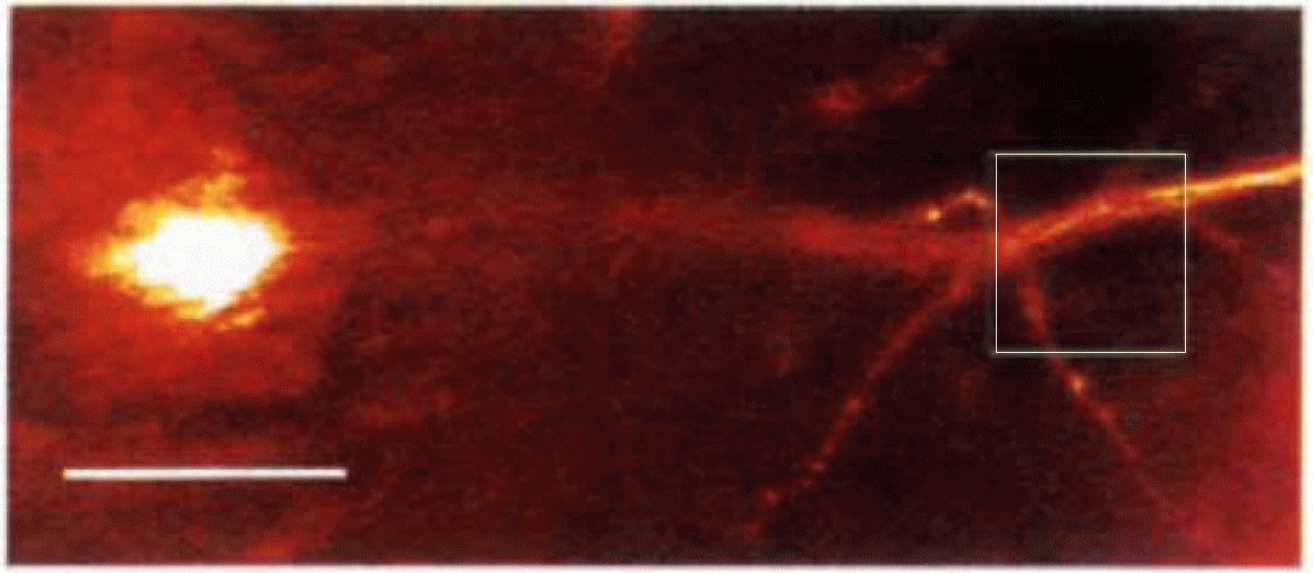
# The NMDA Receptor

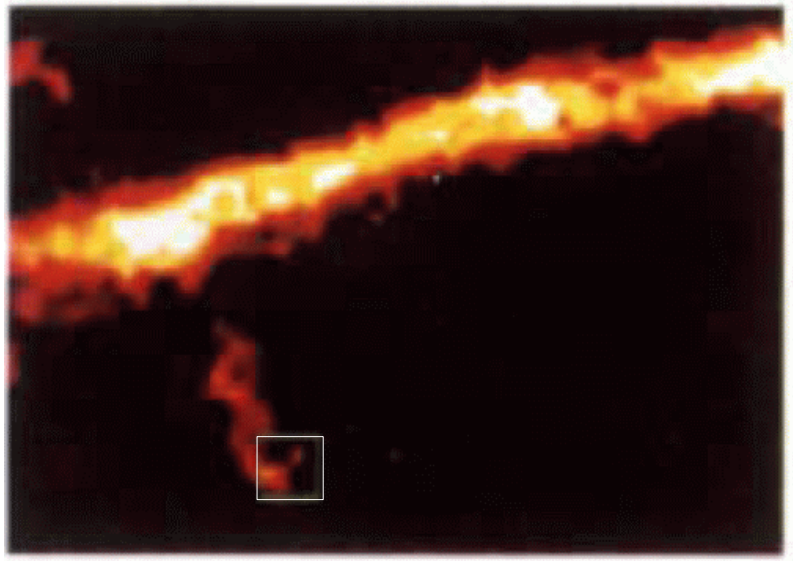



Magnesium block: very little NMDA current

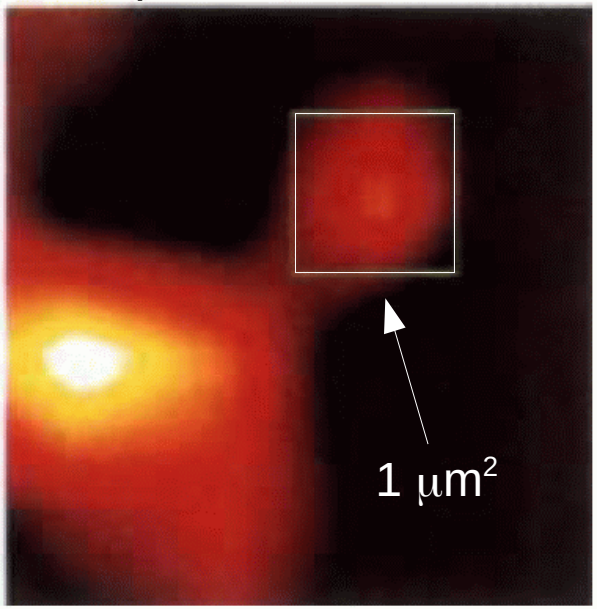
Malenka 1999

# Fluorescence Imaging of Calcium in Dendritic Spine

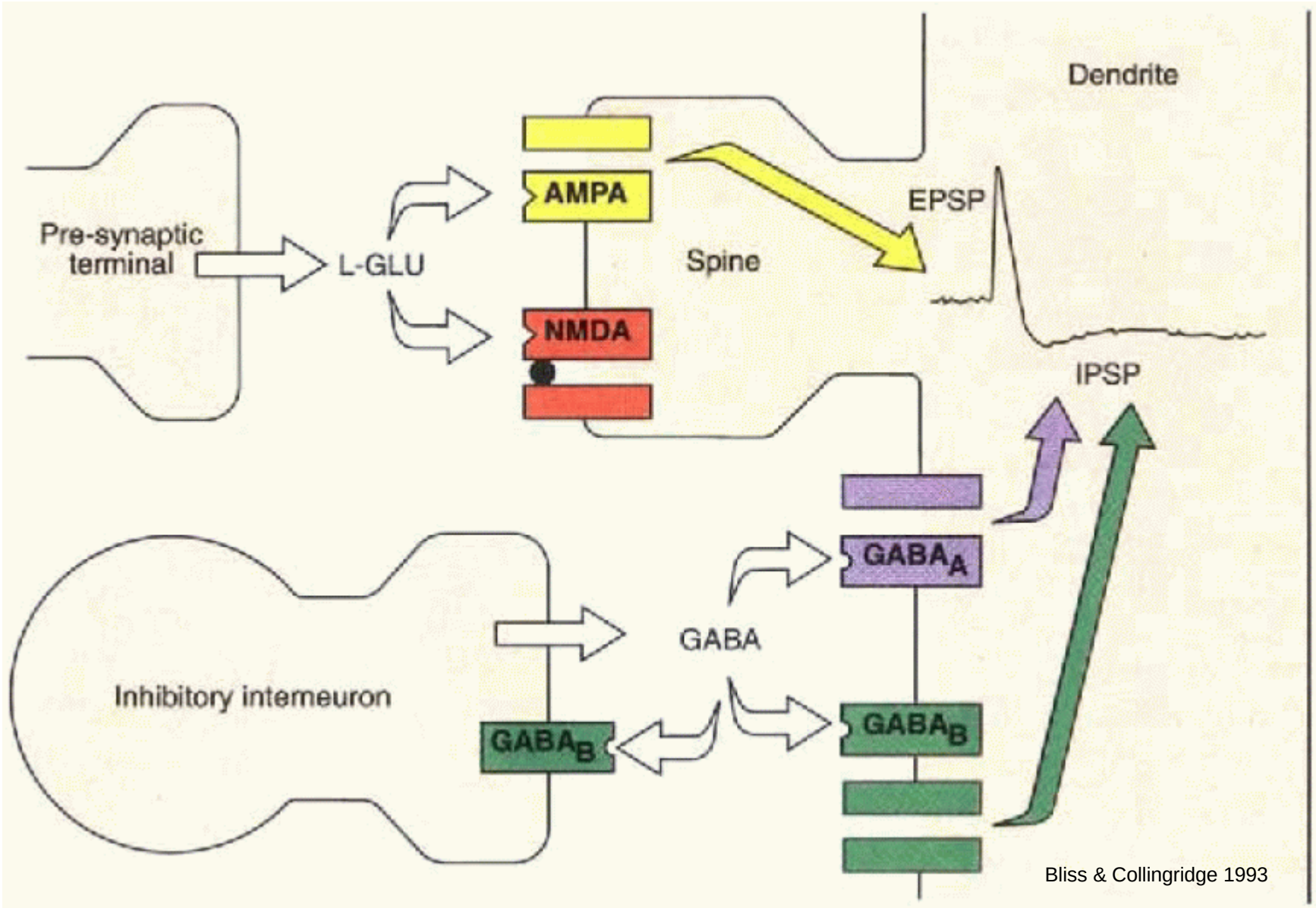




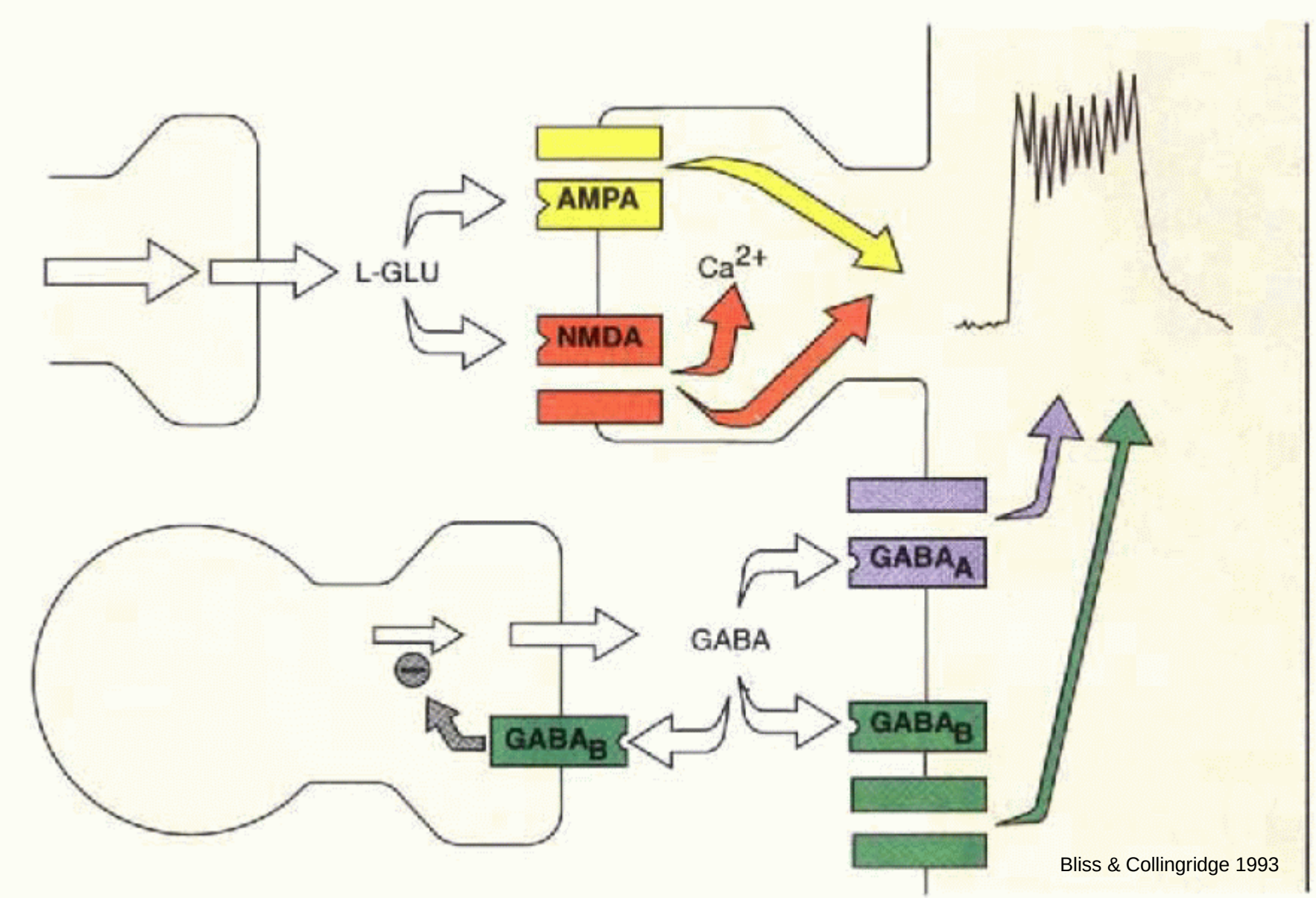
Calcium influx in a CA1 pyramidal cell in response to HFS



