From Science Magazine, 2005

Synaptic Plasticity — Lecture 4

LTP induction

Neuronal Physiology and Plasticity

Aug 2018 Semester

In the previous class…

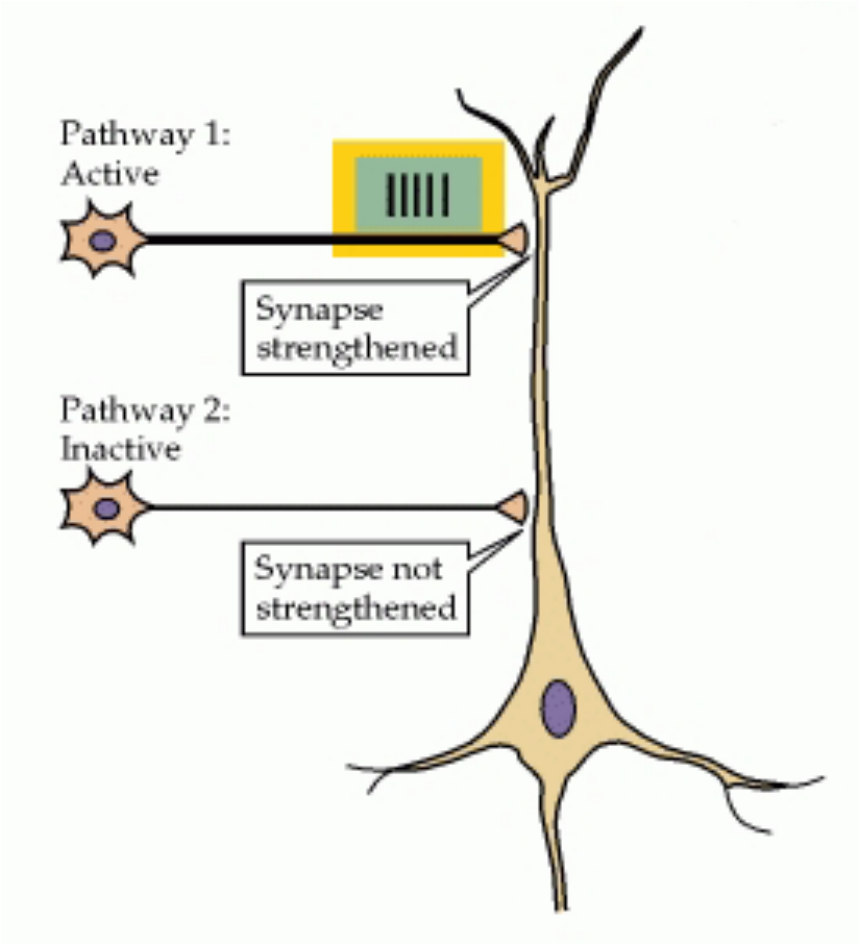
Basic LTP properties

Persistence

Input specificity

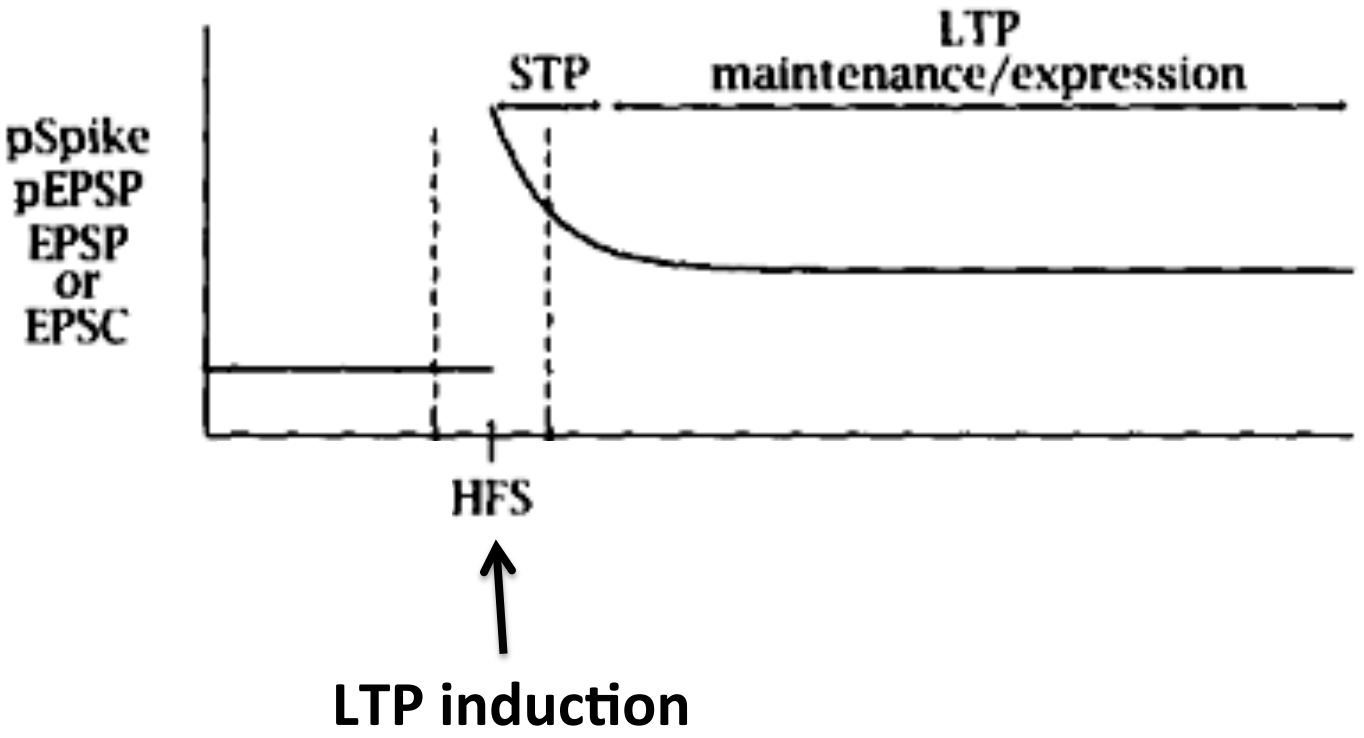
Cooperativity

Associativity



Purves, Neuroscience book

Induction is the point where the plasticity is induced!!!



Johnston and Wu book, 1995

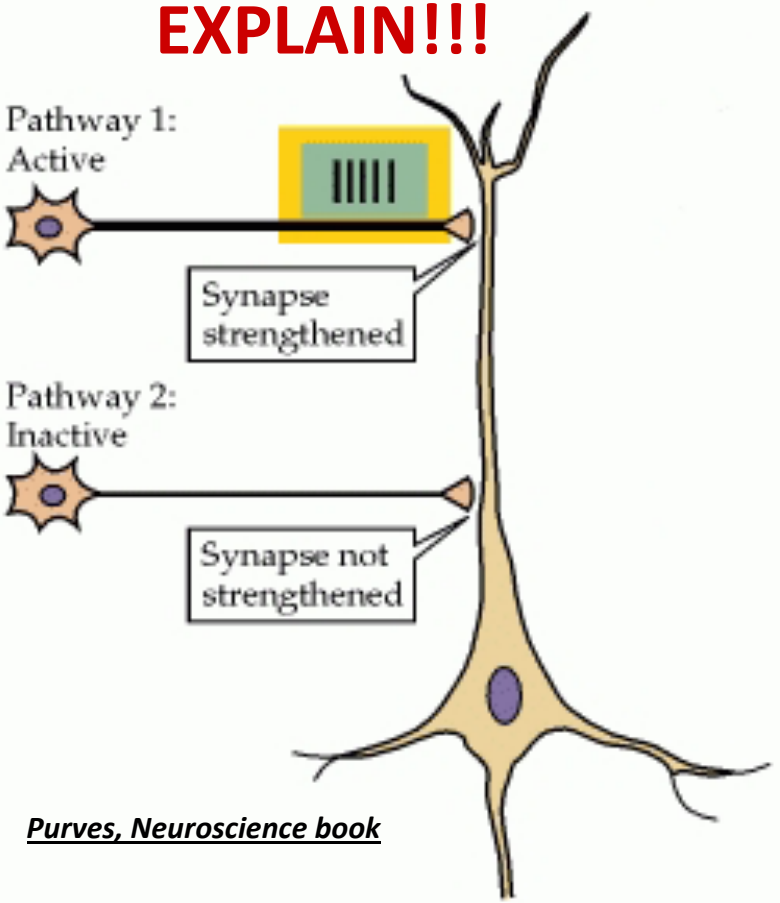
So, what happens at induction, and what drives these properties?

Early (1980's) hypothesis:

— **It is local postsynaptic depolarization!** Potentiation occurs if and only if the synapse is active at a time when the region of the dendrite at which it terminates is sufficiently depolarized

—input specificity, associativity and cooperativity can all be explained under this framework

EXPLAIN!!!



Purves, Neuroscience book

How to test this hypothesis experimentally?

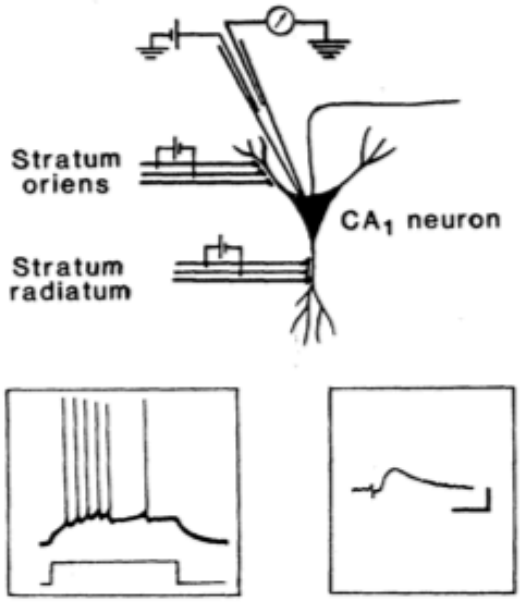
Tetanus is not required, just depolarization during test pulses is sufficient for PTP/LTP!

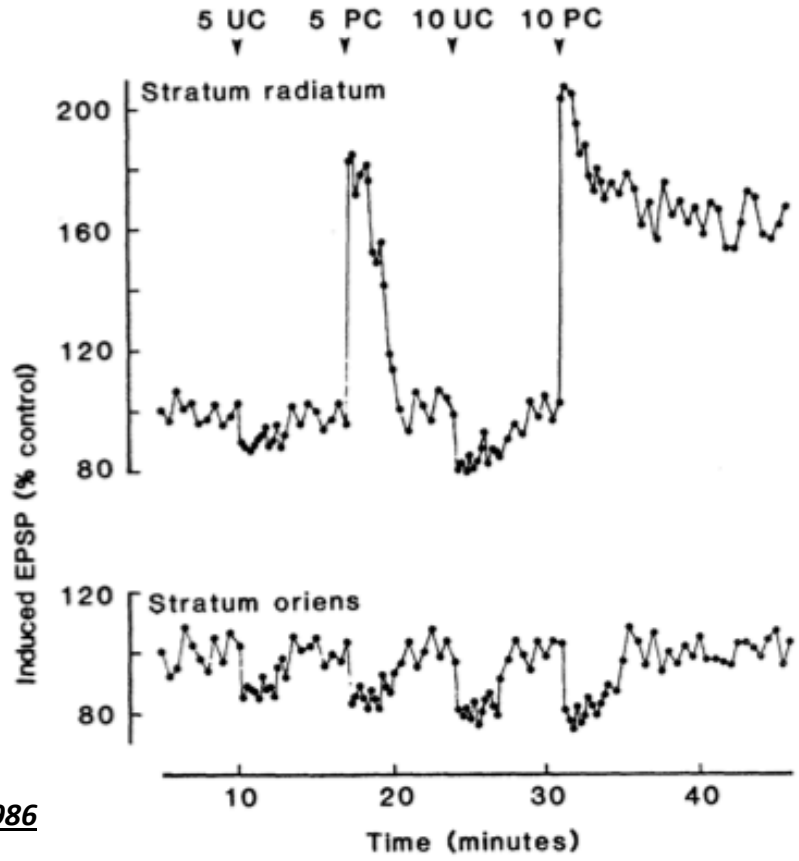
Sufficiency of depolarization + non-tetanic synaptic stimulation for inducing LTP

UC: unpaired conditioning trains
PC: paired conditioning trains

0.2 Hz stimulation!

Conditioning pulse is depolarization occurring before the synaptic stimulation





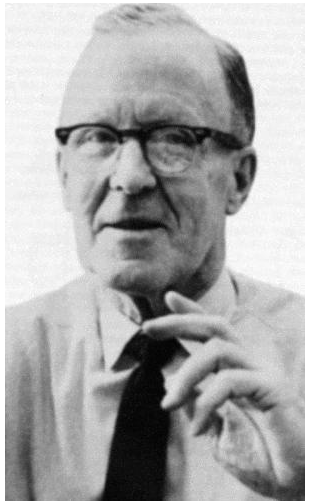
Sastry et al., Science, 1986

Evidence for the necessity of depolarization for LTP was provided by (Malinow and Miller, Nature, 1986), where they injected hyperpolarizing current during tetanus, and got NO LTP!

