A Cooperative Switch Determines the Sign of Synaptic Plasticity in Distal Dendrites of Neocortical Pyramidal Neurons

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Learning and memory are due to changes in the strength of individual synaptic connections.

Hebb: synaptic strengthening occurs during persistent simultaneous pre- and postsynaptic activity.

**Backpropagation of the AP** into the dendrites is a critical requirement for triggering synaptic changes.

The backpropagating AP (bAP) is typically strongly **attenuated in distal dendrites**.

bAP-dependent learning rules may be **different at proximal and distal synapses**.
Introduction

- They studied neocortical layer 5 (L5) pyramidal neurons:
  - large apical dendritic arbor extends across several cortical layers
  - L5-to-L5 synapses are on the proximal, basal dendritic tree
  - L2/3-to-L5 synapses are found on the apical dendrites

- **Question**: How do plasticity rules for L2/3 and L5 inputs to L5 pyramidal neurons depend
  - on the *dendritic location of synaptic contacts*?
  - on the *local electrical properties* of the dendritic tree (efficacy of AP backpropagation)?
A gradient between LTP and LTD

**identical plasticity protocols** (AP-EPSP pairing) at both synaptic connections generates **LTP** at **proximal** L5-to-L5 connections, but **LTD** at **distal** L2/3-to-L5 connections

**gradient** of the polarity of plasticity along the apical dendrite
Identifying the dendritic location of synapses

Cable theory predicts that synaptic location is correlated with **EPSP rise time**

Synaptic location can be quantitatively predicted from EPSP rise time
The sign of plasticity depends on synaptic location

Is synaptic location (estimated by EPSP rise time) correlated with the outcome of the plasticity protocol?

Proximal inputs with fast-rising EPSPs (< 3ms/200µm) exhibit LTP

Distal inputs with slow-rising EPSPs (> 3ms/200µm) undergo LTD

- There is a clear relationship between the sign of plasticity and synaptic location
- Synaptic location, rather than the input origin, is the major determinant of plasticity
Converting LTD to LTP at distal synapses

Increased stimulation strength results in large EPSPs that potentiate when paired with APs

The sign of distal plasticity switches from LTD to LTP once a sufficient number of distal inputs cooperate
Converting LTD to LTP at distal synapses

Activating EPSPs in the absence of postsynaptic spiking results in LTD

Postsynaptic spiking in the absence of presynaptic stimulation does not change synaptic strength

This form of LTD is endocannabinoid-dependent (can be blocked by AM251) (Sjöström et al., 2004)
Boosting of bAPs underlies the switch between distal LTD and LTP

Can the cooperativity requirement for distal LTP be explained by the **boosting of failing bAPs**?

AP-EPSP pairing in conjunction with a brief subthreshold dendritic current injection (0.4nA, 200ms)

**Dendritic depolarization** switches distal plasticity from LTD to LTP

Dendritic, but not somatic, depolarization determines the sign of distal plasticity
Boosting of bAPs underlies the switch between distal LTD and LTP

How does dendritic depolarization influence AP backpropagation?

Dendritic depolarization boosts the amplitude, width, and area of bAPs, increasingly with distance from the soma.
Boosting of bAPs underlies the switch between distal LTD and LTP

Boosting of bAPs can be examined using imaging of bAP-induced Ca\(^{2+}\) signals

Supralinear Ca\(^{2+}\) signals reveal that boosting occurs over large parts of the distal dendritic tree and increases with distance from the soma.
LTP at proximal synapses also requires reliable AP backpropagation

Weakening AP propagation should also affect the plasticity of proximal inputs

Strong, brief hyperpolarization impairs backpropagation into basal dendrites (reduction of Ca^{2+} signal increases with distance from the soma), but leaves axonal signals unaffected
LTP at proximal synapses also requires reliable AP backpropagation

AP-EPSP pairing during hyperpolarization abolishes LTP at proximal connections:

Reliability of AP backpropagation determines the plasticity in L5 neurons, regardless of synapse location
The resulting model of plasticity

Two principles for the organization of synaptic plasticity:

- graded change in sign and magnitude of plasticity with distance from the soma
- dendritic depolarization switches between LTD and LTP given identical patterns of pre- and postsynaptic activity

Both principles are governed by the amplitude of the backpropagating AP at the site of the active synapses
Discussion

**Inverted sign of plasticity at distal synapses**

- The same standard AP-EPSP pairing protocol produces LTP at proximal synapses and LTD at distal synapses
- Such an inversion depending on dendritic distance has not been demonstrated previously
- Synaptic location is a critical determinant not only of the extent, but also of the polarity of plasticity at each given synapse
- This finding may help to explain some of the notorious variability in the outcome of plasticity experiments
Discussion

A dendritic switch for regulating plasticity at distal synapses

- Distal synapses undergo LTP in the presence of either cooperative synaptic input or dendritic depolarization
- The same stimuli that boost bAPs also promote the conversion from LTD to LTP
- Neurons with different dendritic branching patterns may exhibit a different spatial distribution of learning rules
- Background synaptic activity may tune the transition point between LTD and LTP
Discussion

**Functional implications**

- The plasticity gradient may lead to a distribution of strong proximal and weak distal inputs.
- These weak distal inputs must act cooperatively to trigger an AP, otherwise they are penalized.
- Distal LTP can be gated by relatively proximal depolarization, demonstrating a mechanism for associative learning not just within, but also across neocortical layers.
- E.g., proximal L2/3-to-L5 connections could gate and “instruct” learning at distal L1-to-L5 inputs.
- The state-dependent switch between LTD and LTP at distal synapses may both:
  - regulate synaptic efficacy as a function of network activity
  - provide a means for associating and storing information carried by synchronous activity in different cortical layers.
References

A cooperative switch determines the sign of synaptic plasticity in distal dendrites of neocortical pyramidal neurons.

Dendritic excitability and synaptic plasticity.

Endocannabinoid-dependent neocortical layer-5 LTD in the absence of postsynaptic spiking.