# Response to Single Stimulus

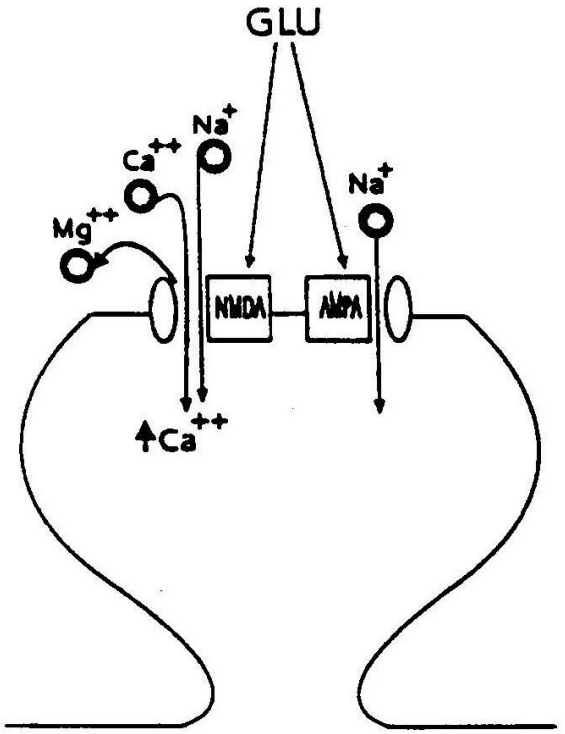


# Response to High Frequency Spike Train



# 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).

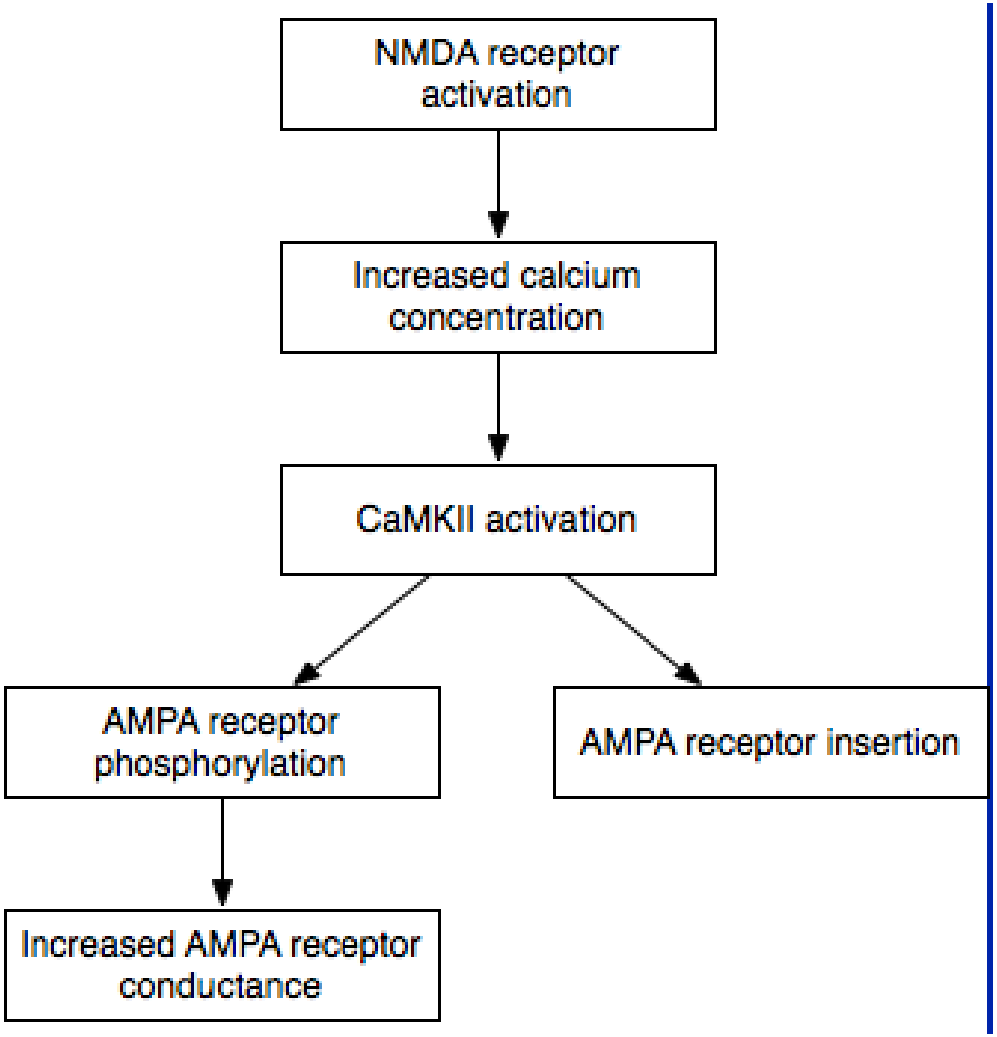


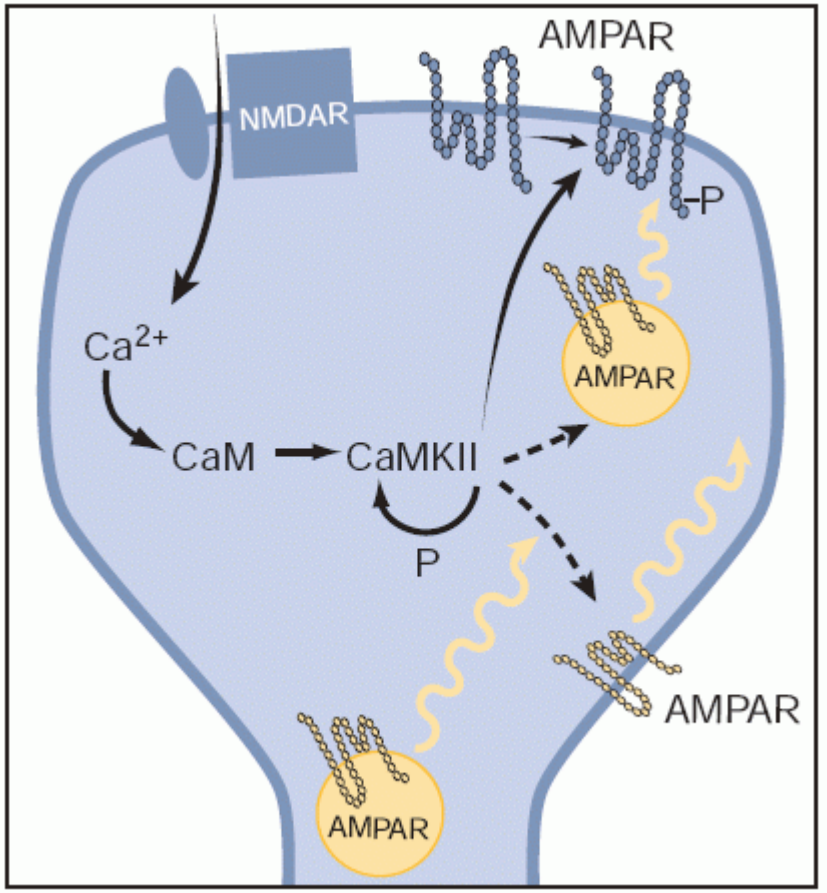
# Phases of LTP

- 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)