Hebb's postulate

LTP is a coincidence detector of presynaptic activity and postsynaptic depolarization!

"When an axon of cell A is near enough to excite a cell B and repeatedly and 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, increases."



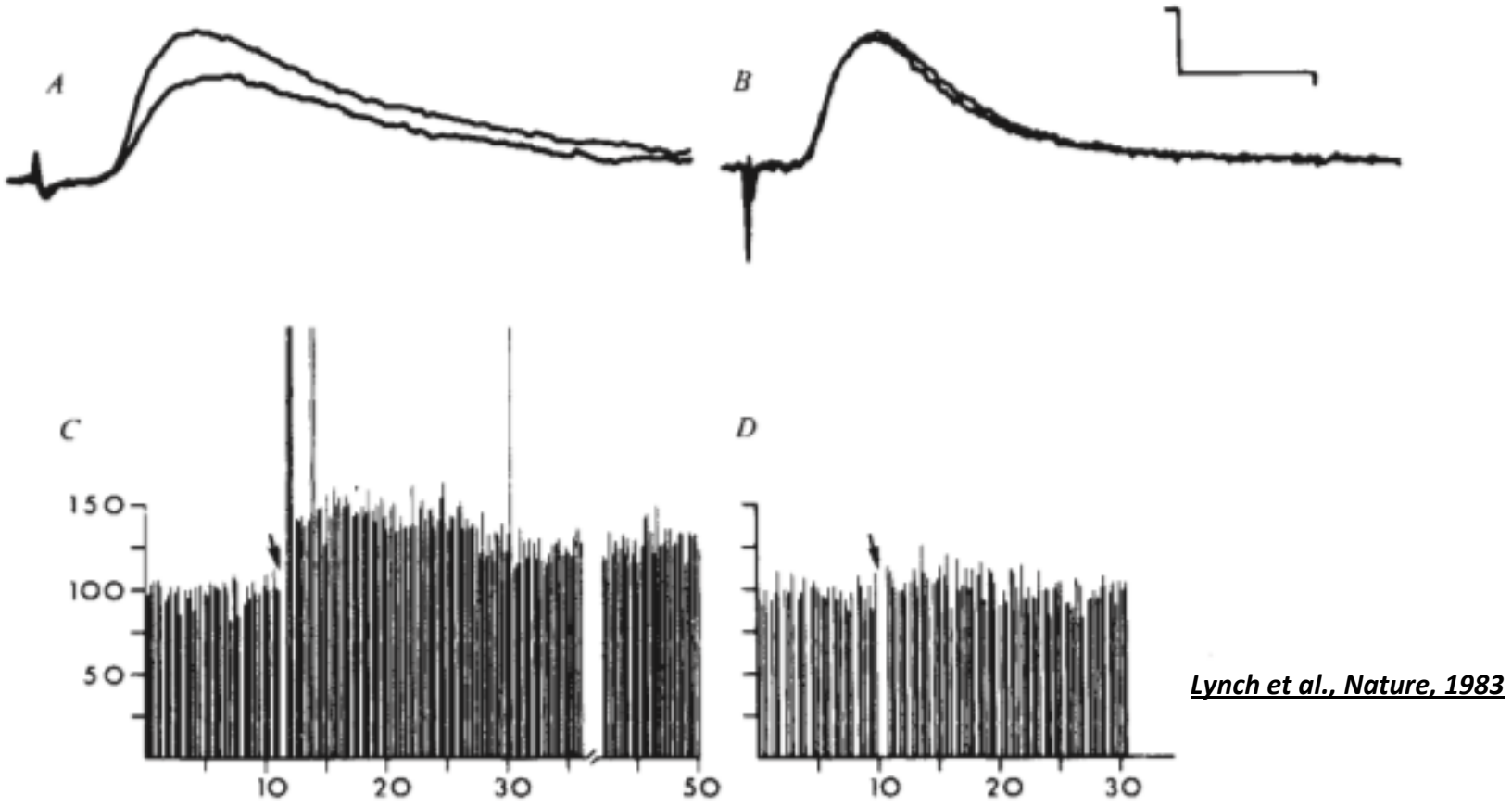
Donald Hebb

With depolarization, you just increase the probability that A fires B!

Requirement 1: Detecting coincidence of pre- and post-synaptic activity

Calcium: The all important ion!!

No EGTA **EGTA in postsynaptic pipette**

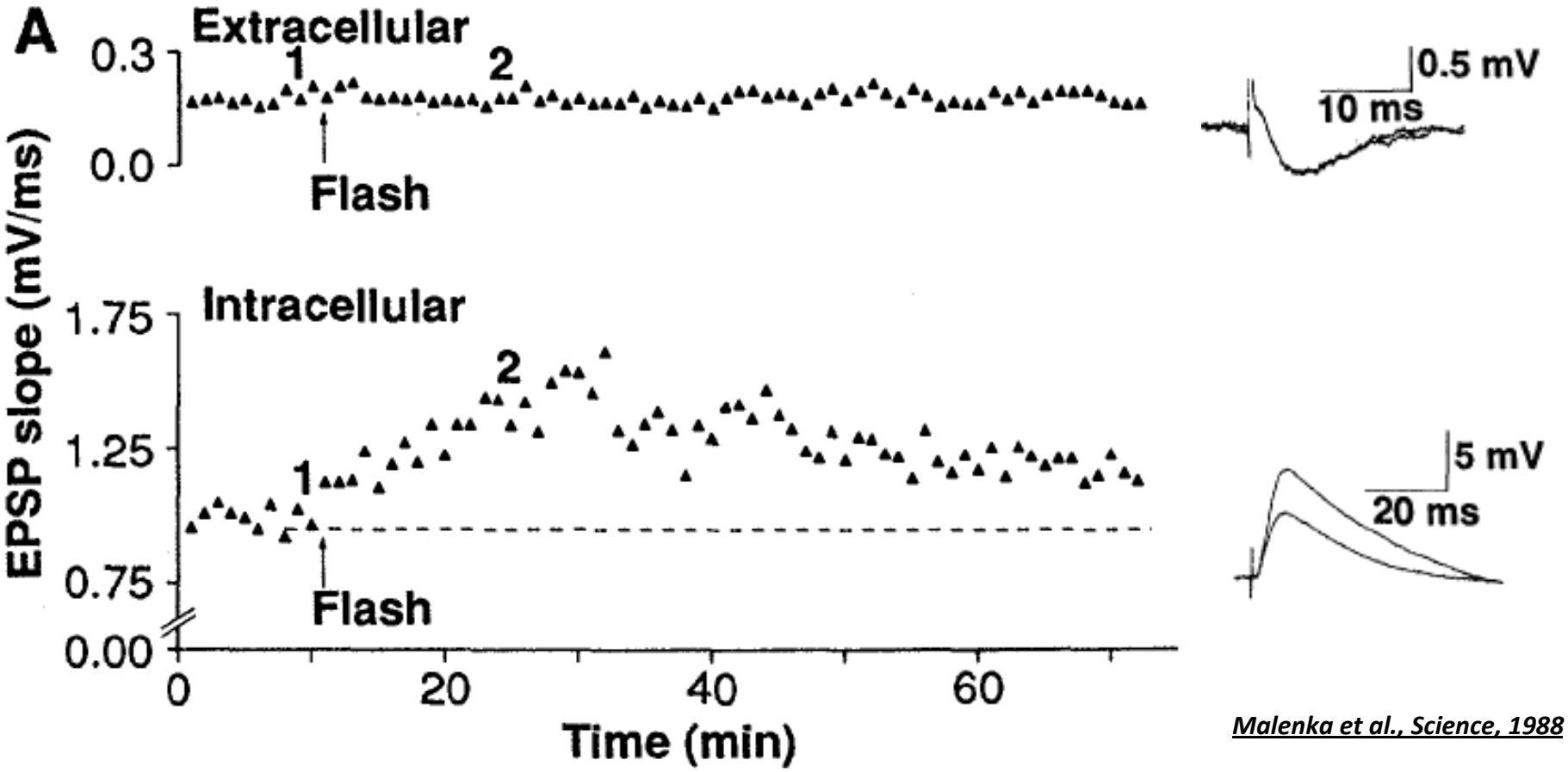


Lynch et al., Nature, 1983

Postsynaptic calcium elevation is **necessary** for LTP induction!

Postsynaptic calcium elevation is sufficient to induce LTP

Nitr5 is present postsynaptically, and releases free calcium on UV Photolysis

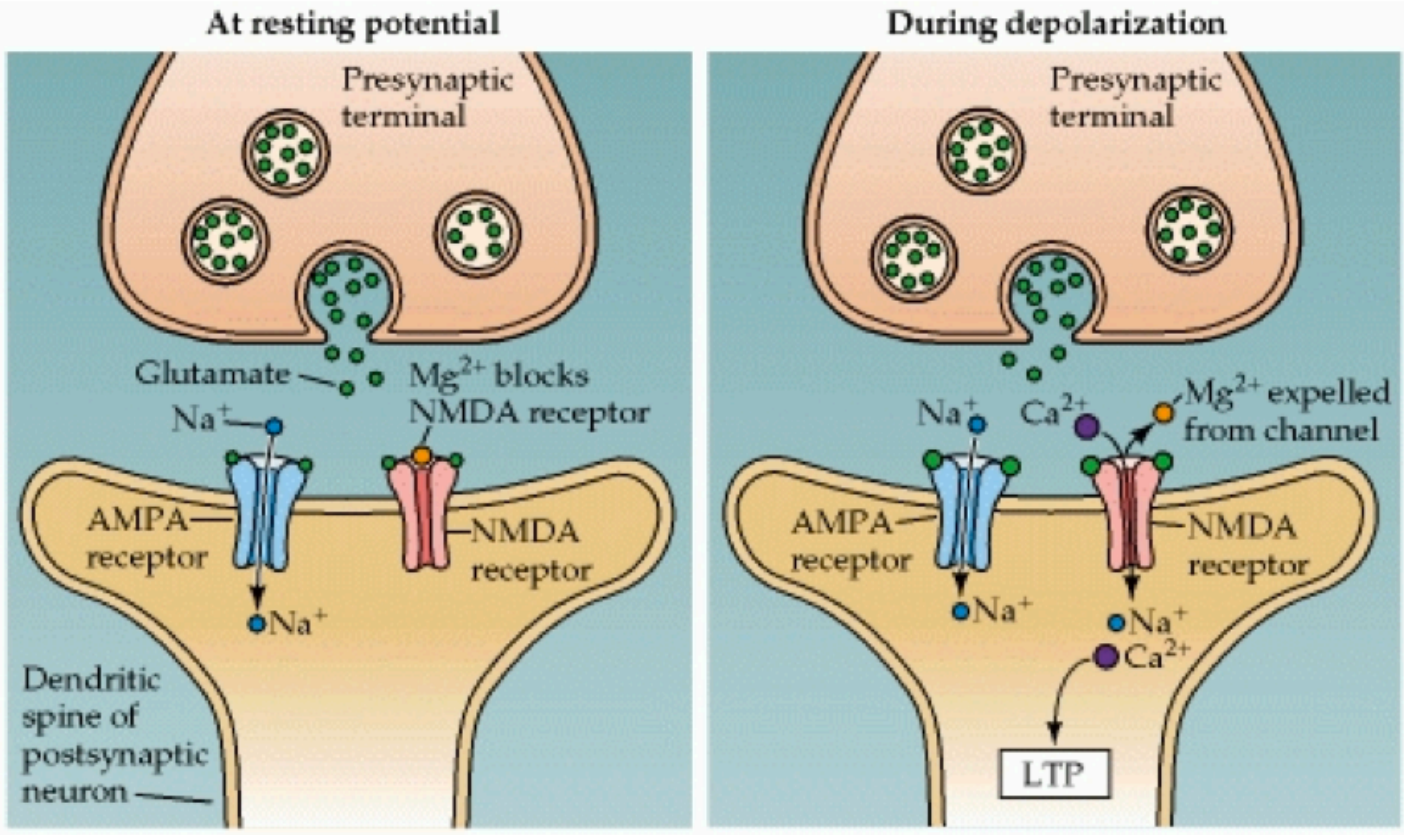


Malenka et al., Science, 1988

Requirement 2: Elevation in postsynaptic calcium

Wish list!

A coincidence detector of pre- and post-synaptic activity that would let calcium in when it detects coincidence!

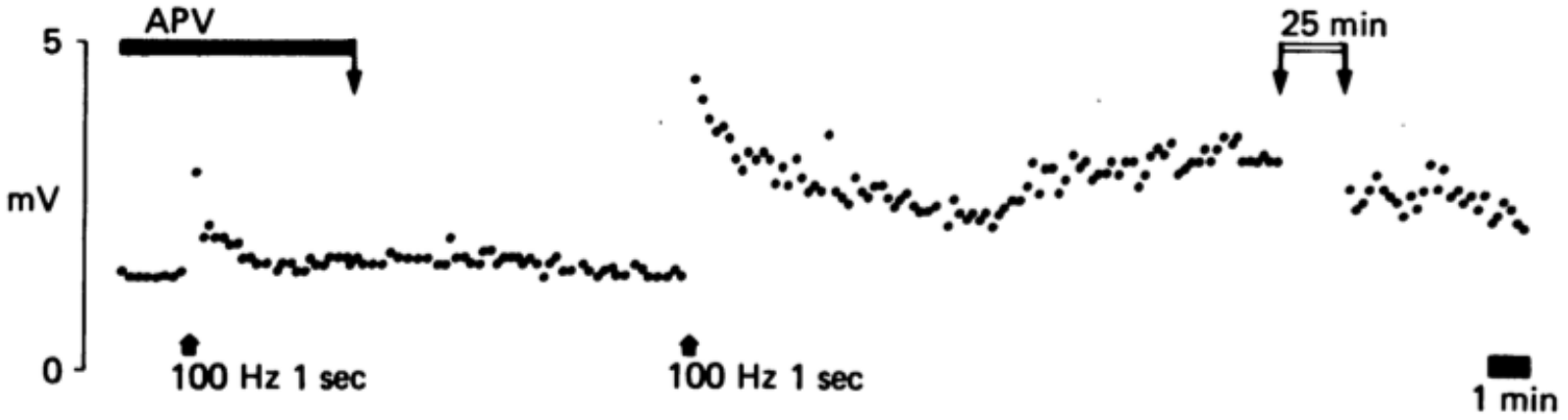


Purves, Neuroscience Book

"NMDAR is Hebb Molecule"

How do you test the link between NMDAR and LTP?

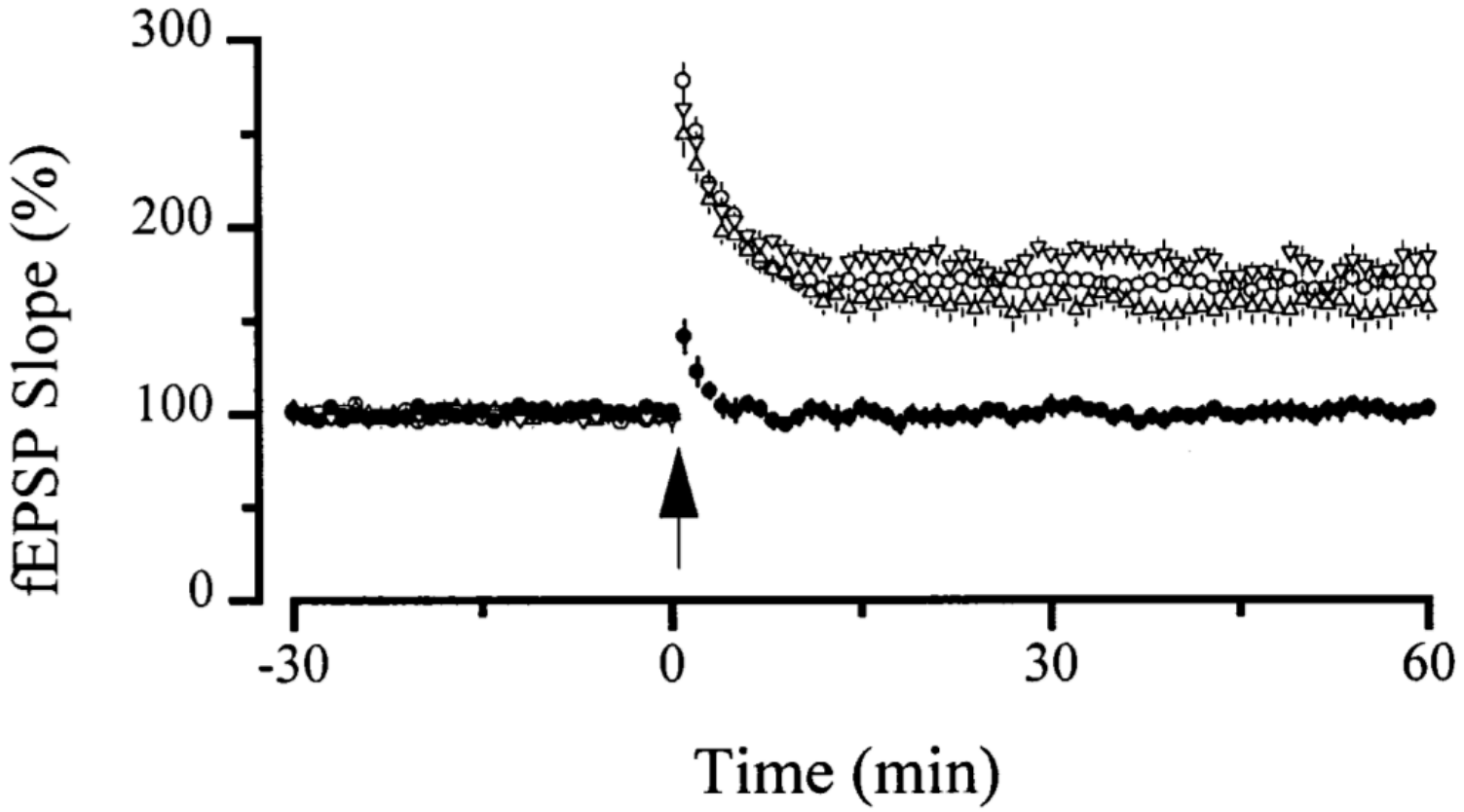
Necessity: Pharmacological agents



Collingridge et al., J. Physiology, 1983

How do you test the link between NMDAR and LTP?

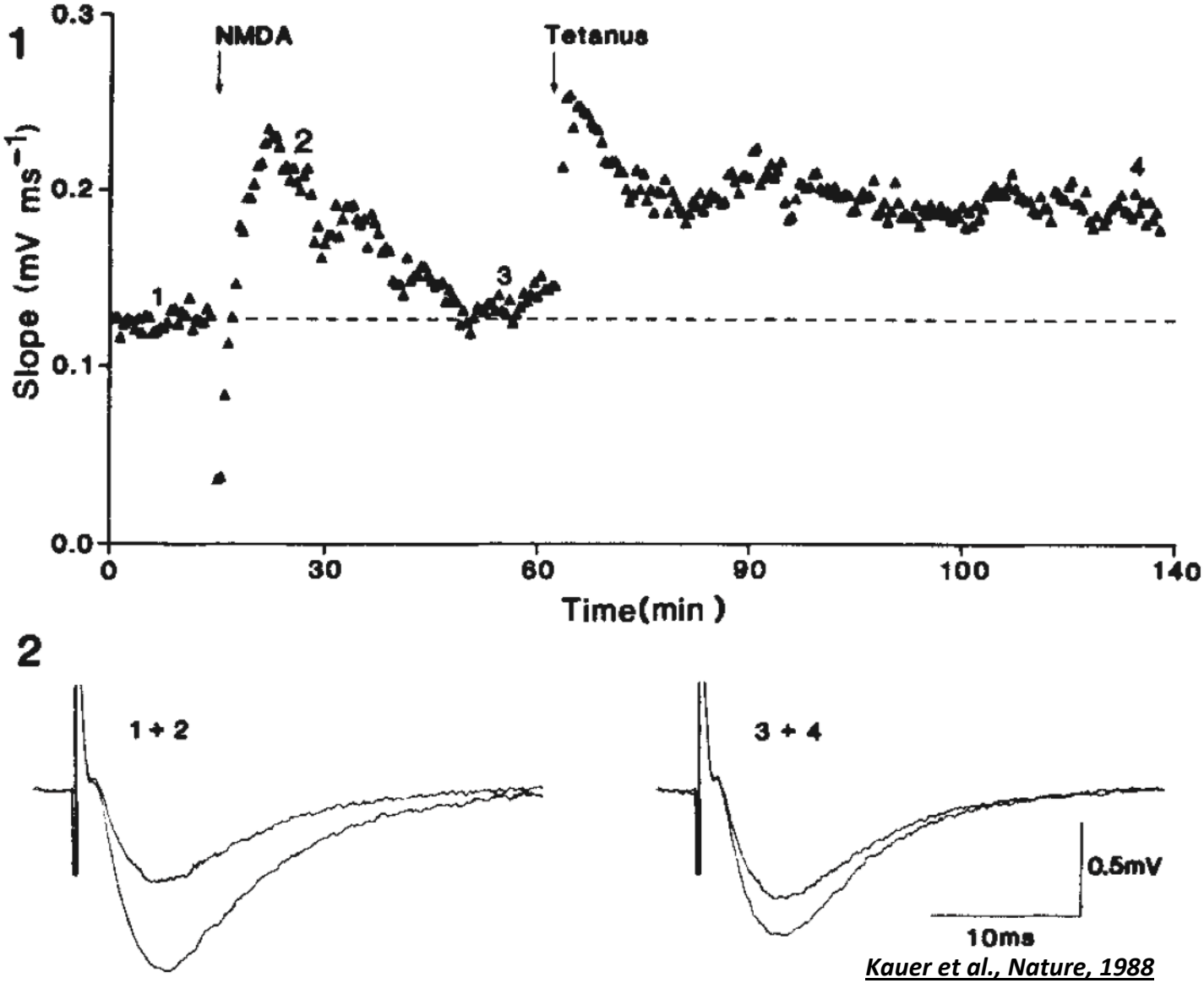
Necessity: Gene knockout



Tsien et al., Cell, 1996

How do you test the link between NMDAR and LTP?

Sufficiency?