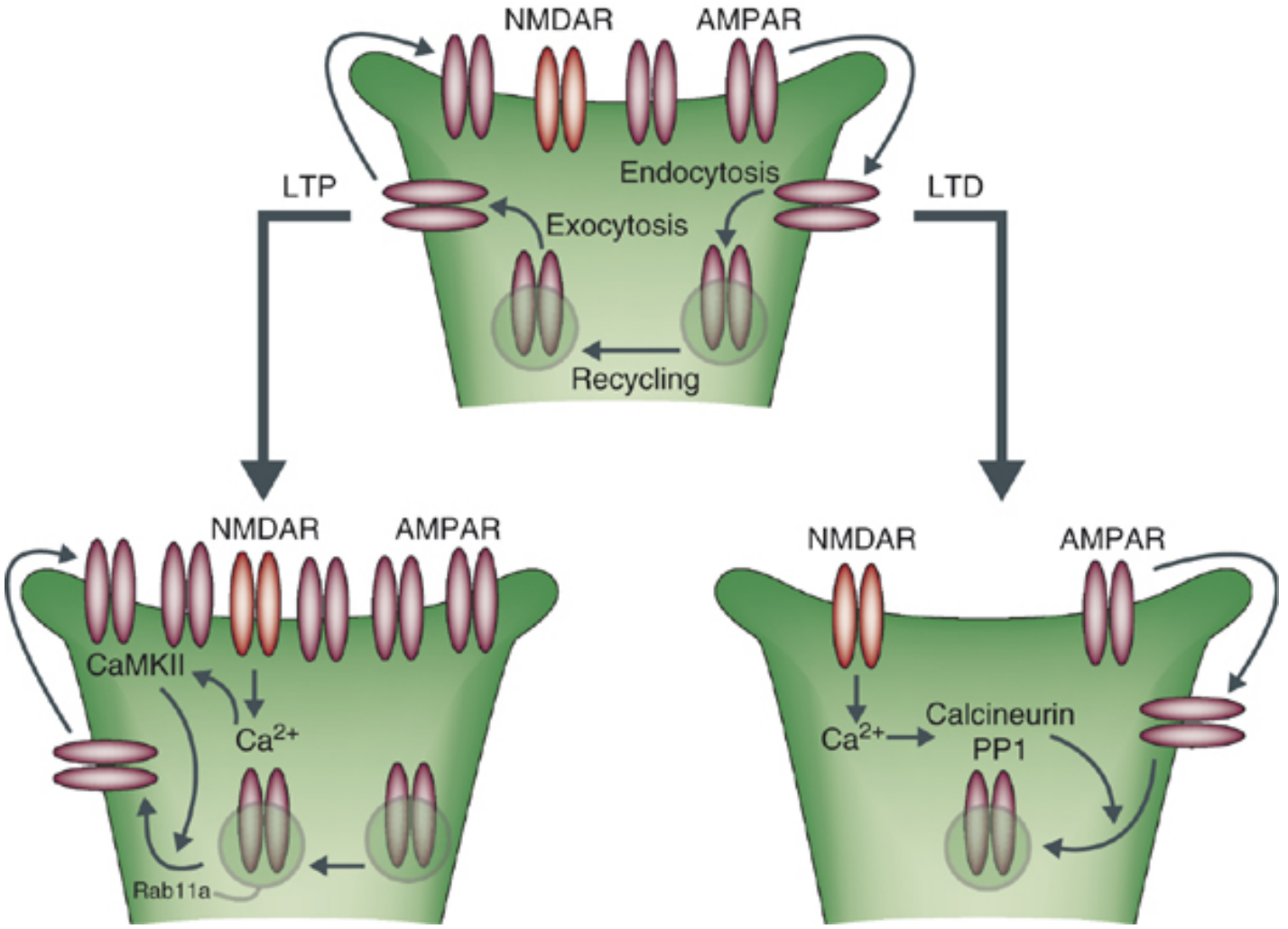
dependent on protein synthesis

# Early Phase LTP



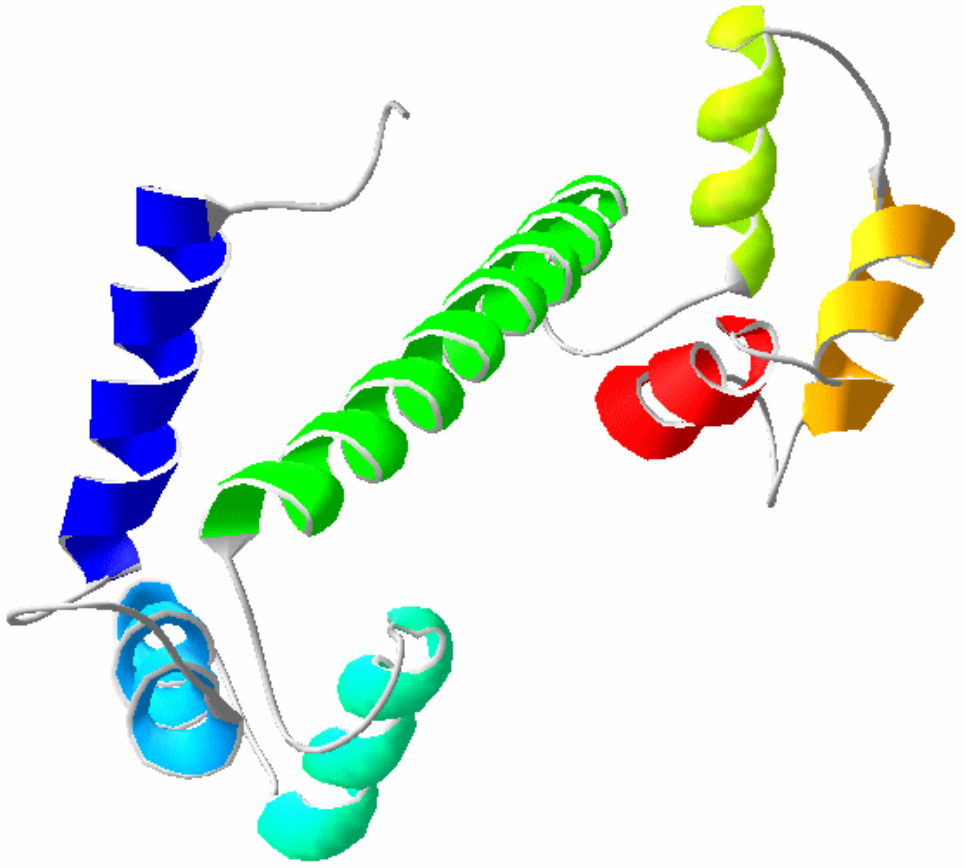
# AMPA Receptor trafficking




Citria & Malenka (2008)

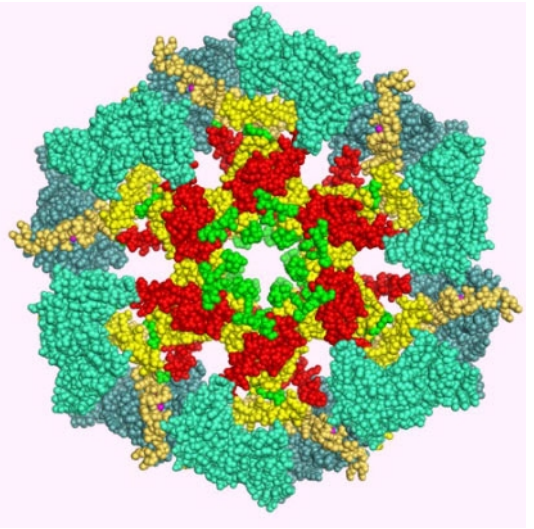
# Calmodulin

- 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.



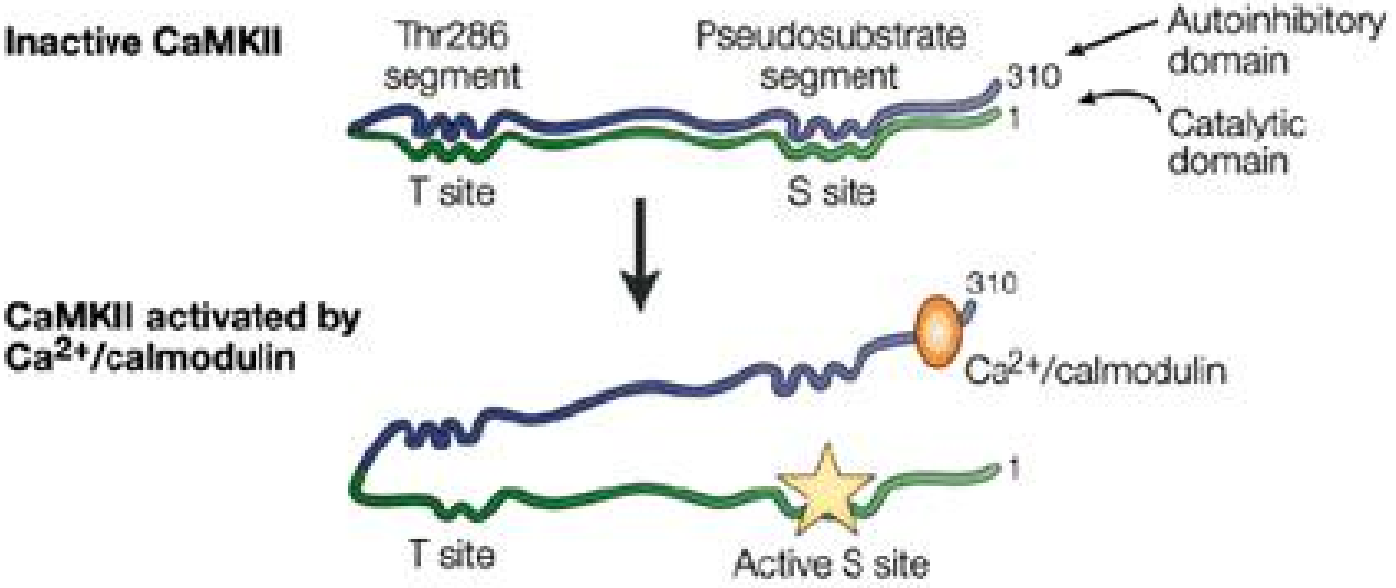
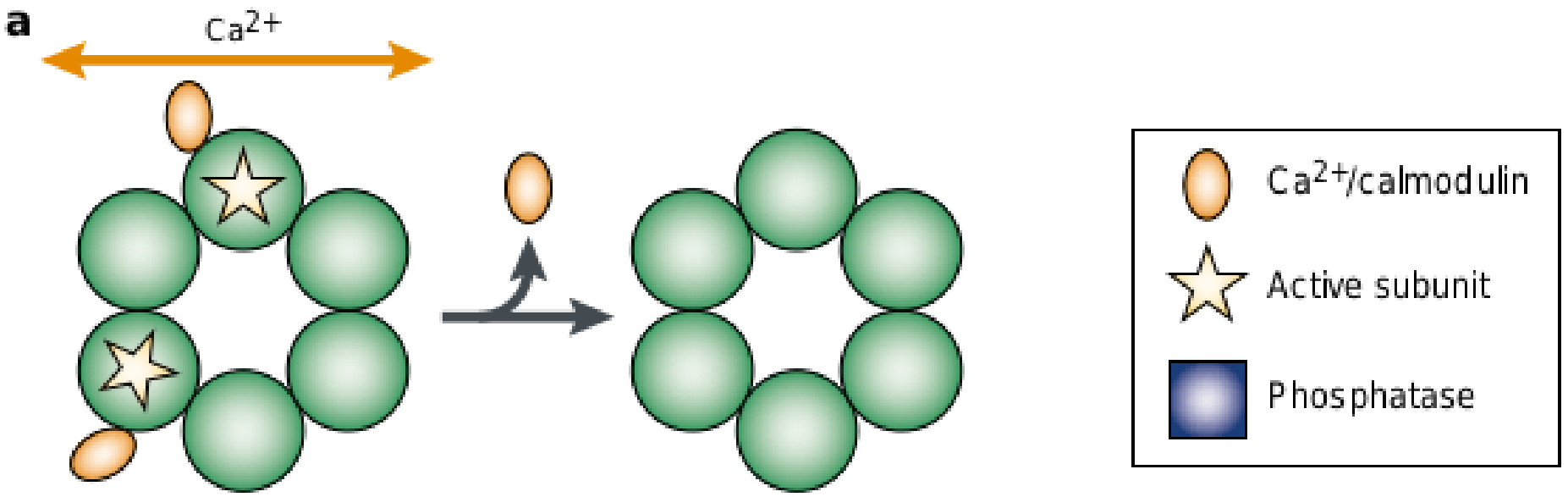


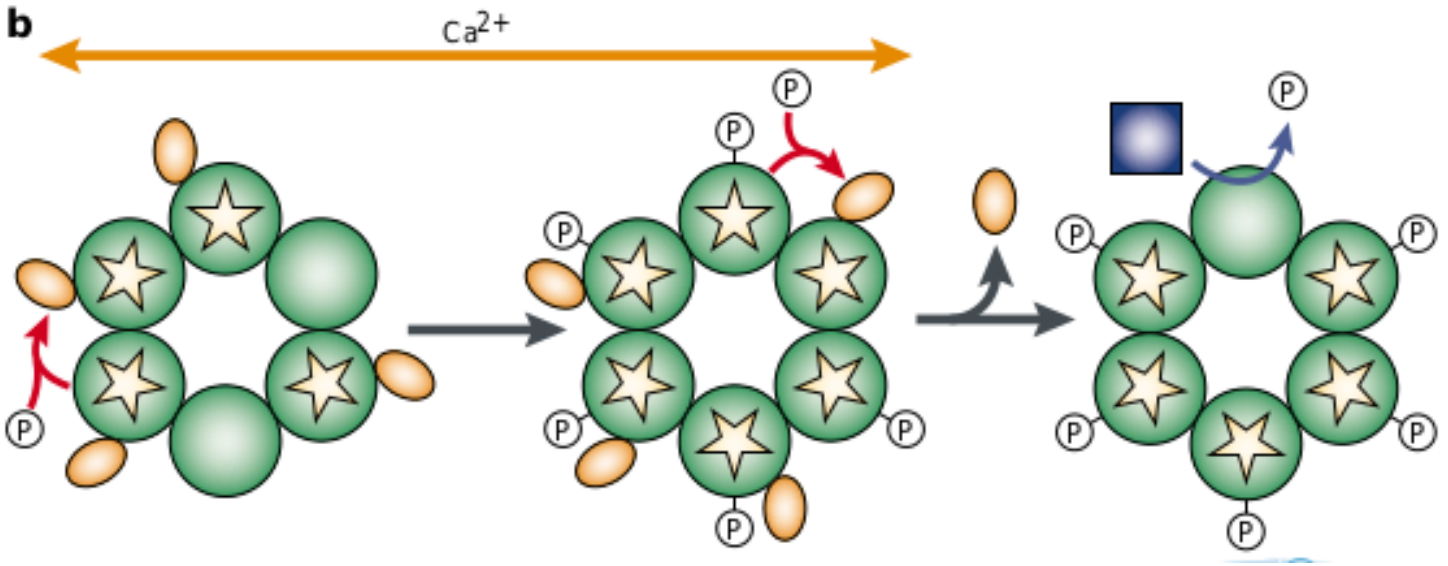

*Figure 2. Regulation of CaMKII. John Lisman et al. Nature 2002; 3: 179-190*
*At basal Calcium ion concentrations, the kinase will be blocked, because the autoinhibitory domain stays bound to the catalytic domain. $Ca^{2+}$/Calmodulin binding will activate the kinase* [2].