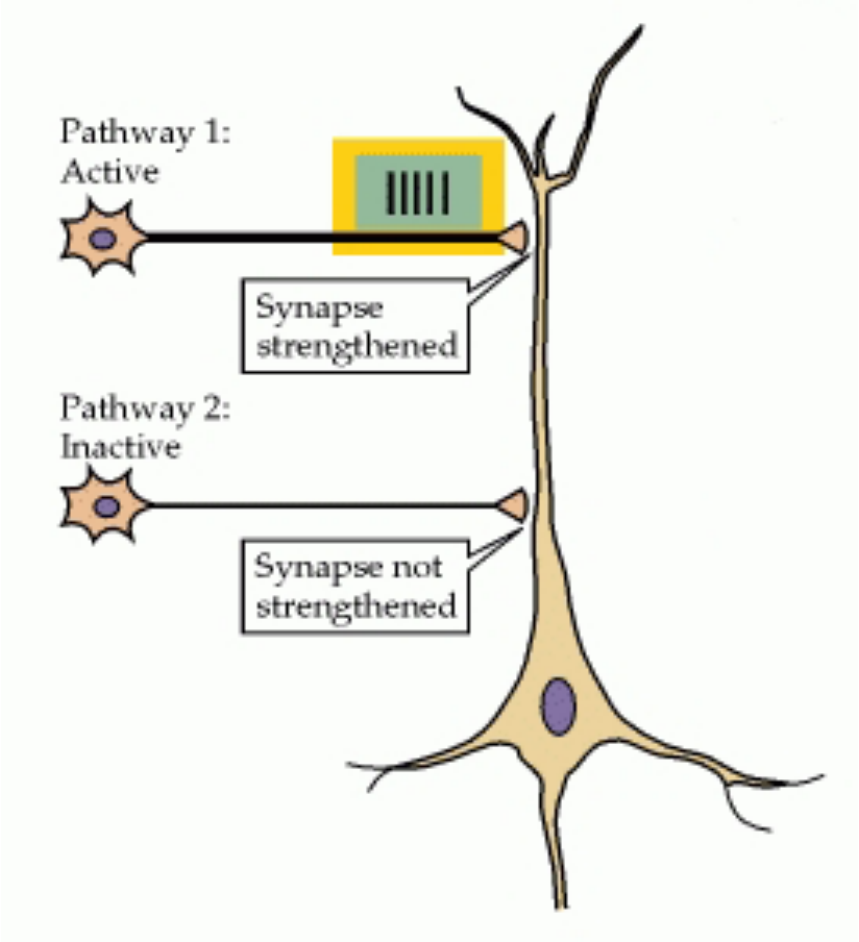
Kauer et al., Nature, 1988

Explain in terms of NMDAR activation

Input specificity

Cooperativity

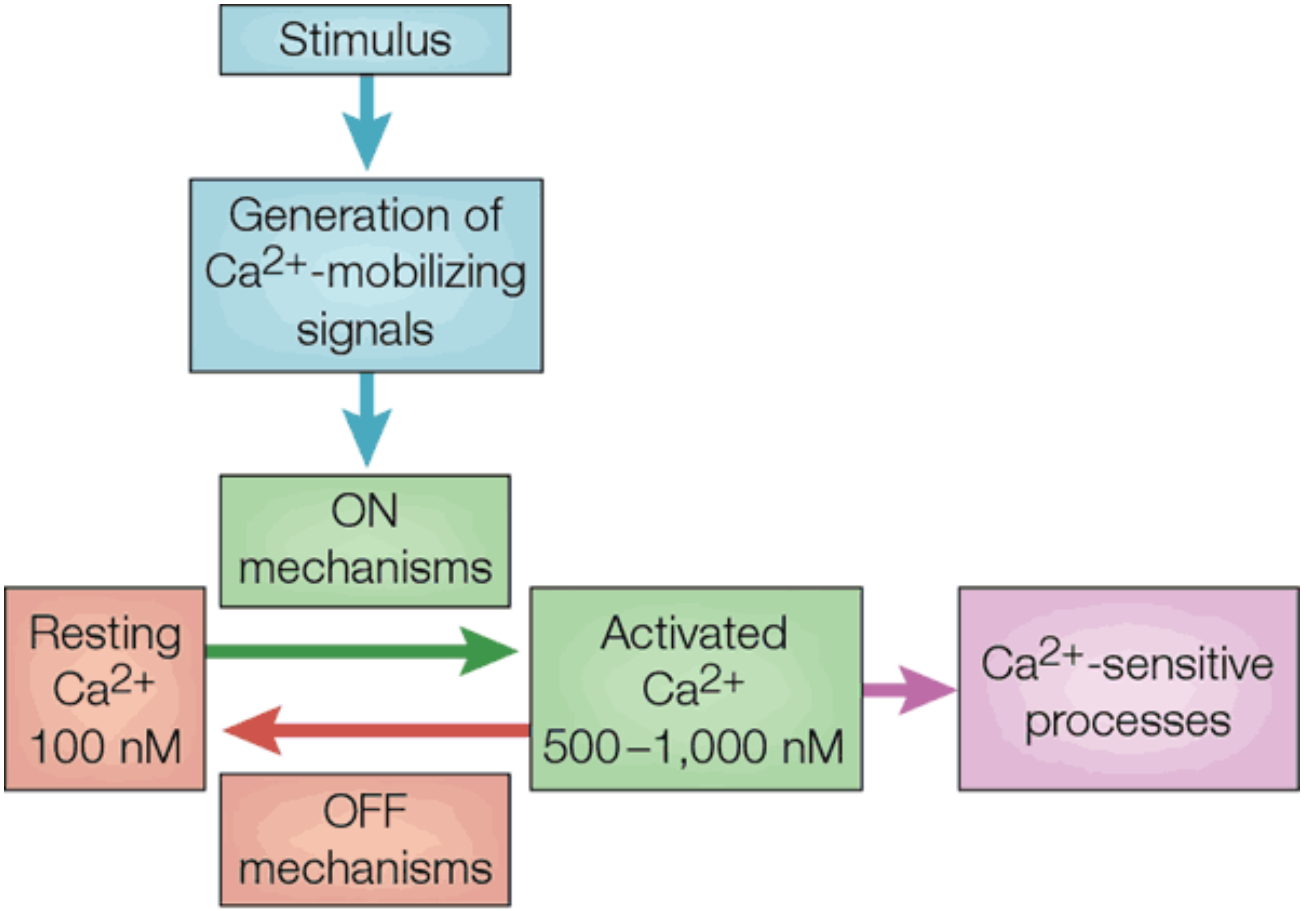
Associativity



Purves, Neuroscience book

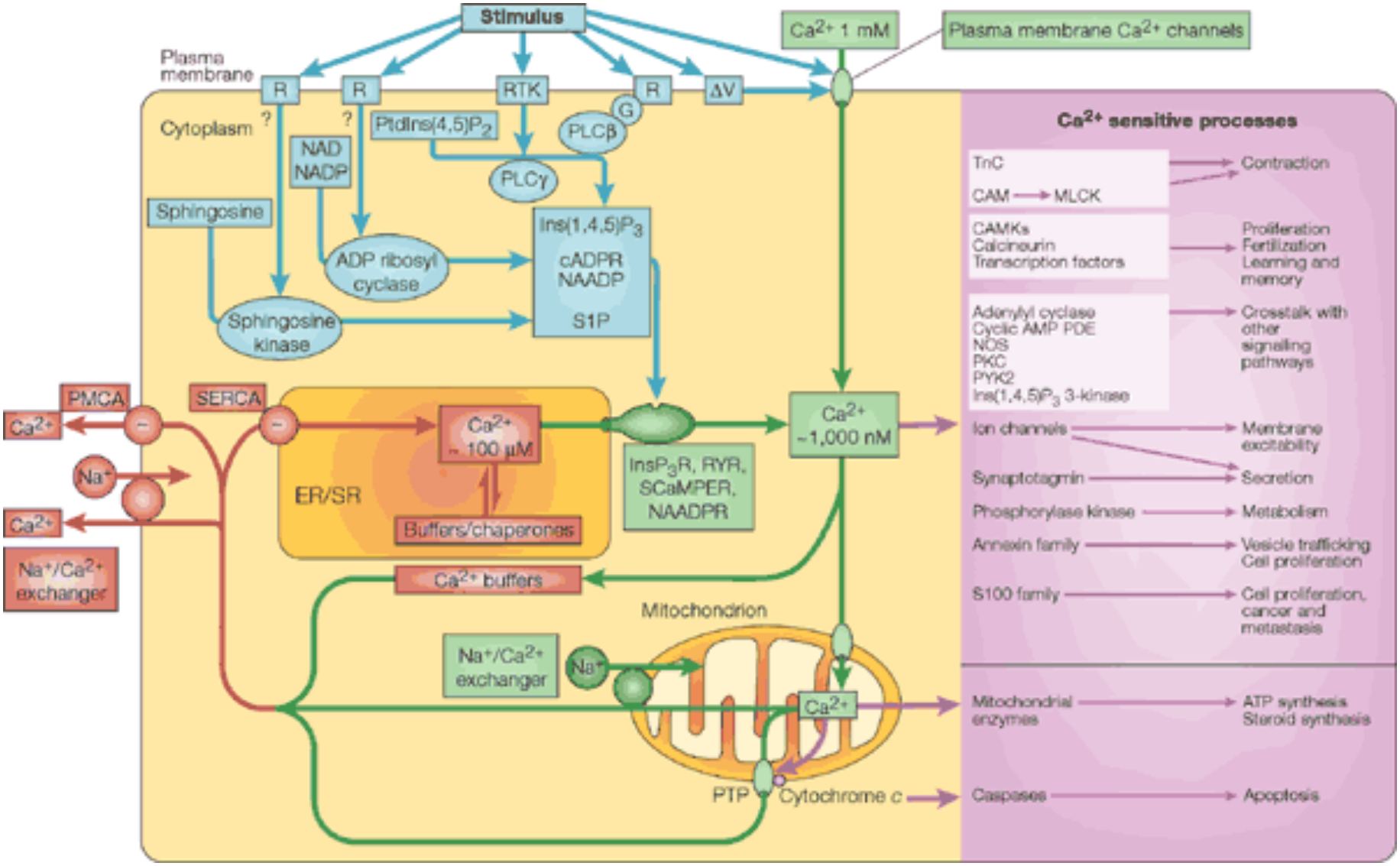
Are NMDA receptors the only possible calcium source for induction of LTP?

Calcium is a very tightly regulated intracellular messenger



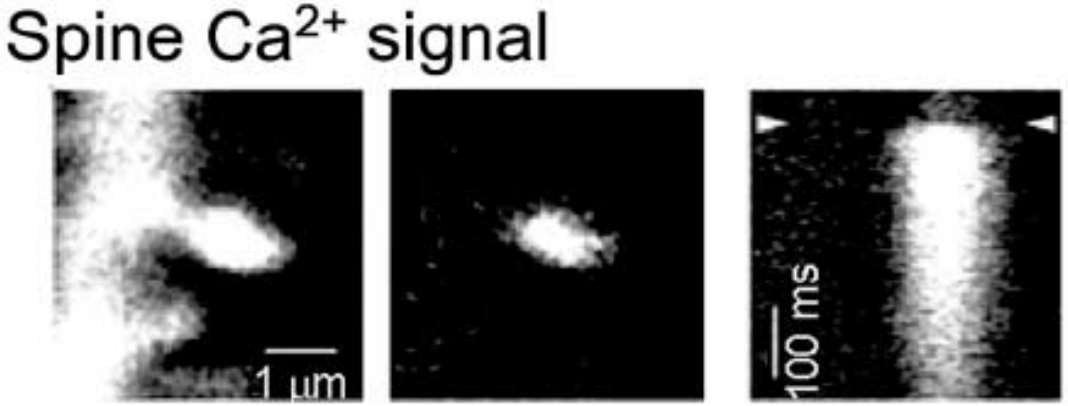
Berridge et al., Nature Reviews Molecular Cell Biology (2000)

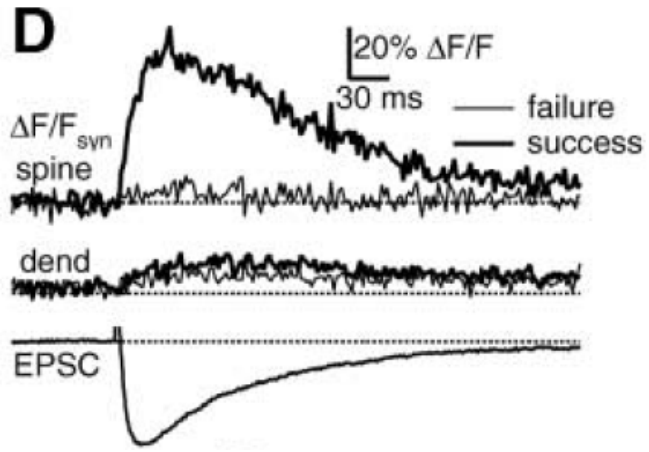
The multiple ON and OFF mechanisms



Berridge et al., Nature Reviews Molecular Cell Biology (2000)

Synaptically evoked calcium signals are localized





Sabatini et al., Neuron, 2002

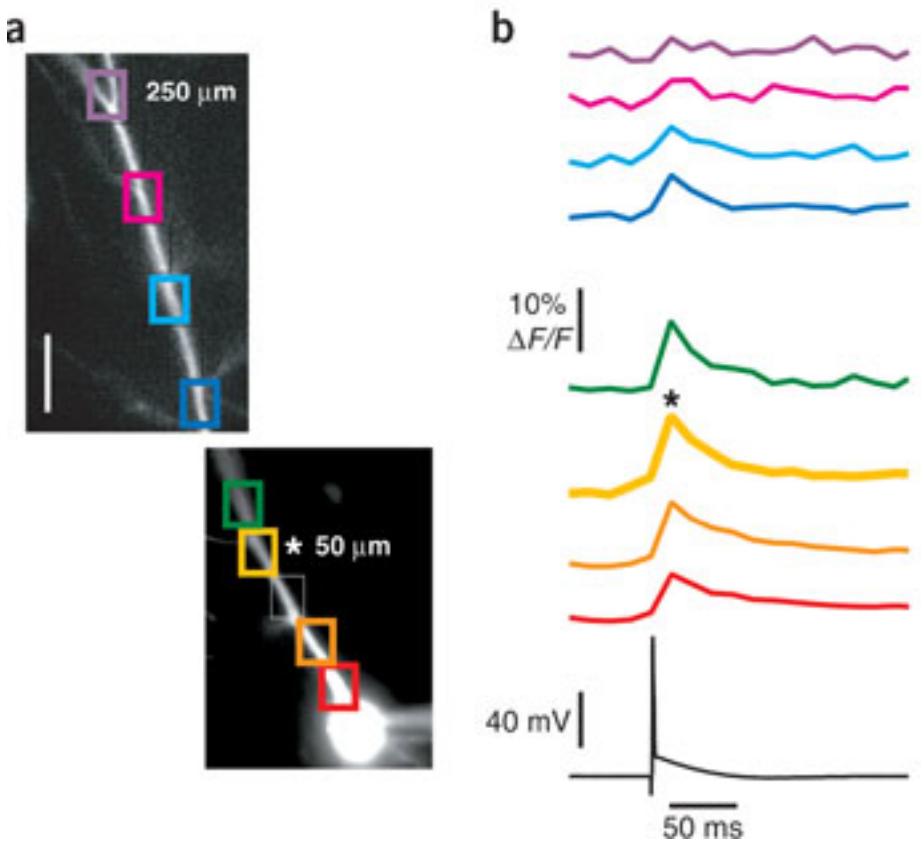
Ca^{2+} (un)certainty principles.