# 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

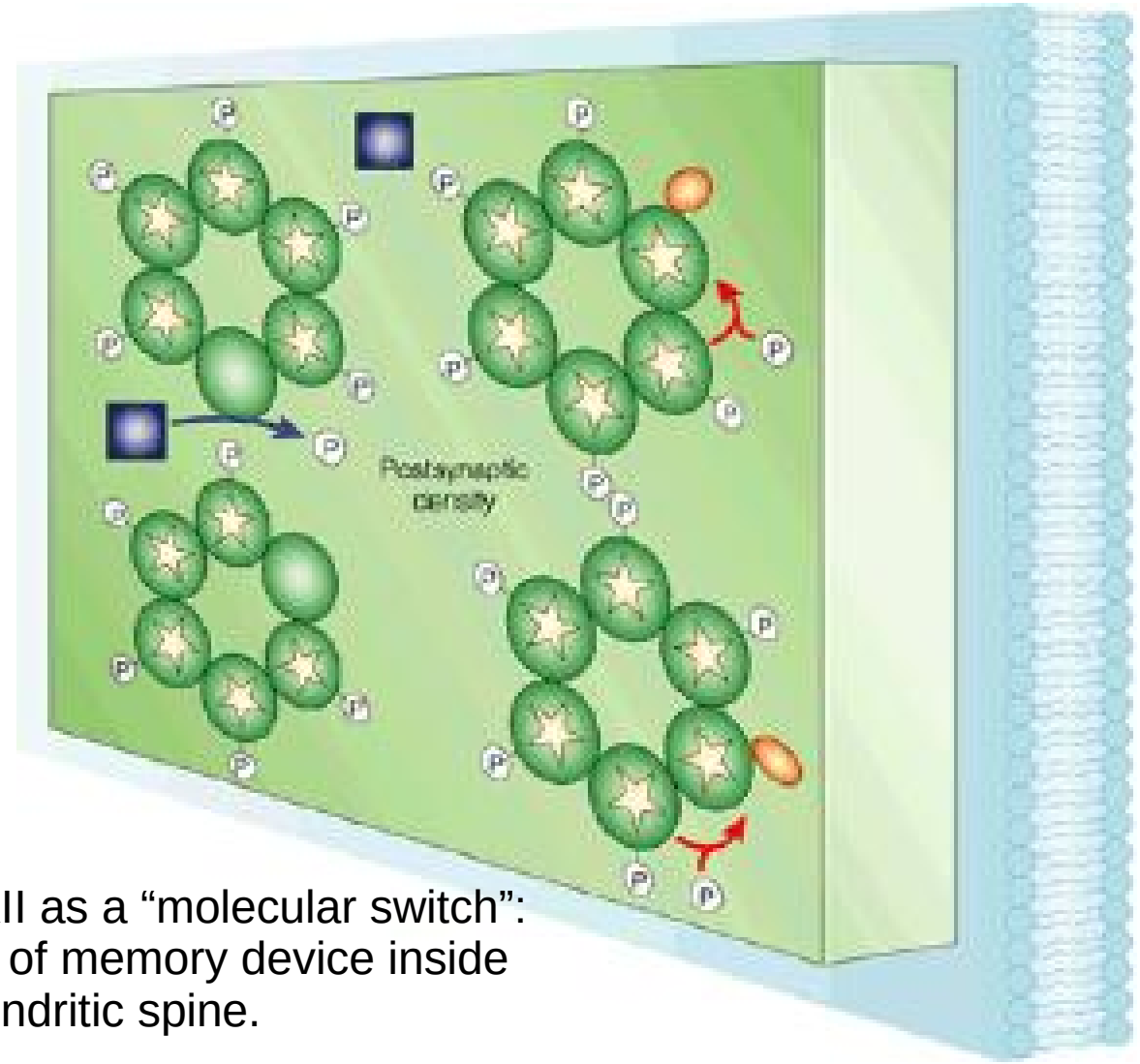
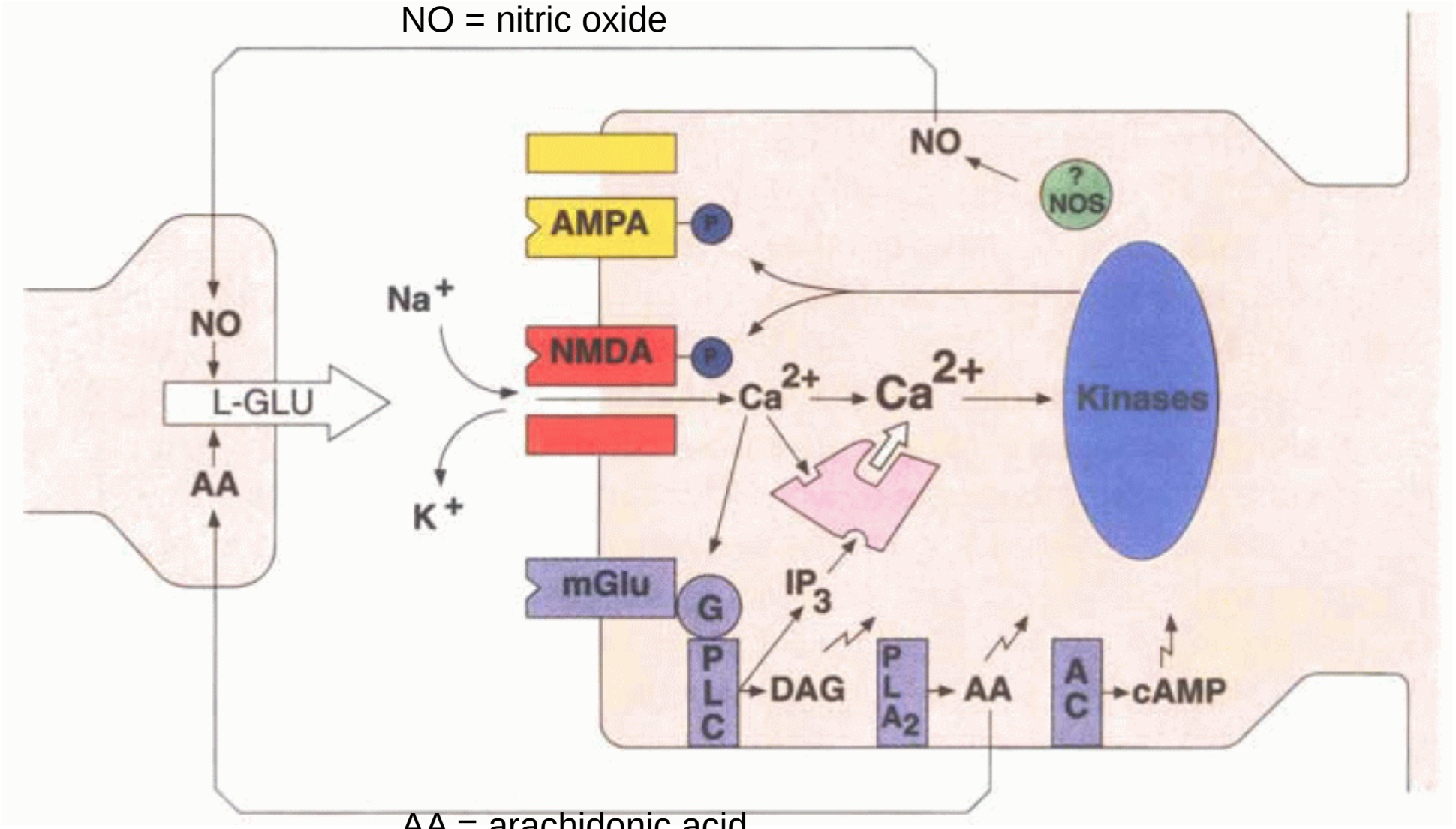



*Figure 4. Long-term persistent Autophosphorylation of CaMKII. John Lisman et al. Nature 2002; 3: 179-190 The autophosphorylation rate exceeds the rate of dephosphorylation [2].*

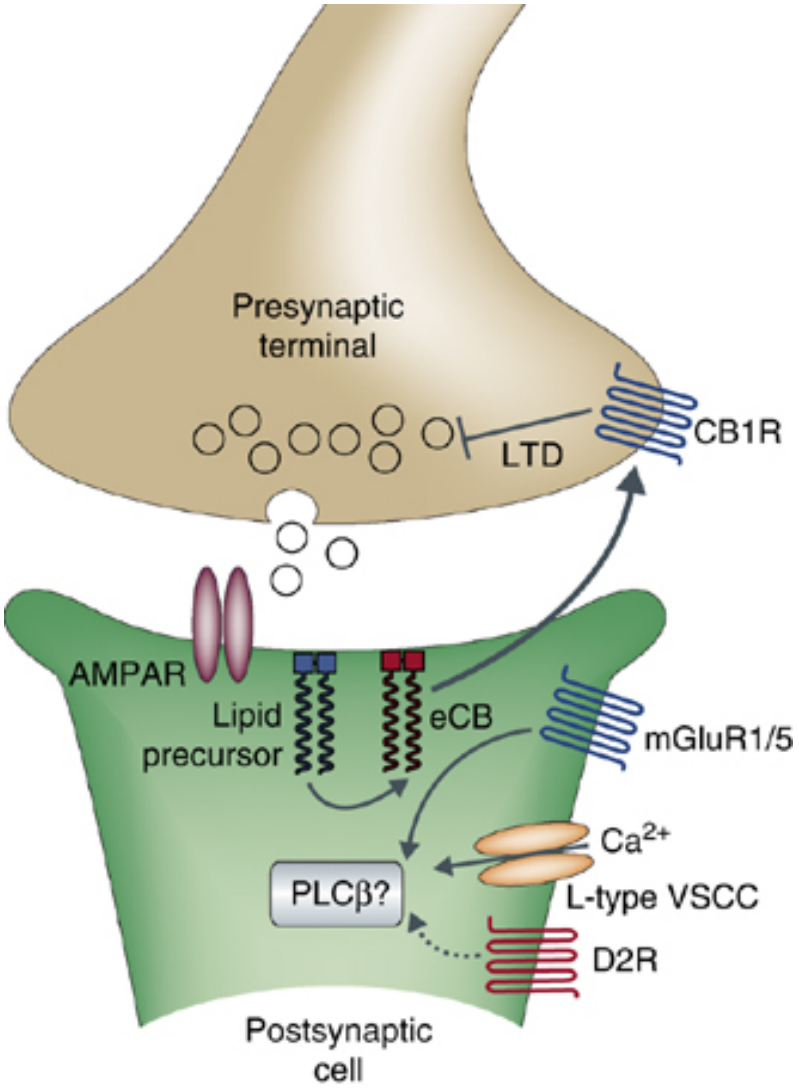

CaMKII as a “molecular switch”: a kind of memory device inside the dendritic spine.

# Retrograde Messengers as a Pre-Synaptic Mechanism for LTP

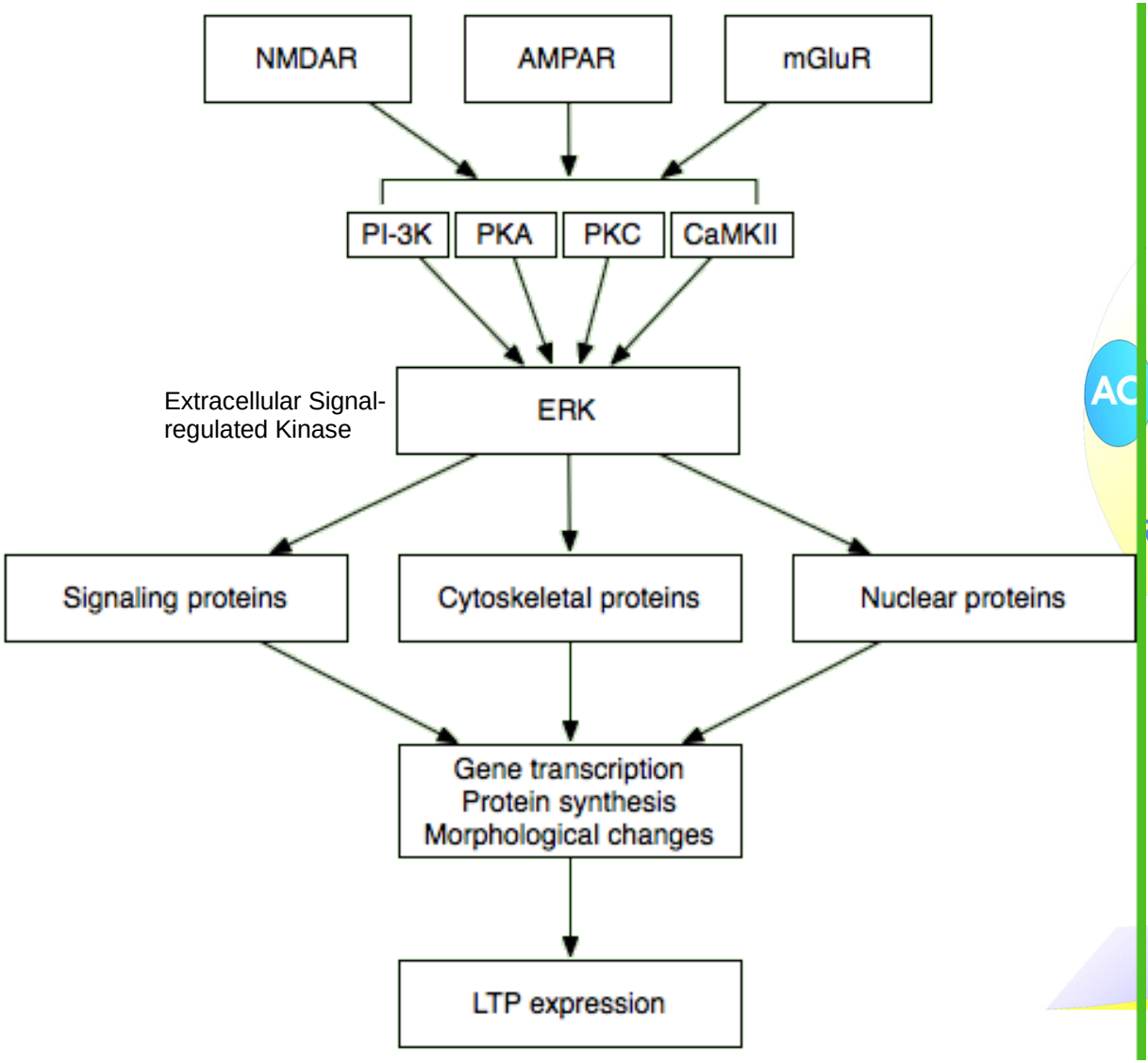


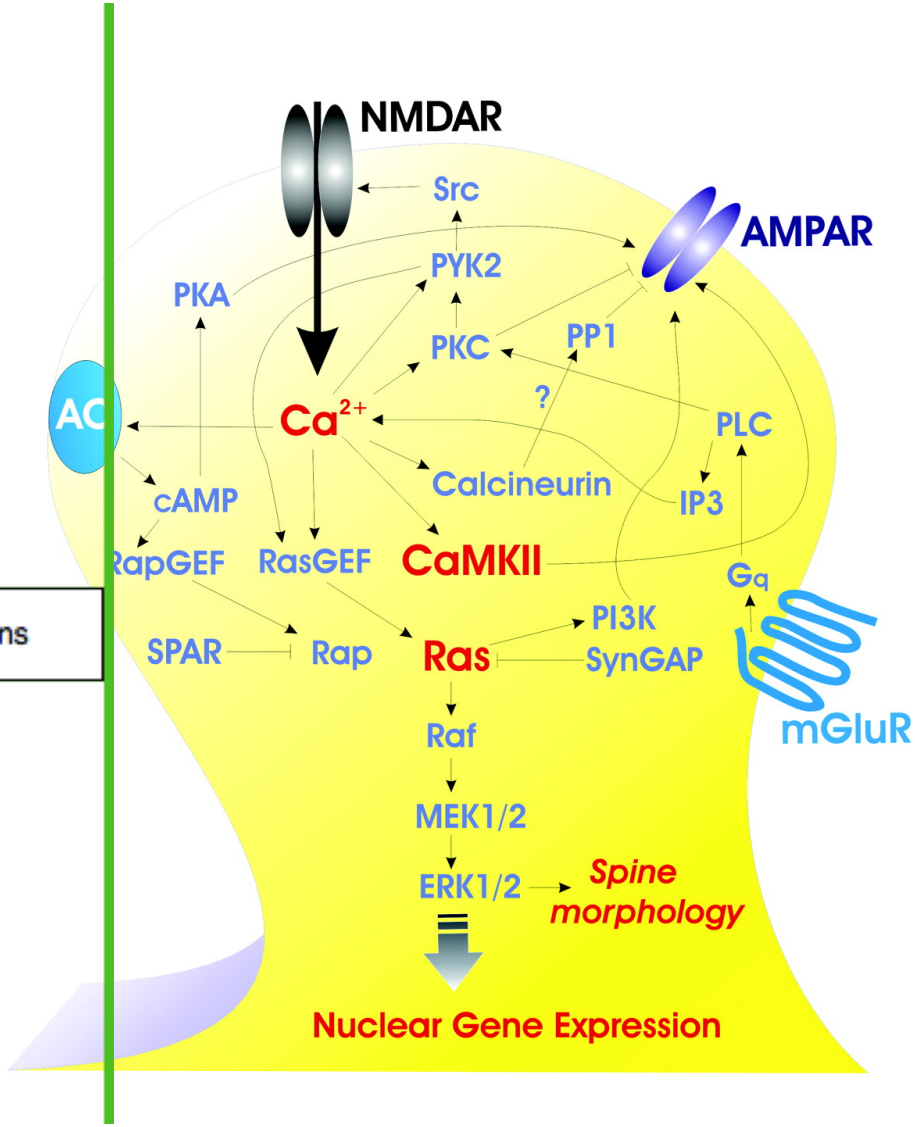
# Retrograde Transmission of Endocannabinoids

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



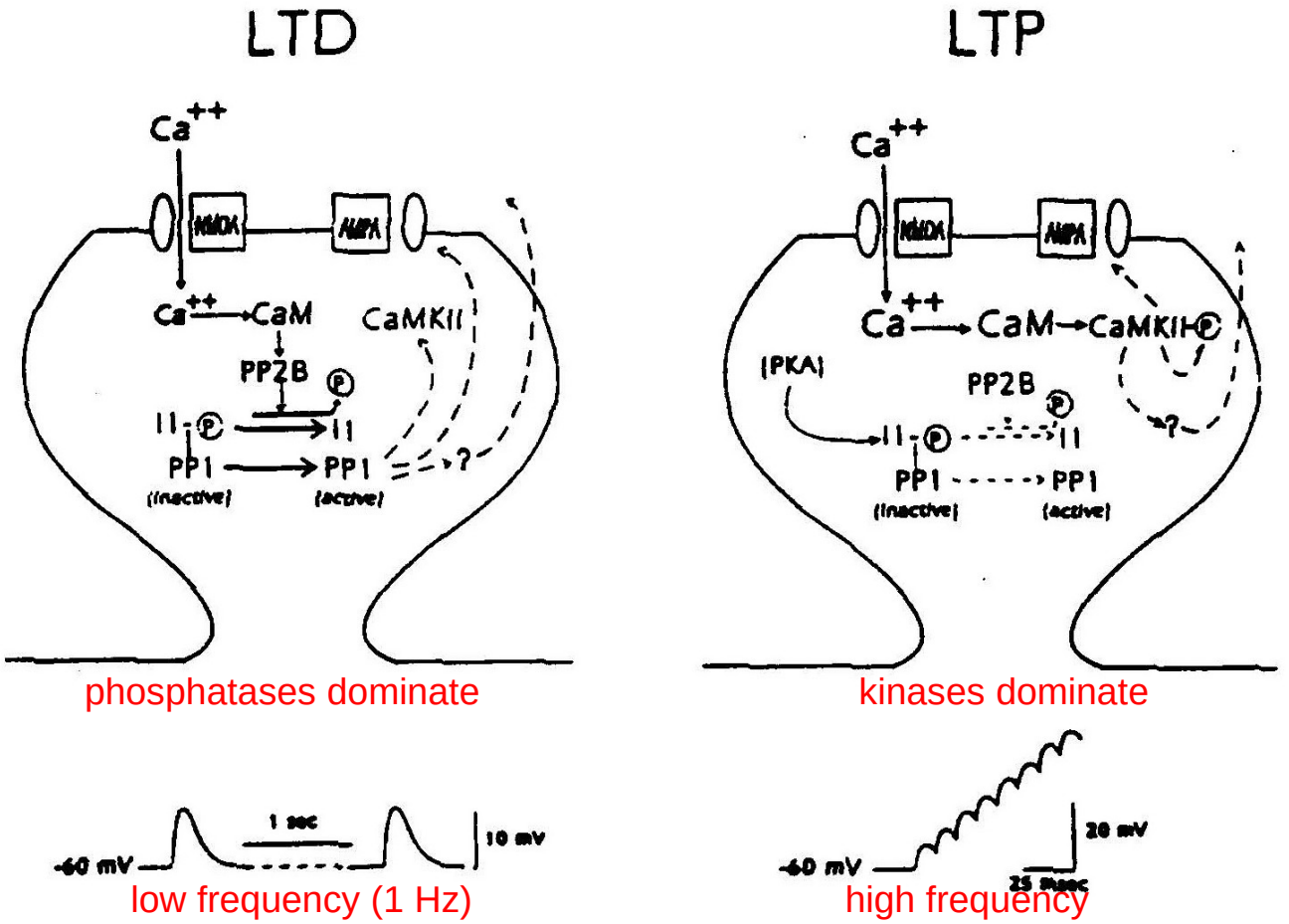
# Late Phase LTP



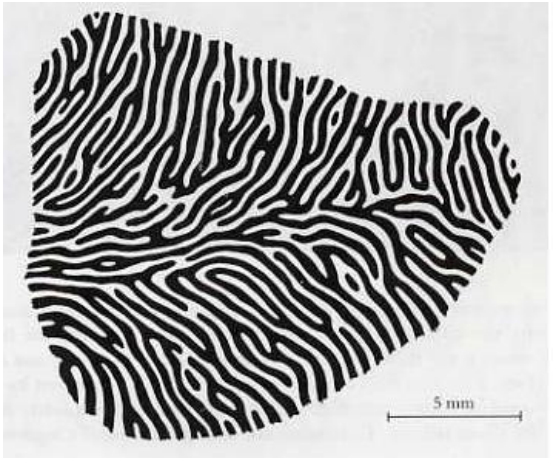
# LTP and LTD

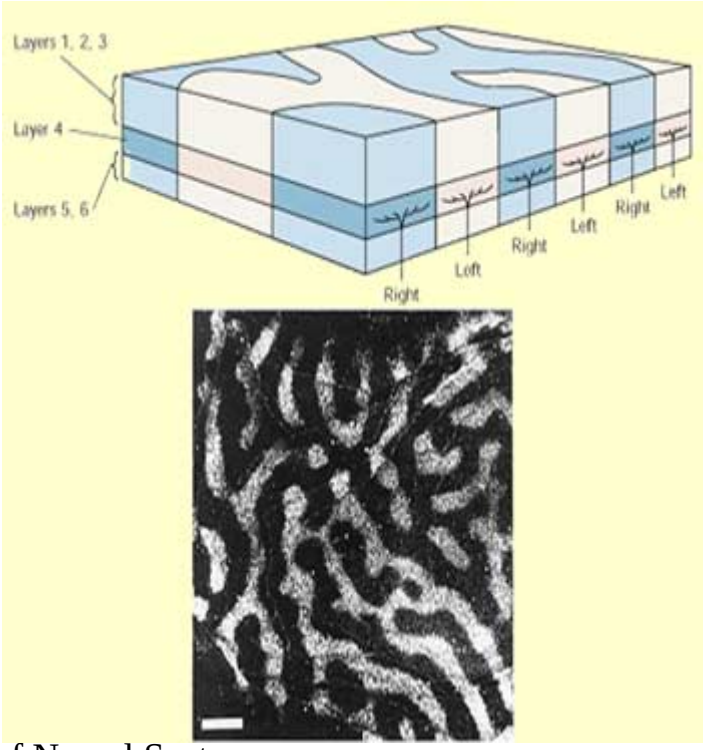
- Most synapses that exhibit LTP also show LTD.
- Hypothesis: the balance between phosphatases and kinases determines potentiation vs. depression.