Introducing a Ca^{2+} indicator distorts the amplitude, time course and spread of [Ca^{2+}] signals because they compete to bind calcium and their diffusion is different

For more info, see (Sabatini et al., Current Opinion Neurobiology, 2001), (Yasuda et al., Science STKE, 2004) and (Higley and Sabatini, CSHL Persp. Biol., 2012)

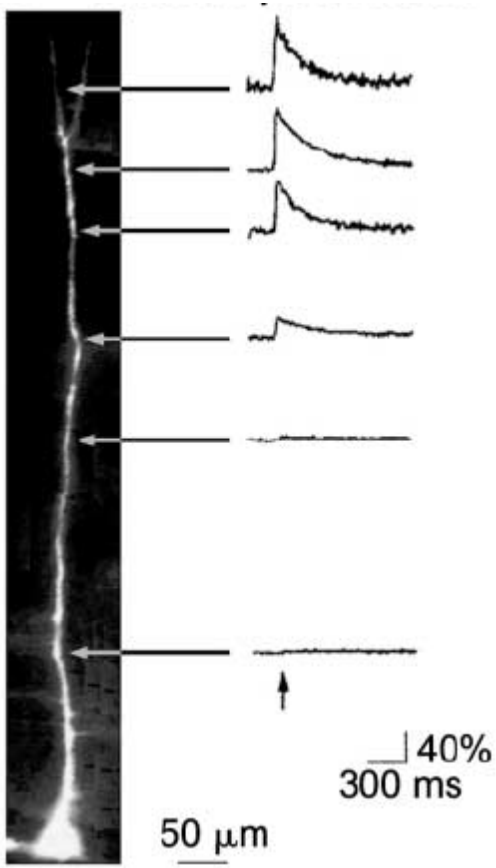
Spike-evoked calcium transients spread

Backpropagating action potential



Frick et al., Nat. Neurosci., 2004

Dendritic spikes

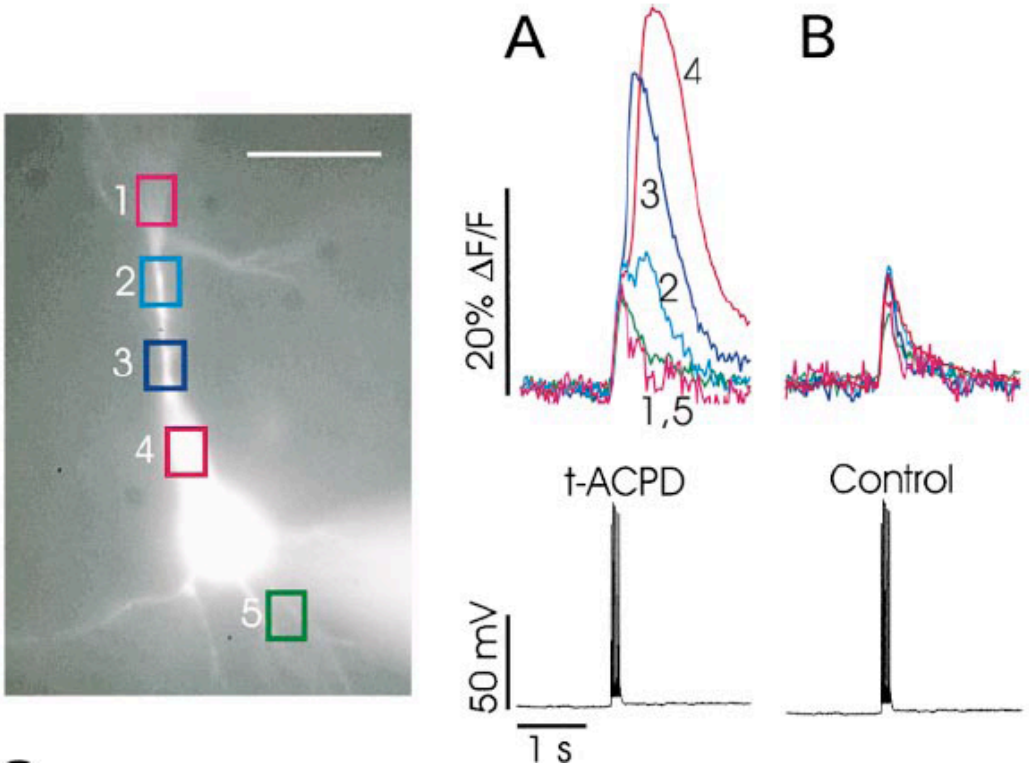


Schiller et al., J Phys., 1997

Calcium influx is largely due to voltage gated calcium channels on the dendritic membrane opened with depolarization induced by action potentials (see Miyakawa et al., Neuron, 1992)

Intracellular waves can be initiated with calcium release from the endoplasmic reticulum

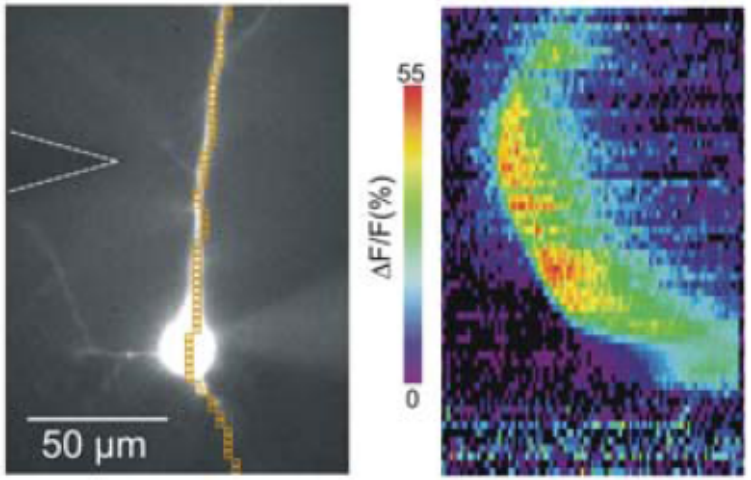
bAP in the presence of mGluR agonists



Nakamura et al., Neuron, 1999

Synaptic stimulation

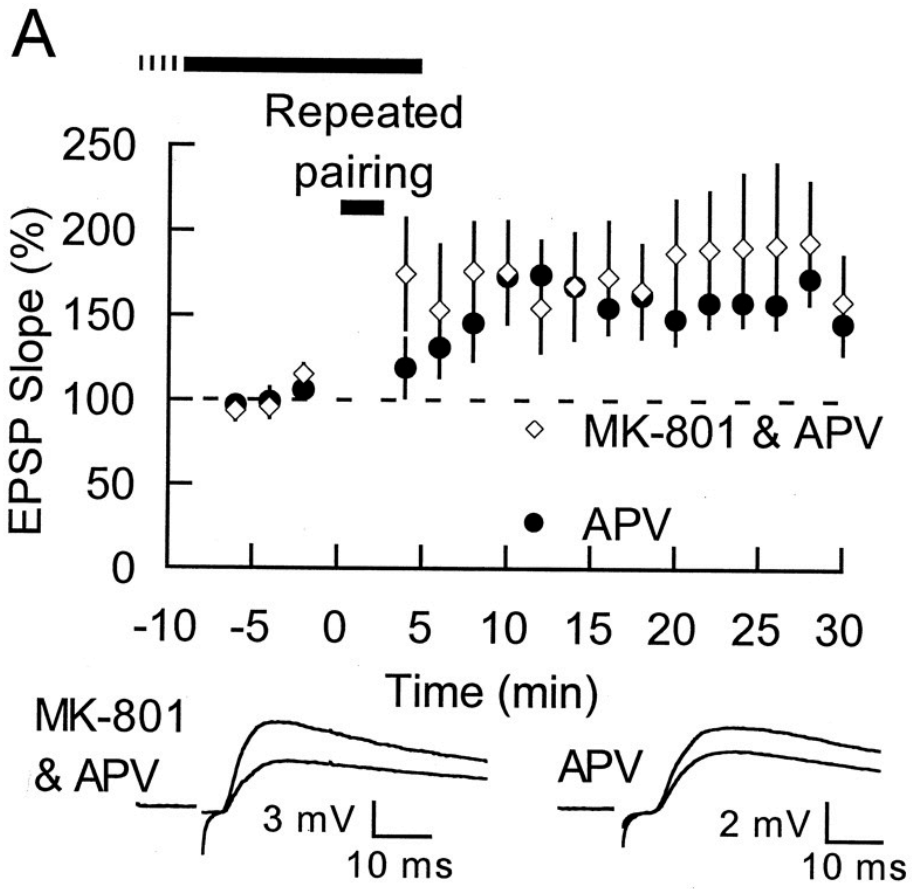
Stimuli at 100 Hz for 0.5 s

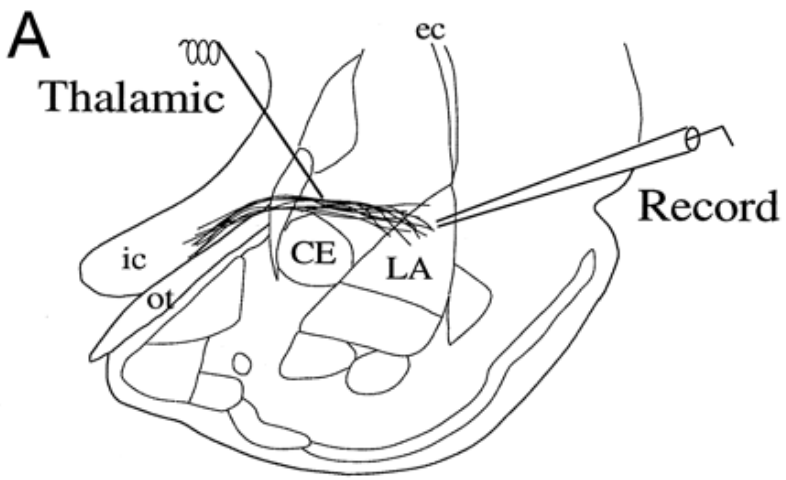


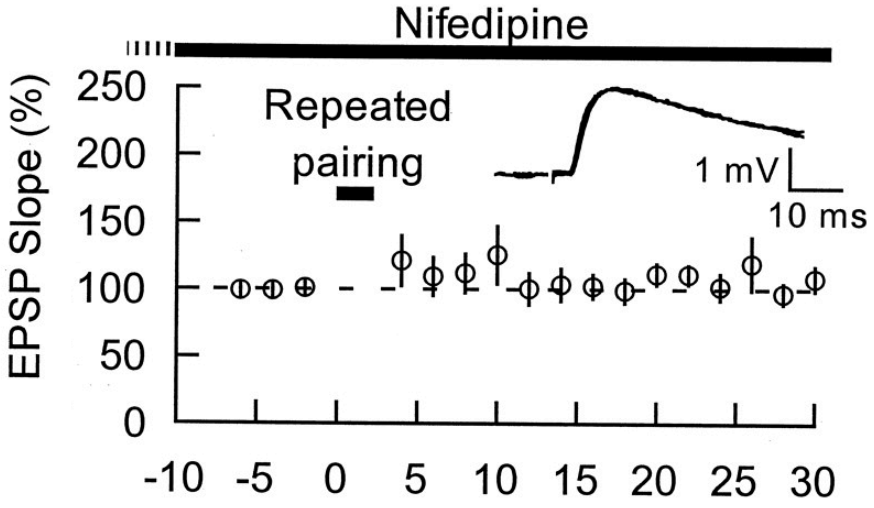
Watanabe et al., J. Phys. 2006

Release of calcium from stores are typically mediated by $InsP_3$ and Ryanodine receptors located on the endoplasmic reticulum

Example for VGCC-dependent LTP



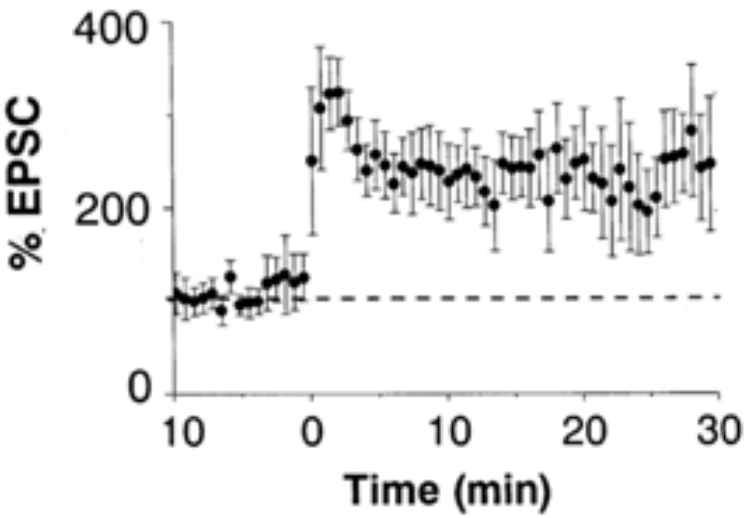


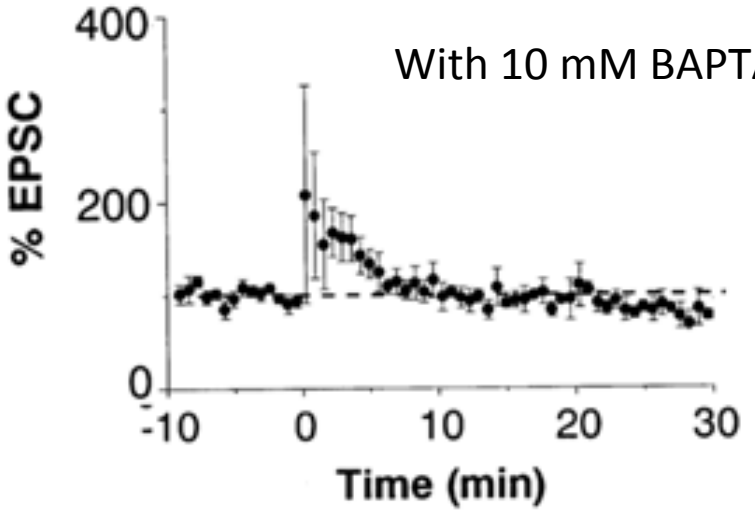


Weisskopf et al., J. Neurosci., 1999

Example for CPAMPAR-dependent LTP

EPSC plasticity in Amydalar interneurons





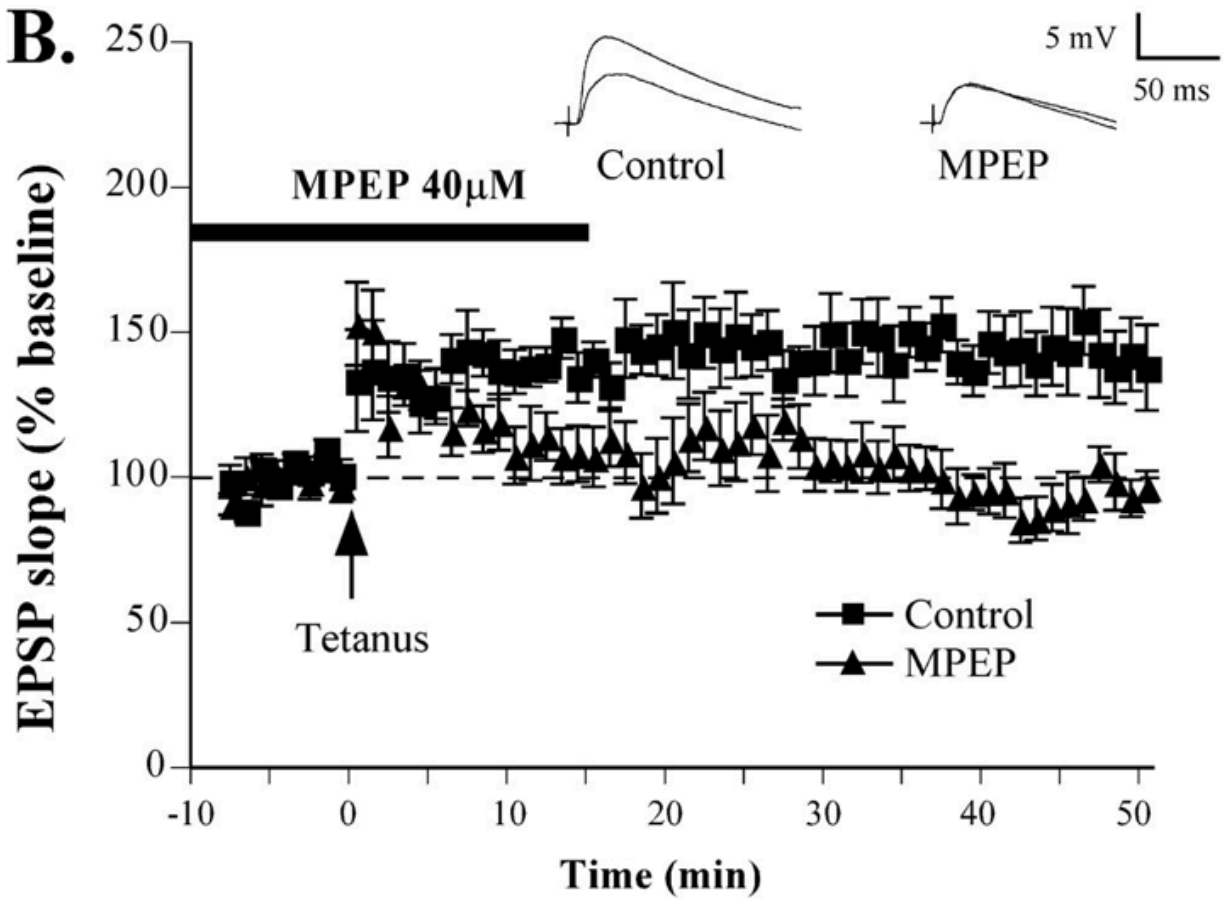
Done by voltage clamping @ -70 mV, so no VGCC's are activated!

These synapses do not have NMDA receptors

Mahanty and Sah, Nature, 1998

Example for mGluR-dependent LTP

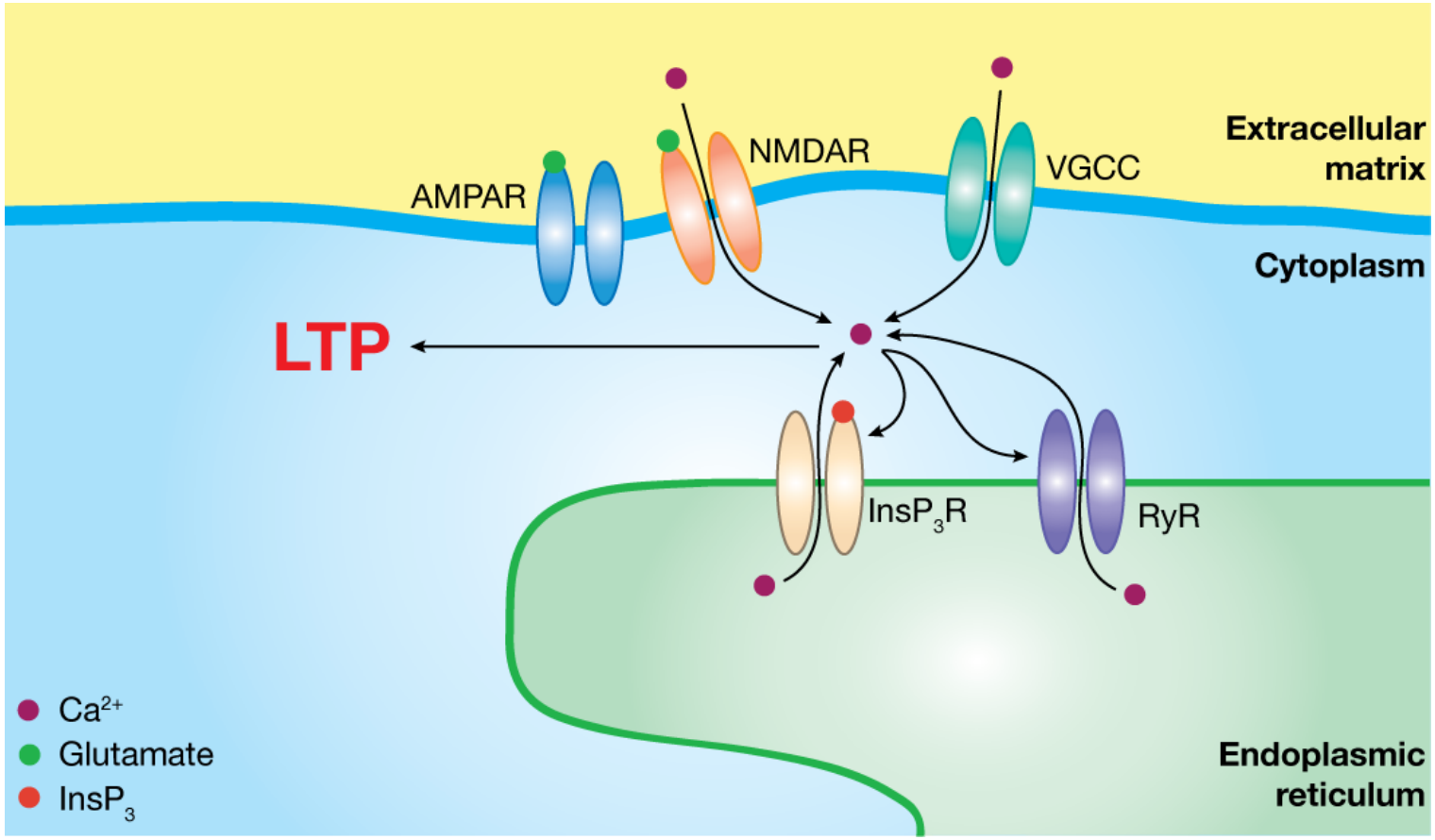
Group I mGluR's could lead to release of calcium from ER through $InsP_3Rs$



Rodrigues et al., J. Neuroscience., 2002

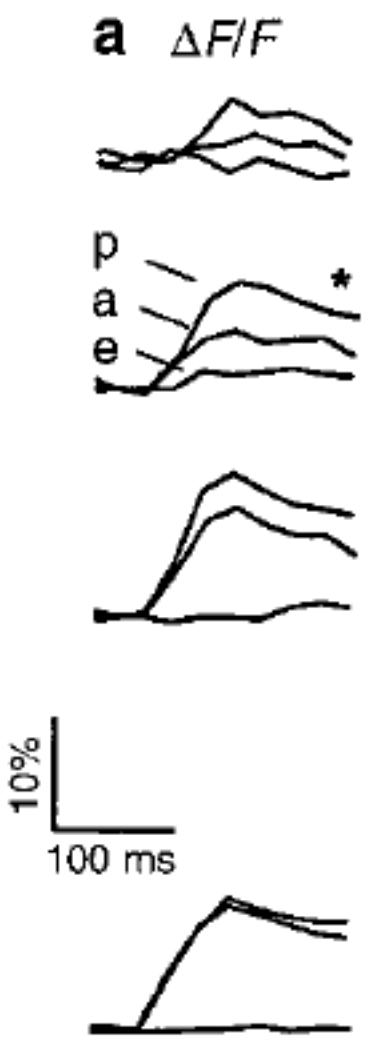
Alright, so there are multiple calcium sources!