# Ocular Dominance Formation in Area 17 (V1)

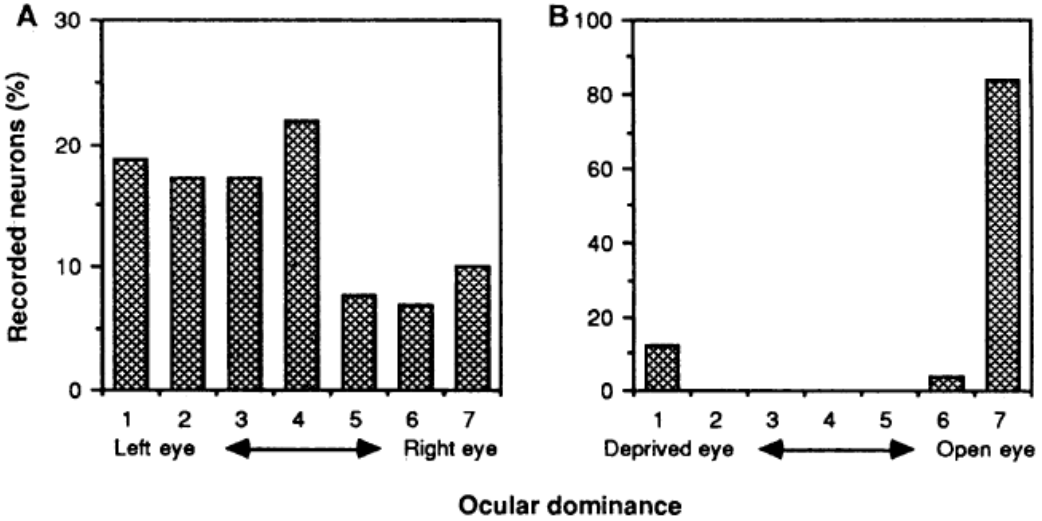
- Most neurons in area 17 show some ocular dominance (OD)
- Critical period for OD formation in kittens: up to 3 months
- OD column formation depends on activity of visual receptors
  - Demonstrated through ocular deprivation experiments
- Also depends on postsynaptic activity; NMDA-dependent



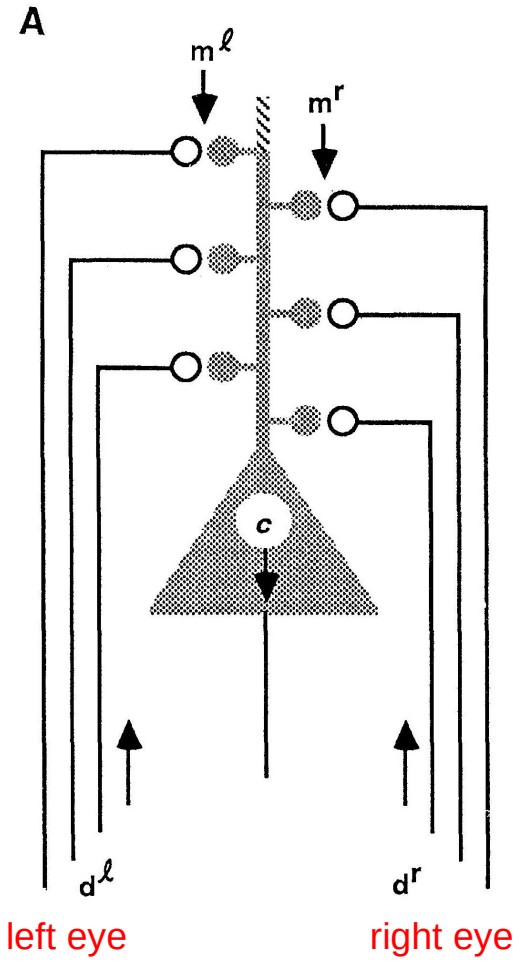
# BCM Rule and Ocular Dominance in Area 17 (V1)

- 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



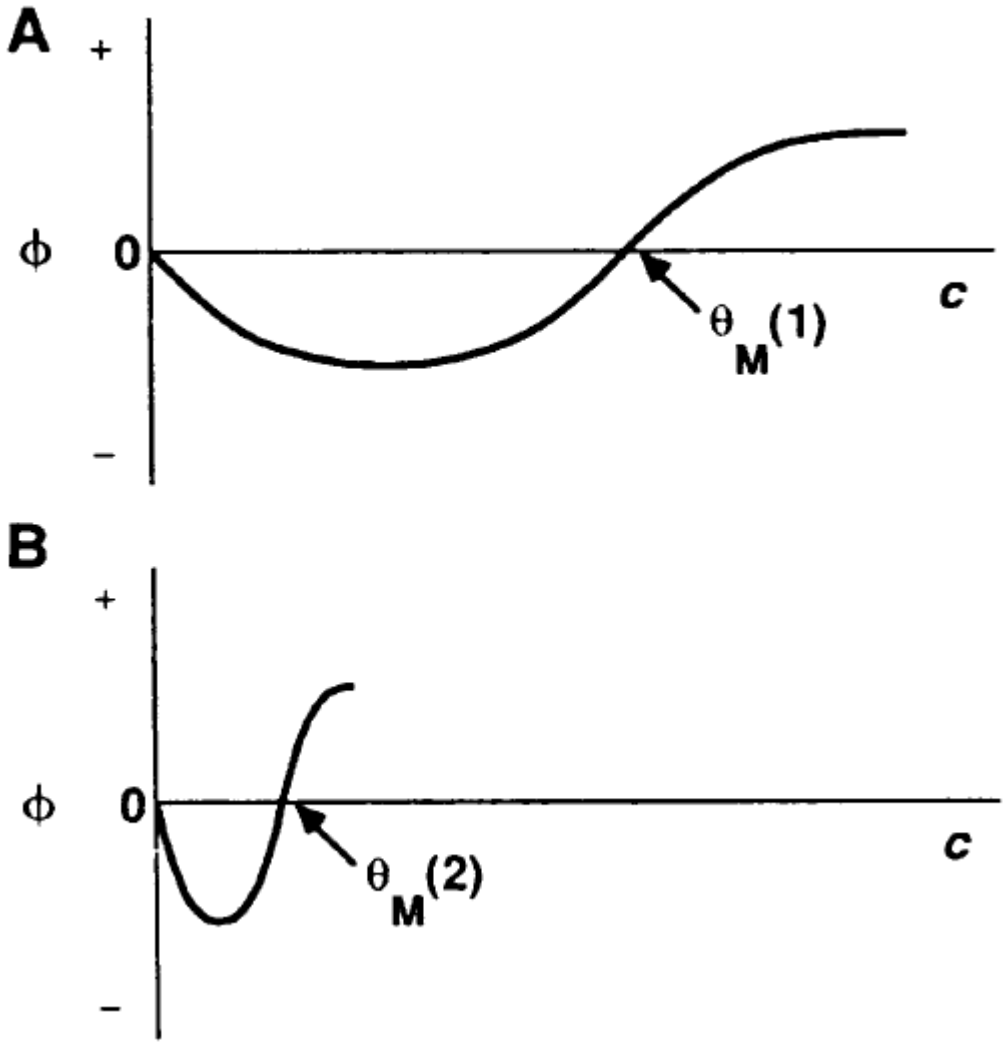

$$c = m^l \cdot d^l + m^r \cdot d^r$$

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

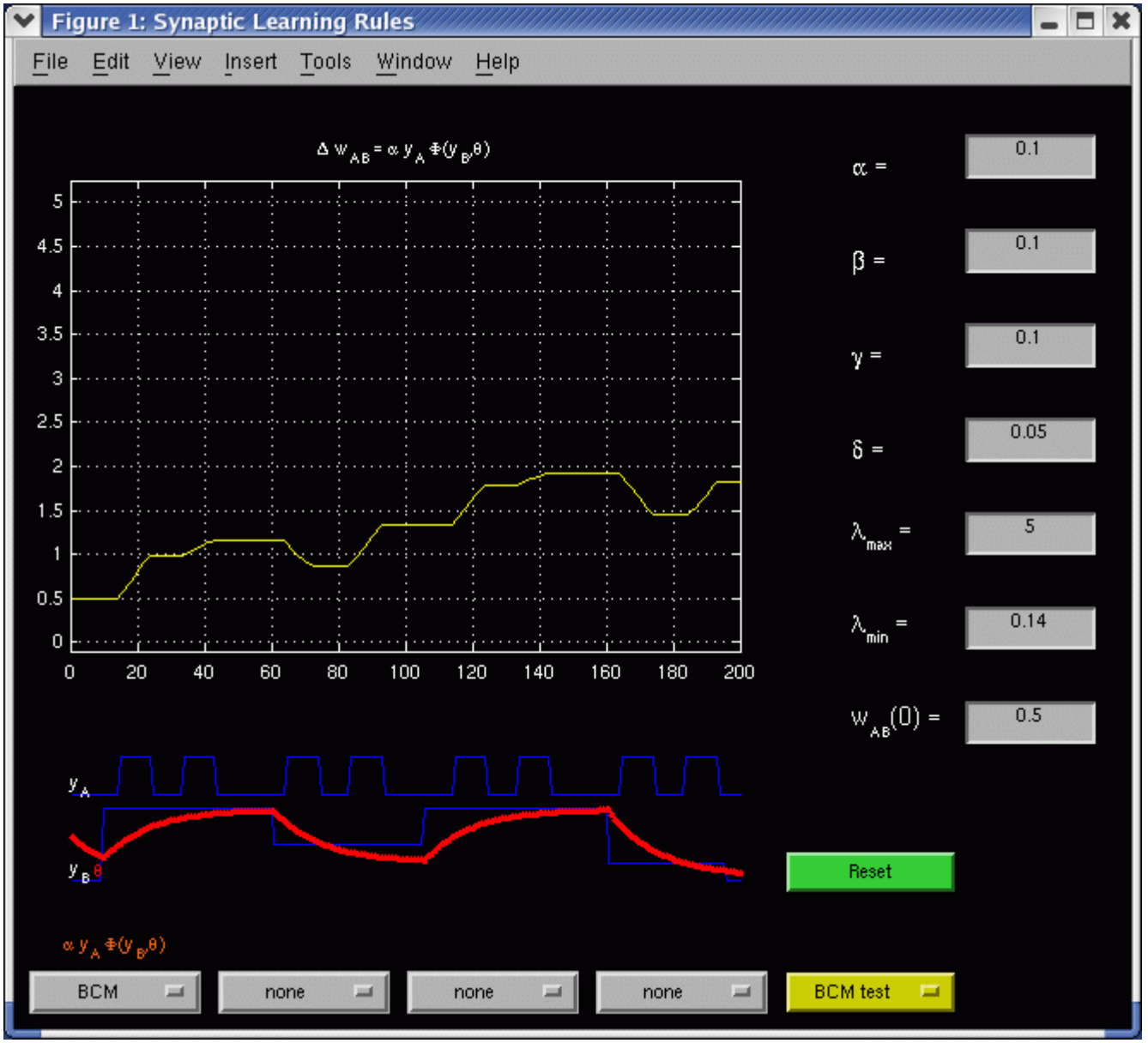
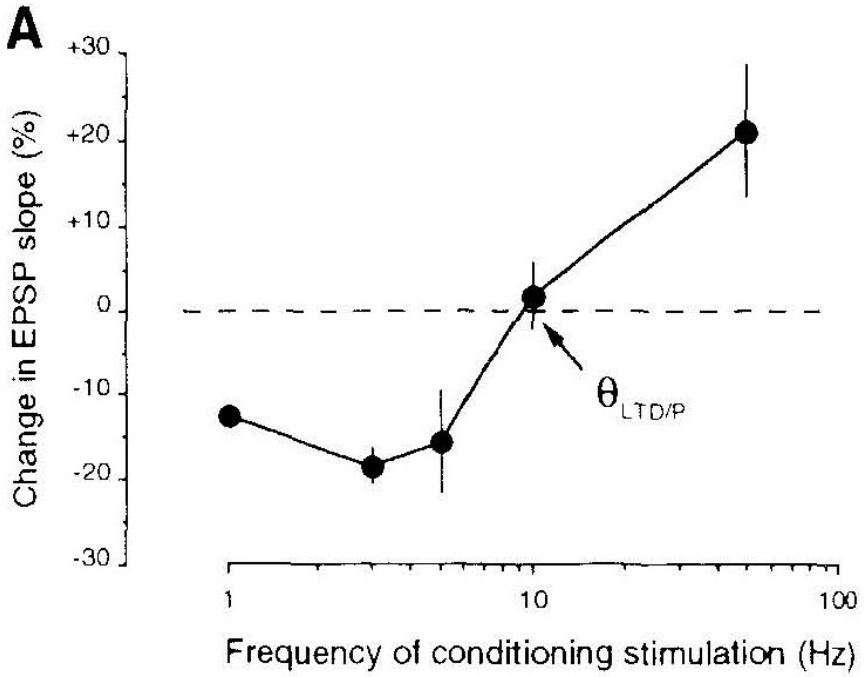
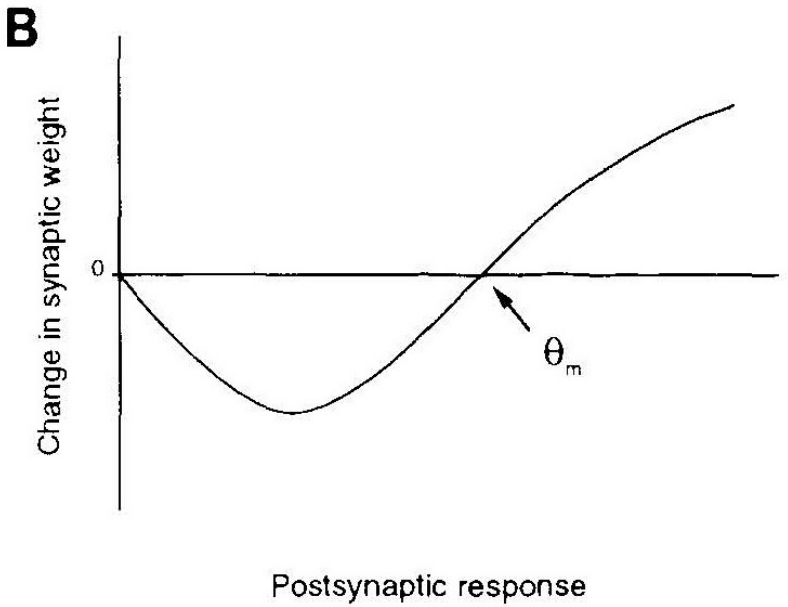


Figure 1: Synaptic Learning Rules
File Edit View Insert Tools Window Help
Δ w_AB = α y_A Φ(y_B,θ)
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0 20 40 60 80 100 120 140 160 180 200
α = 0.1
β = 0.1
γ = 0.1
δ = 0.05
λ_max = 5
λ_min = 0.14
w_AB(0) = 0.5
y_A
y_B θ
Reset
α y_A Φ(y_B,θ)
BCM
none
none
none
BCM test

# BCM Rule Can Cause Increase or Decrease

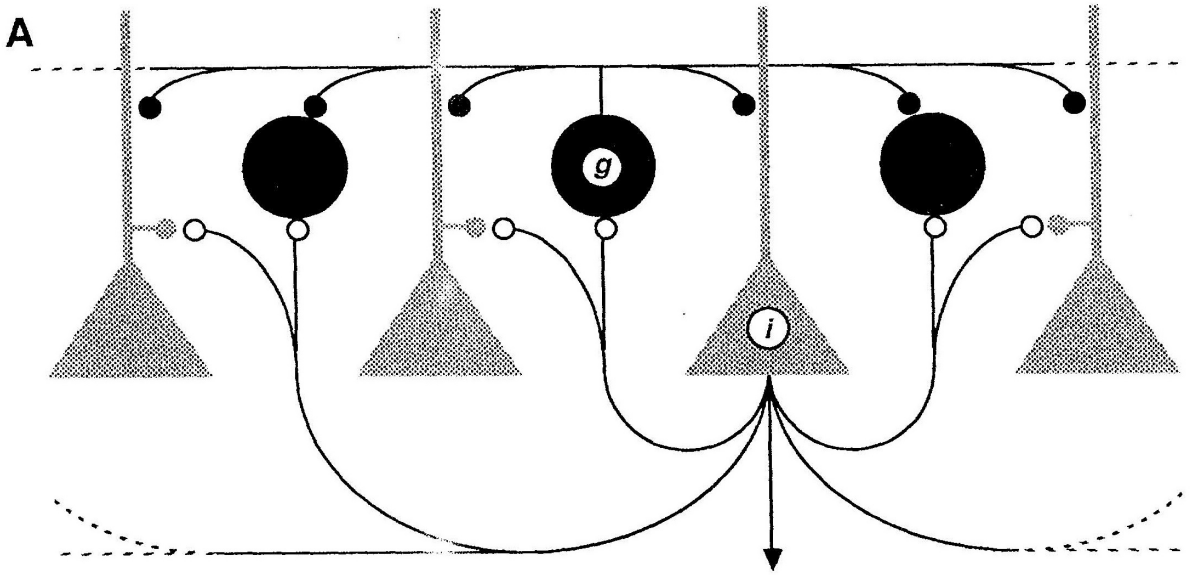



900 pulses delivered
at the frequencies shown

# 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.



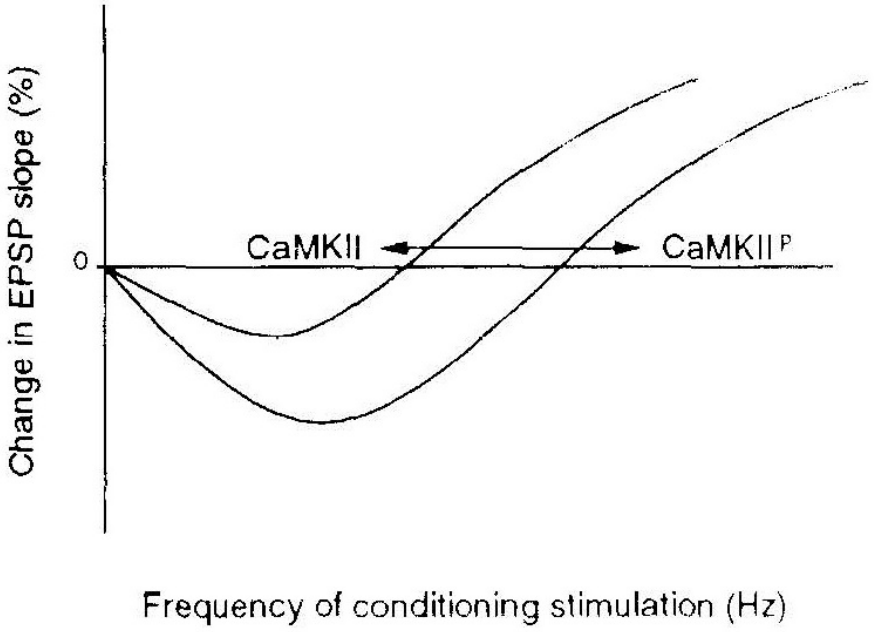

$$c = m^l \cdot d^l + m^r \cdot d^r + \sum L_{ij} c_j$$

# 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 $\theta$ be Altered?

- Could level of CaMKII auto-phosphorylation determine the threshold $\theta_M$?
- Auto-phosphorylation increases the affinity of CaMKII for calmodulin by 1000-fold.
  - Could act as a calmodulin buffer

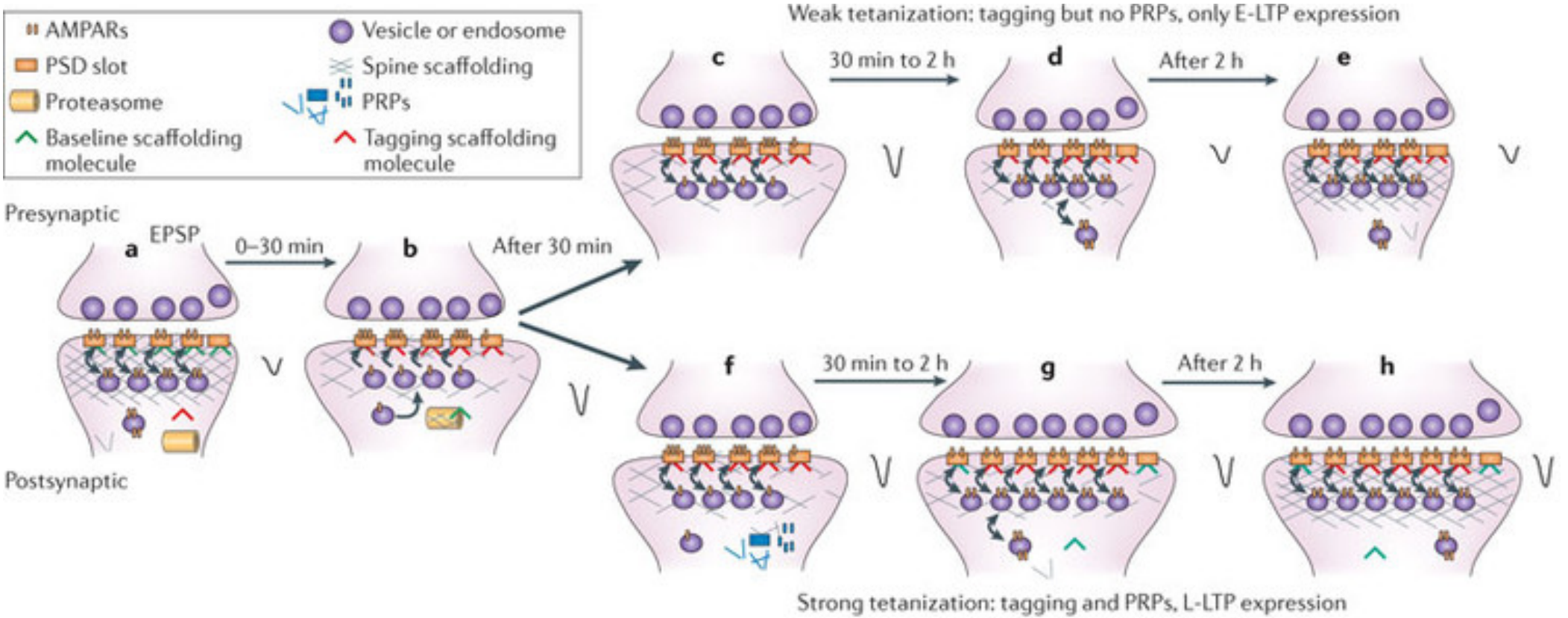


# How Might the Threshold $\theta$ be Altered?

- $\theta_M$ 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?