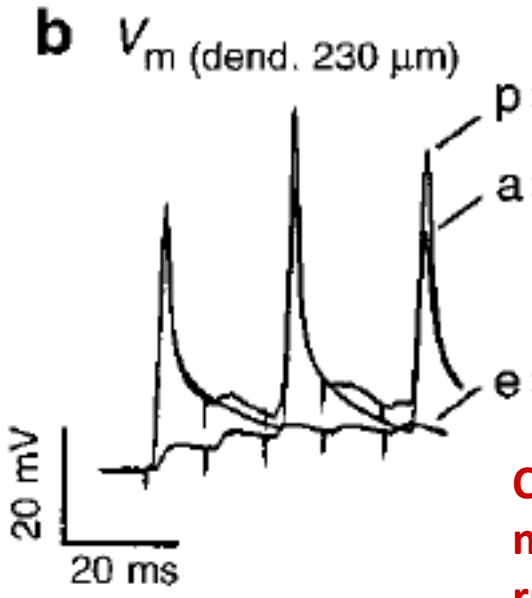
Calcium enters through one or <u>more</u> of them, and leads to the induction of LTP

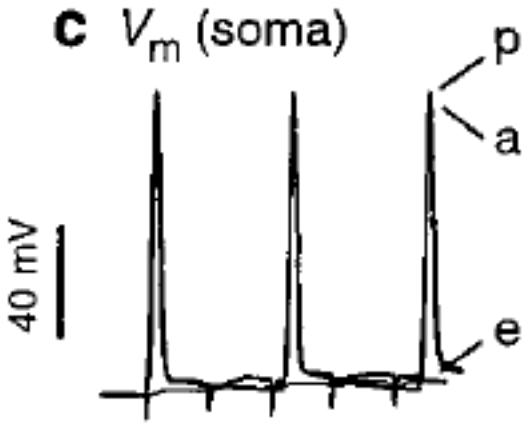


But, how on earth do you get depolarization *in vivo* for either the NMDAR's or the VGCC's to open?

bAP-EPSP coincidence leads to suprathreshold summation very locally!





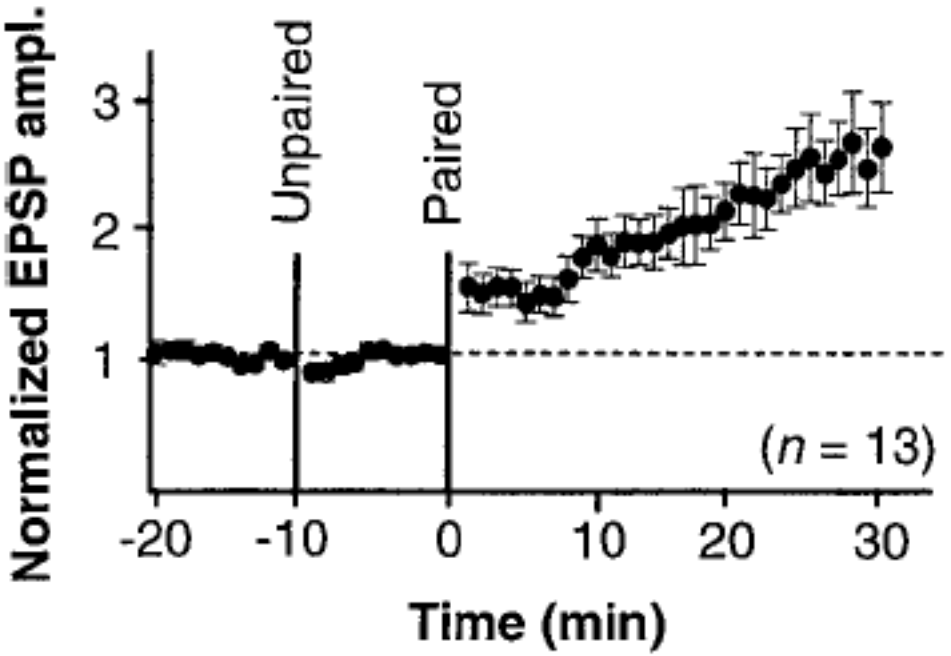


Can this property be a potential mechanism by which Hebb's rule is implemented?

Magee and Johnston, Science, 1997

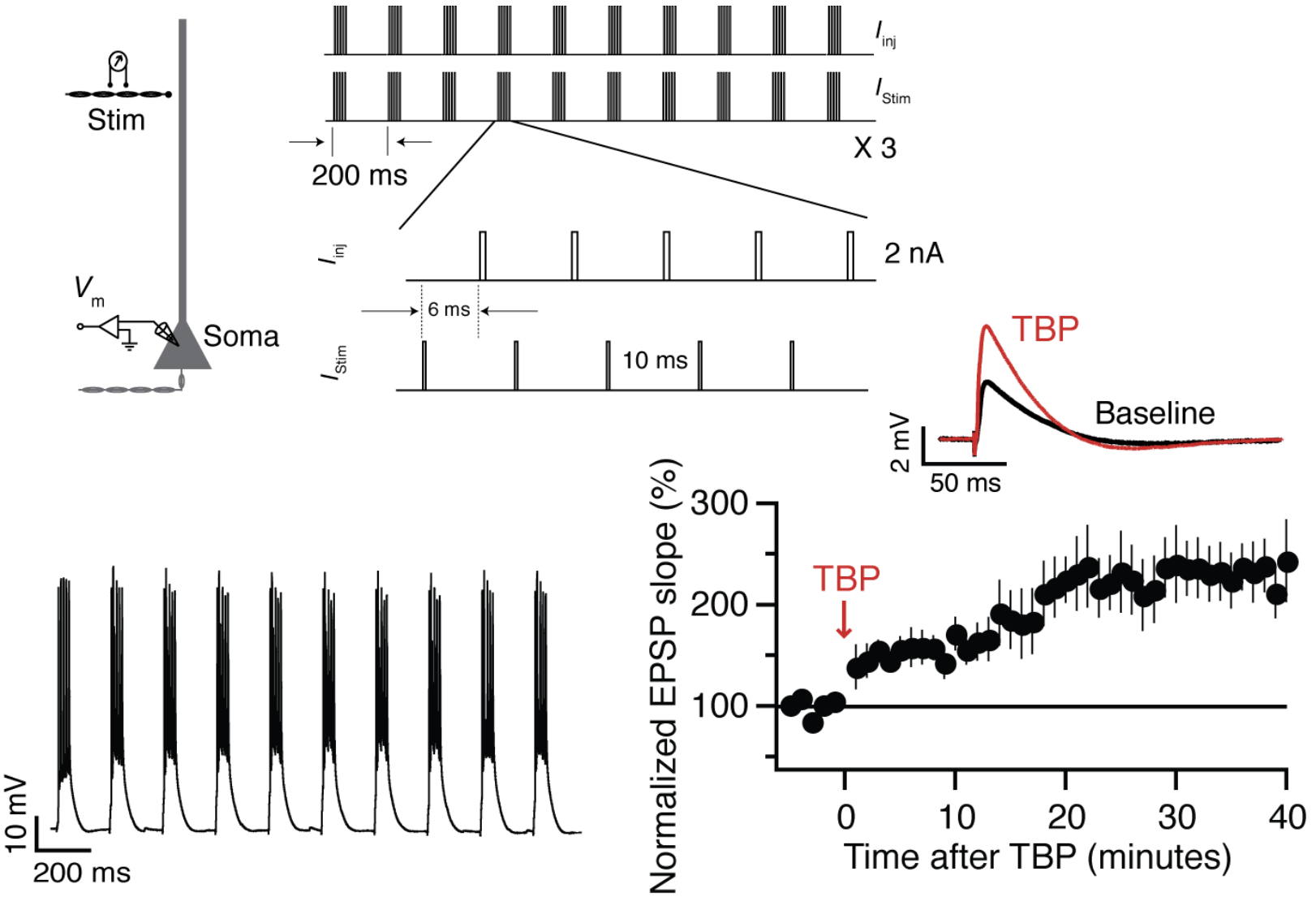
Pairing EPSP and bAP repeatedly induces LTP!

bAP tells when cell B fired! EPSP tells when cell A fired! Both together summate in a suprathreshold manner in voltage, opening more NMDAR and thus in calcium <u>locally</u>!

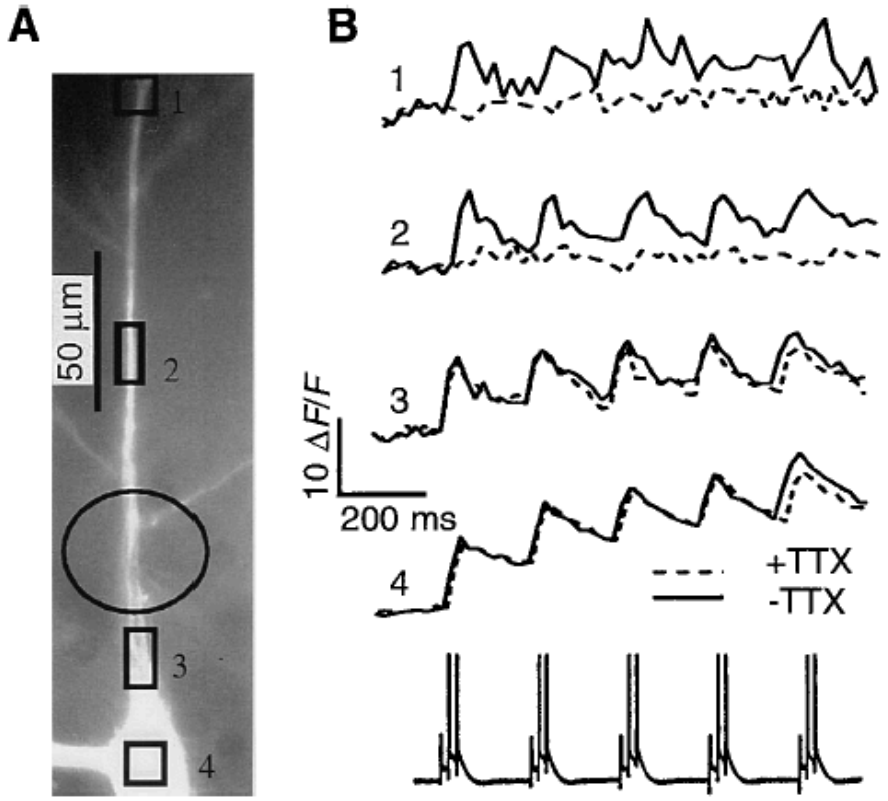


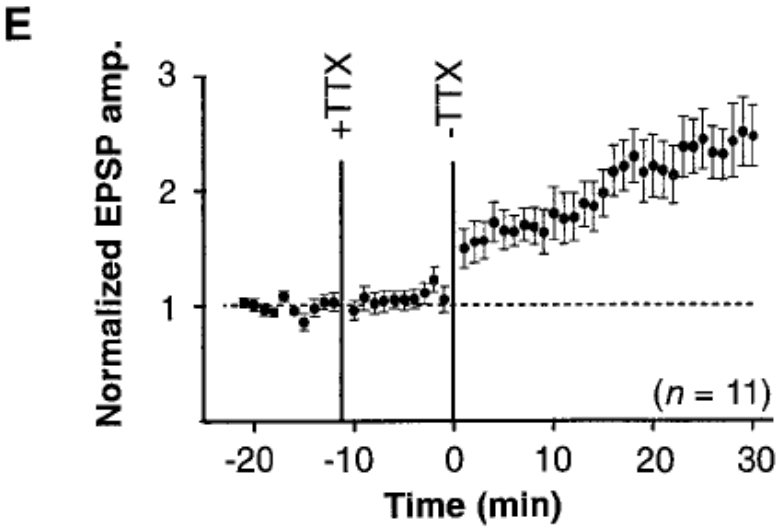
<u>Magee and Johnston, Science, 1997</u>

What kind of pairing? Theta burst



Magee and Johnston, Science, 1997; Frick et al., Nature Neuroscience, 2004; Narayanan and Johnston, Neuron, 2007