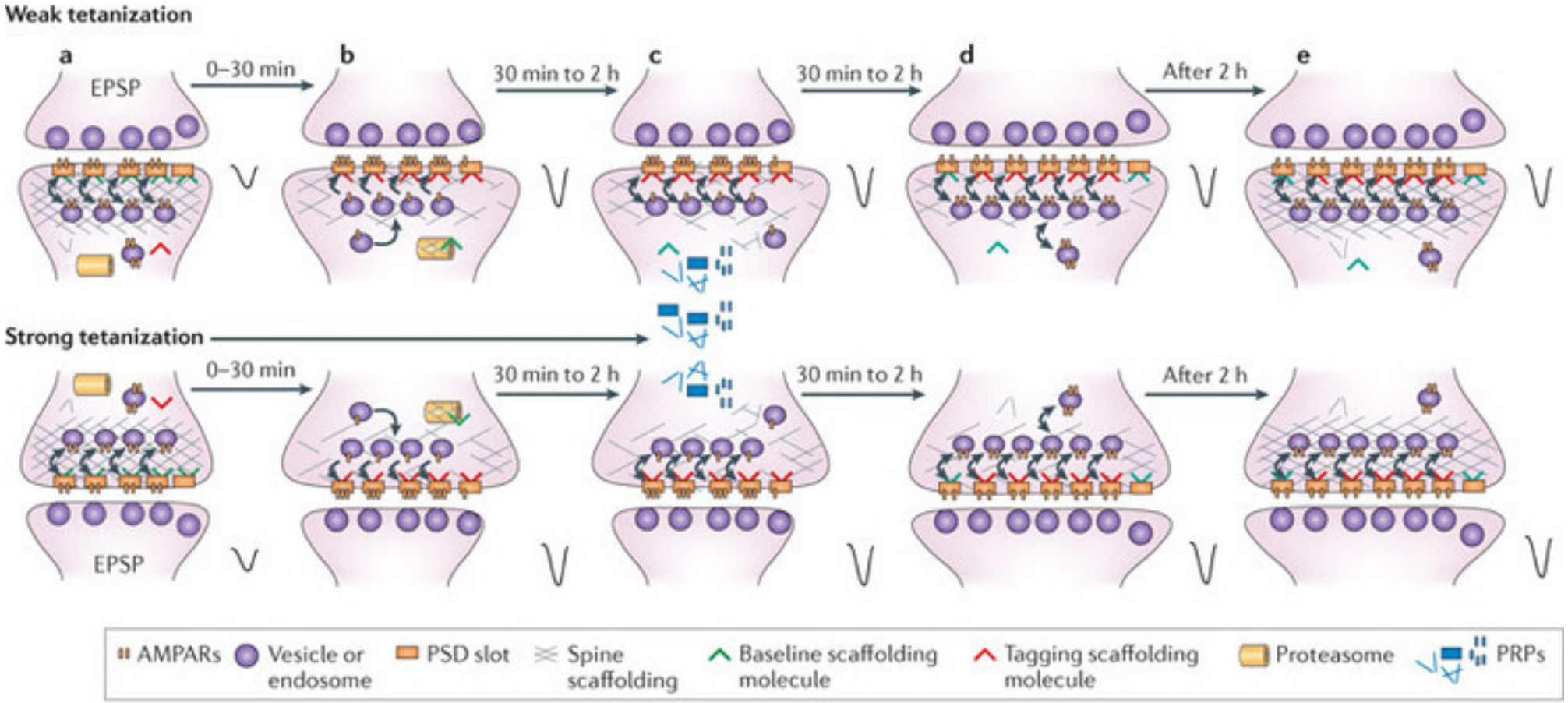



PRP = plasticity-related products
E-LTP = early-stage LTP
L-LTP = late-stage LTP

Nature Reviews | Neuroscience
Redondo & Morris (2011)

# Synaptic Tagging and Capture

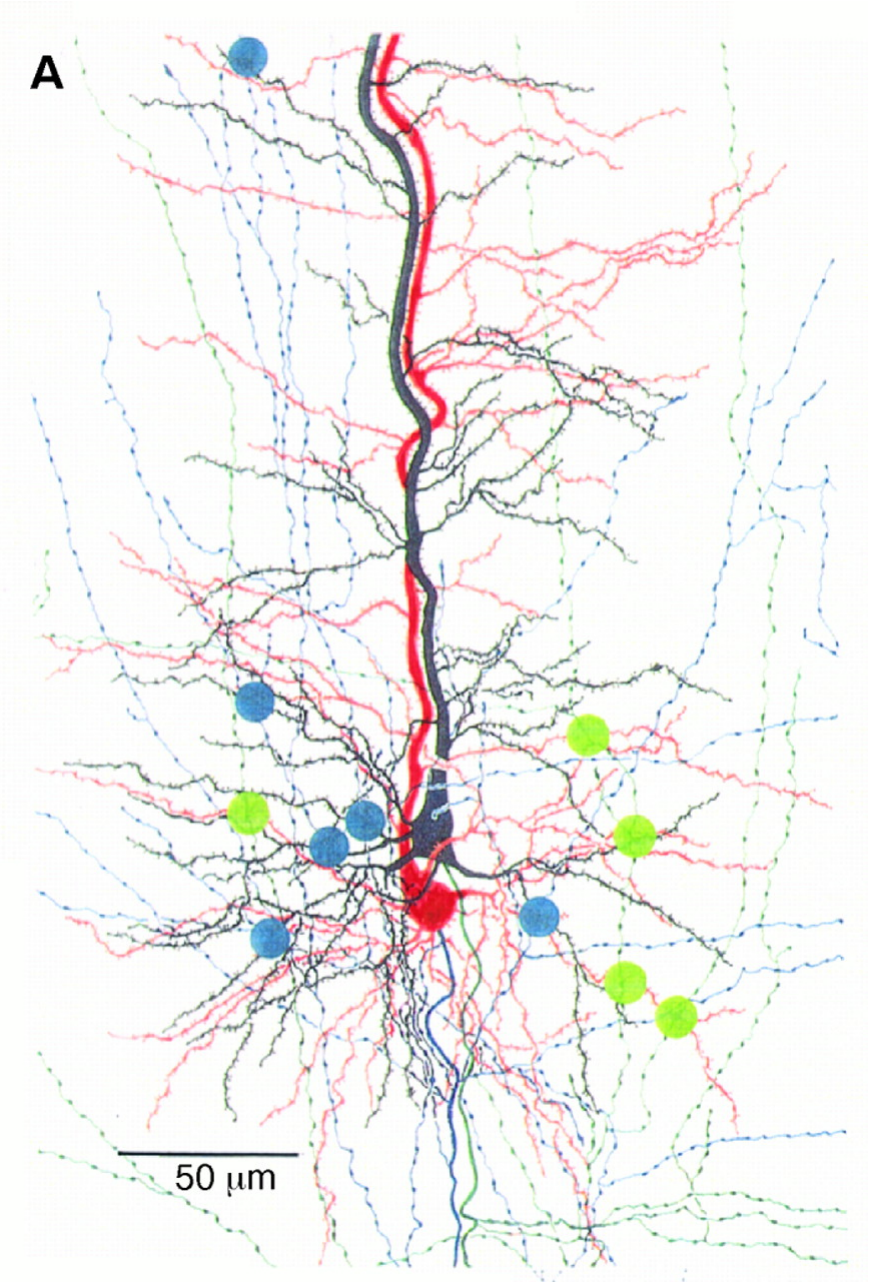
Potentiation of a weakly-stimulated synapse can be rescued by PRPs transported cell-wide as a result of strong stimulation at other synapses.



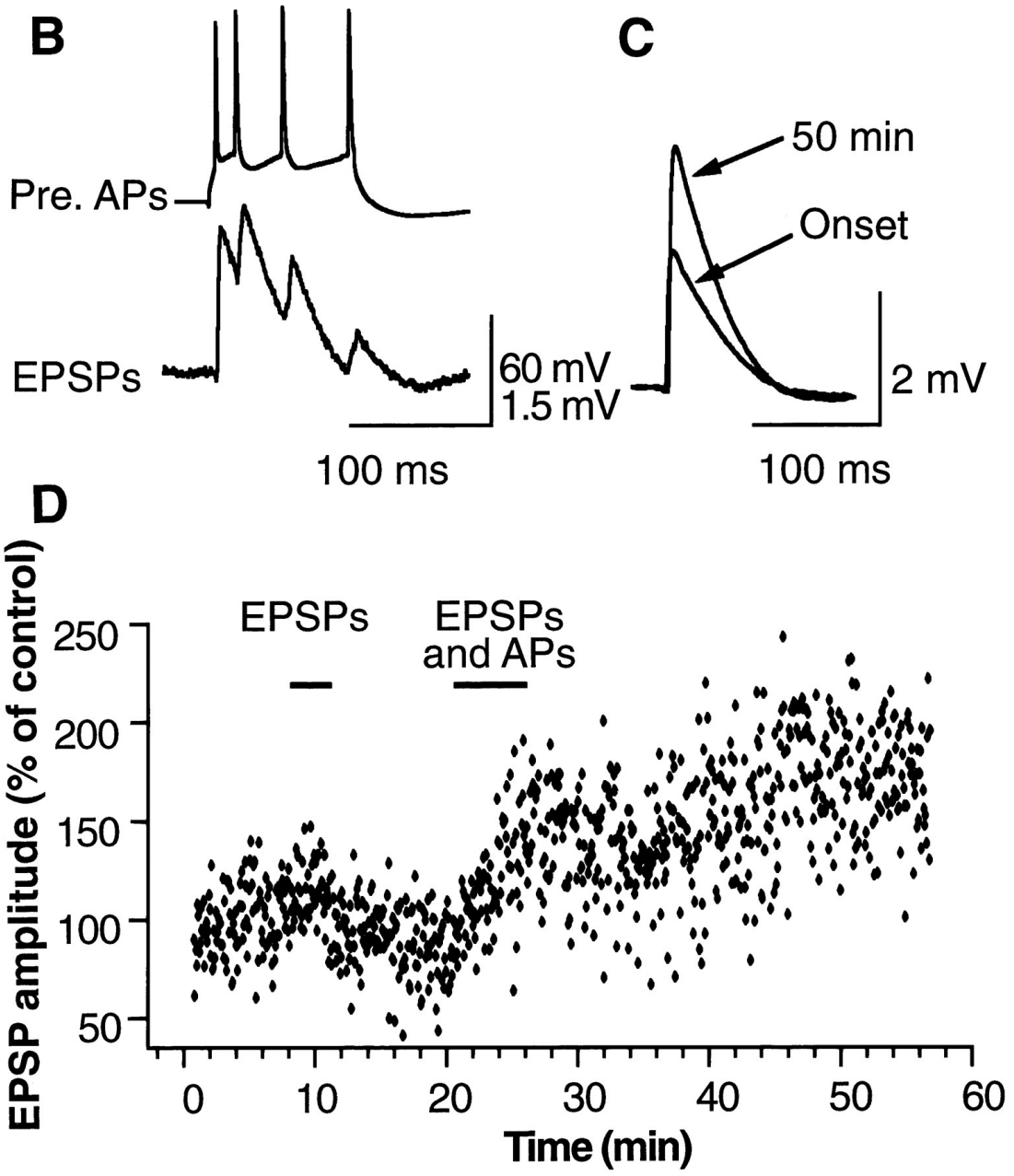

Nature Reviews | Neuroscience
Redondo & Morris (2011)

# 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)



# Spike-Timing-Dependent Plasticity



# Timing Window for STDP