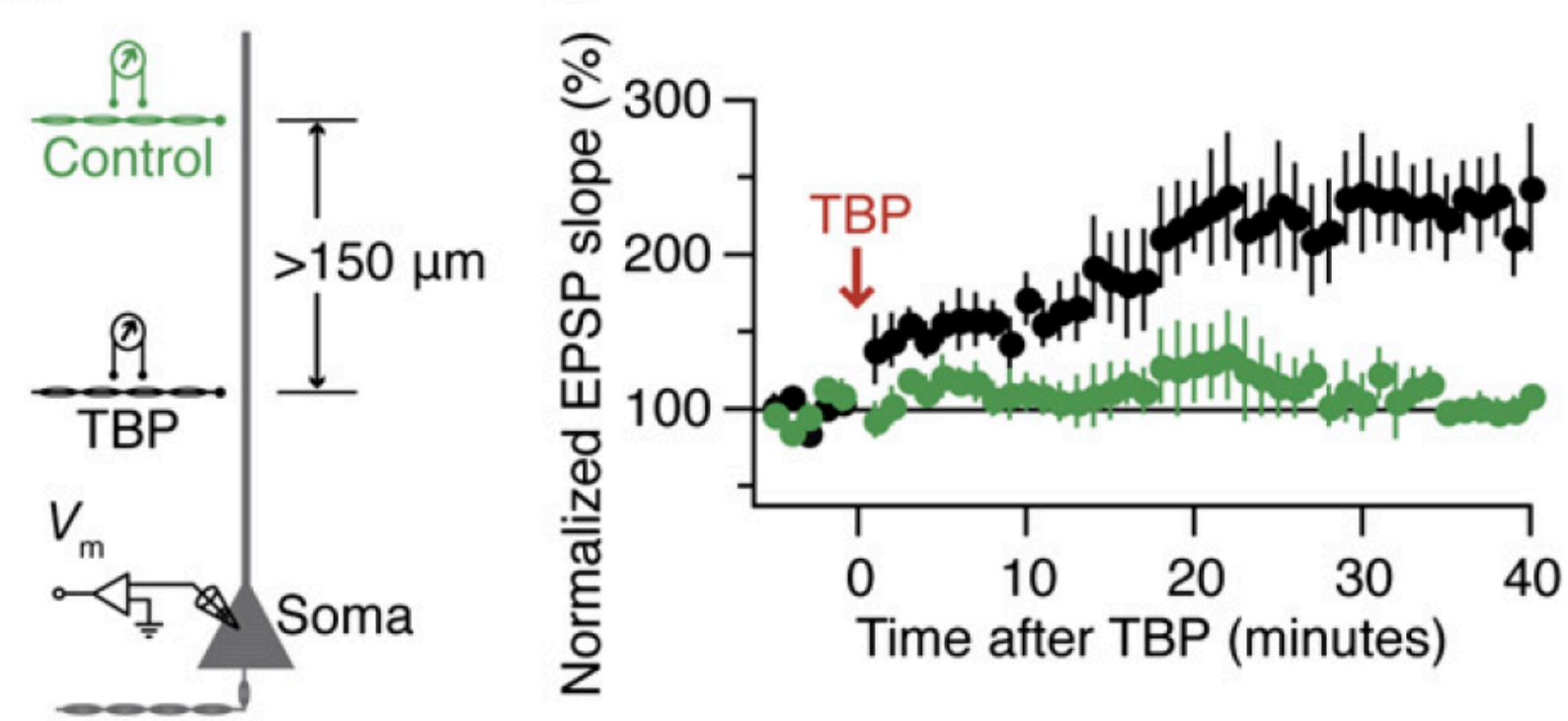




It indeed requires bAPs for LTP to occur

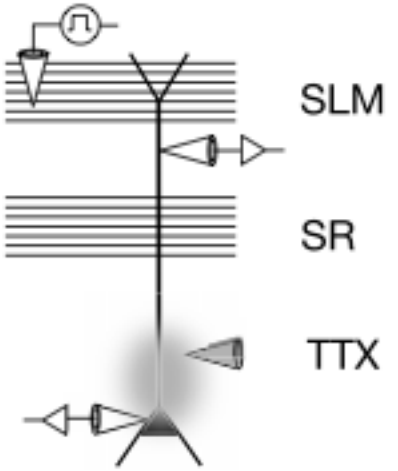
Magee and Johnston, Science, 1997

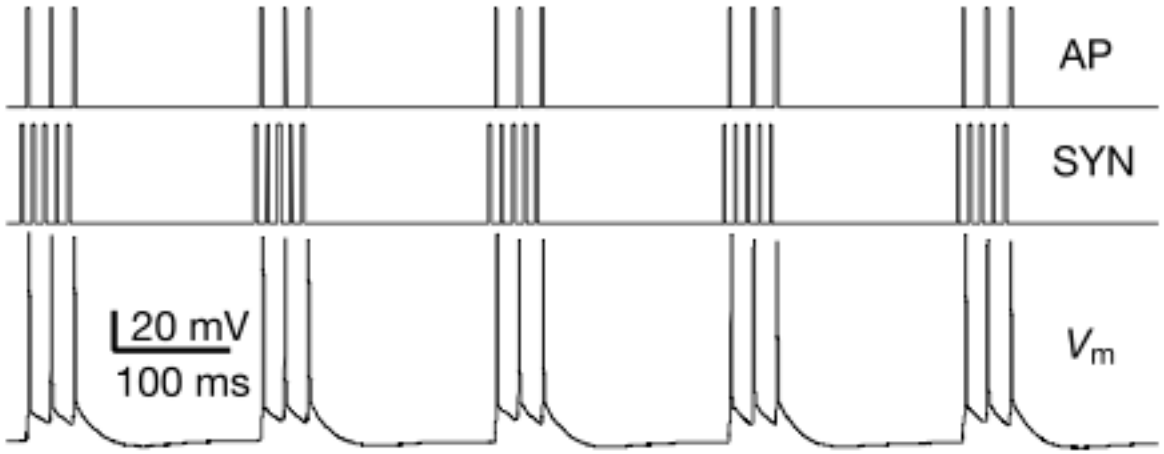
And, is very synapse specific!

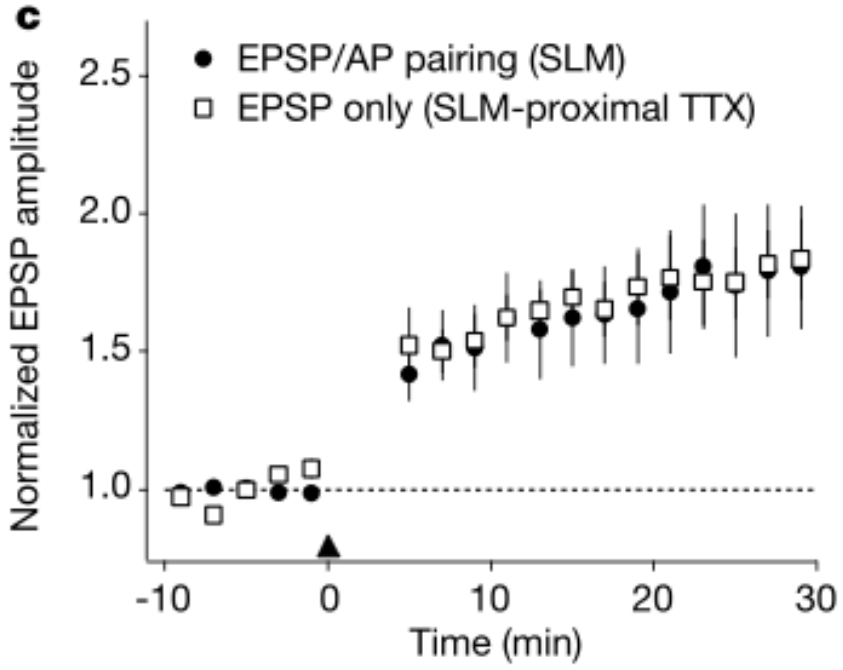


Narayanan and Johnston, Neuron, 2007

What happens at distal dendrites where there is no bAP?





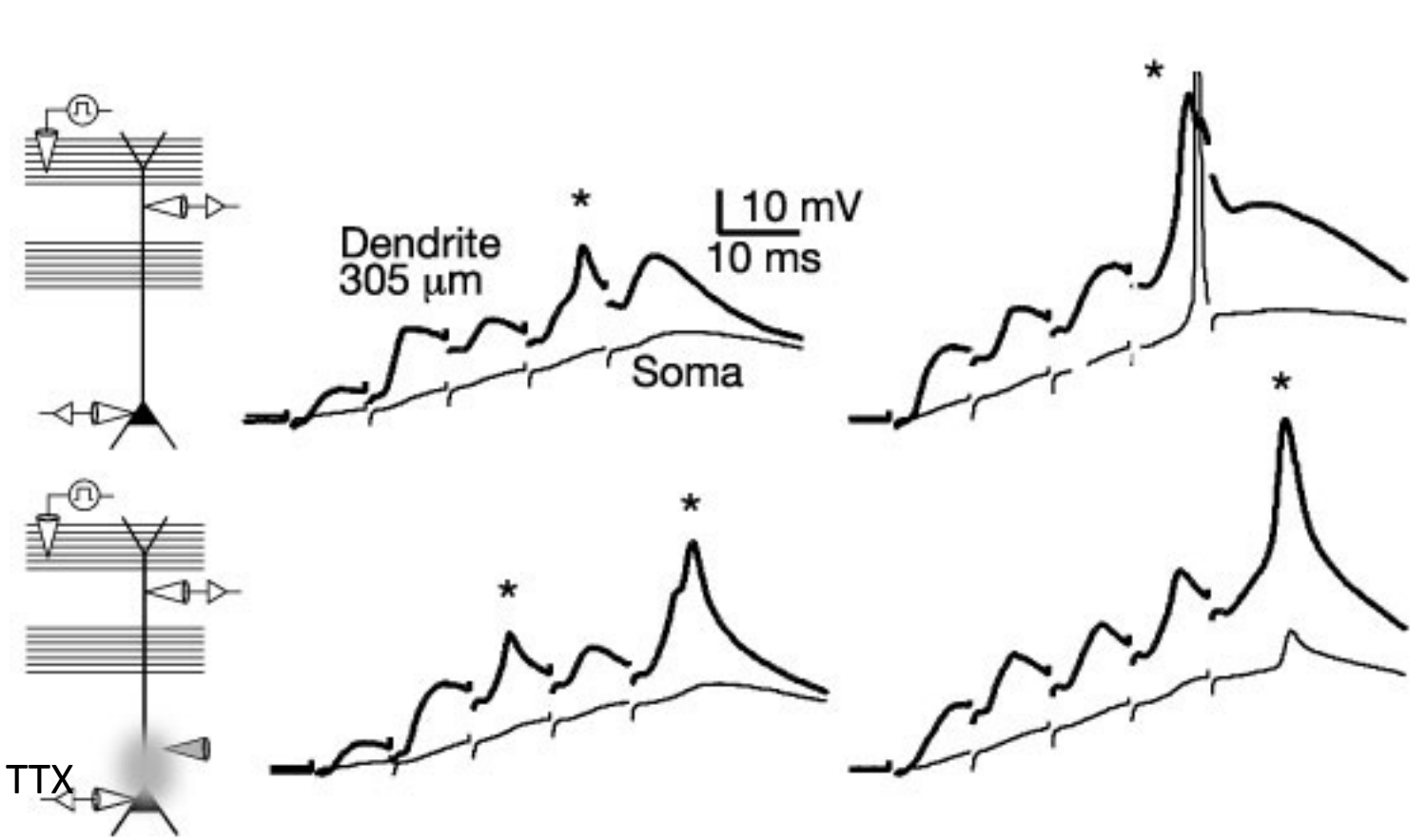


You don't need bAPs up there!

So, what provides the depolarization?

Golding et al., Nature, 2002

Dendritic spikes do the job!



Golding et al., Nature, 2002

So, the rules for plasticity can be dependent on the location of synapses on the dendrites!!

What did we learn today?

HFS leads to LTP through depolarization followed by influx of calcium into the postsynaptic neuron

Multiple sources of calcium could mediate LTP induction: NMDAR, CP-AMPAR, VGCCs, stores

In reality, multiple calcium sources could synergistically contribute to various forms of LTP

Backpropagating action potentials can be a physiological mechanism for induction of synapse-specific LTP

Question 1: Shouldn't plasticity be bidirectional for stability??

Question 2: What comes after calcium in inducing LTP??