

Molecular Mechanisms Underlying Metaplasticity

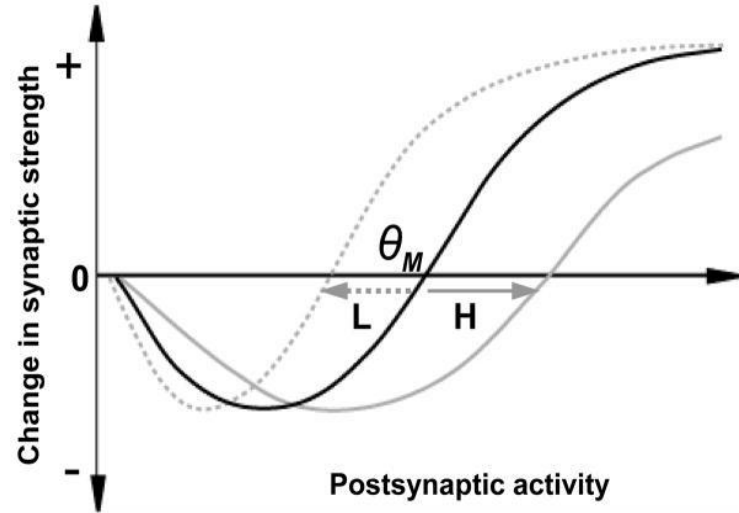
Potential Role of DHHC5 in Regulating the
Plasticity Modification Threshold

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Metaplasticity

BCM Theory: recent activity shifts plasticity modification threshold⁴ to maintain dynamic working range.

Priming activity itself does not cause persistent changes in strength of synaptic transmission.



θ_m = crossover point
from LTD to LTP

Unresolved Issues in Current Literature

Gap in knowledge: What cellular mechanism causes the modification threshold to shift?

- CaMKII, MEF2, etc identified as potential regulators of plasticity thresholds⁵
- However, difficult to identify downstream phosphorylation or transcription targets.

Protein of Interest

DHHC5 = enzyme that palmitoylates δ -catenin

Associates with PSD-95 & Fyn kinase at synaptic membrane

Activity disrupts complex stability \rightarrow DHHC5
endocytosis and interaction with δ -catenin in shafts

δ -catenin plays important role in LTP²

Question/Hypothesis

Question: Is DHHC5 involved in changing the readiness of synapses to undergo LTP or LTD?

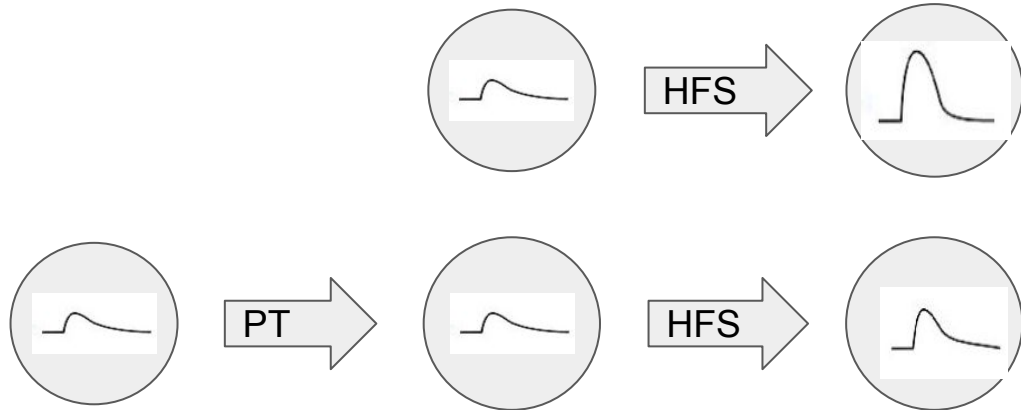
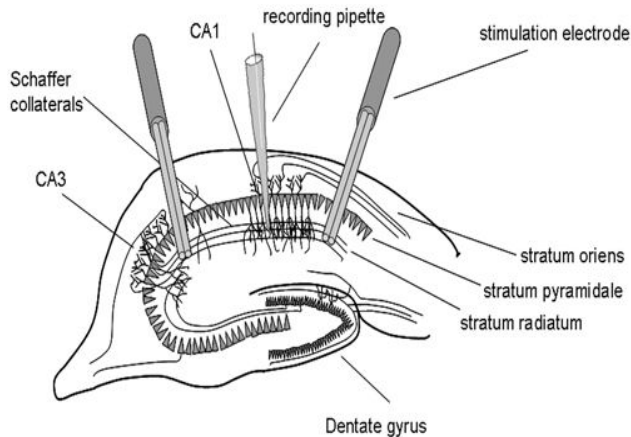
Hypothesis: Pre-training activity results in transient retention of DHHC5 at the synaptic membrane.

Specific Aims

- Induce metaplasticity in rat hippocampal slice with electrophysiological paradigm
- Compare localization of DHHC5 before and after pre-training activity

Part I - Inducing Metaplasticity

- Measure EPSP with stimulating and recording electrodes to ensure pre-training stimulation actually shifts plasticity threshold



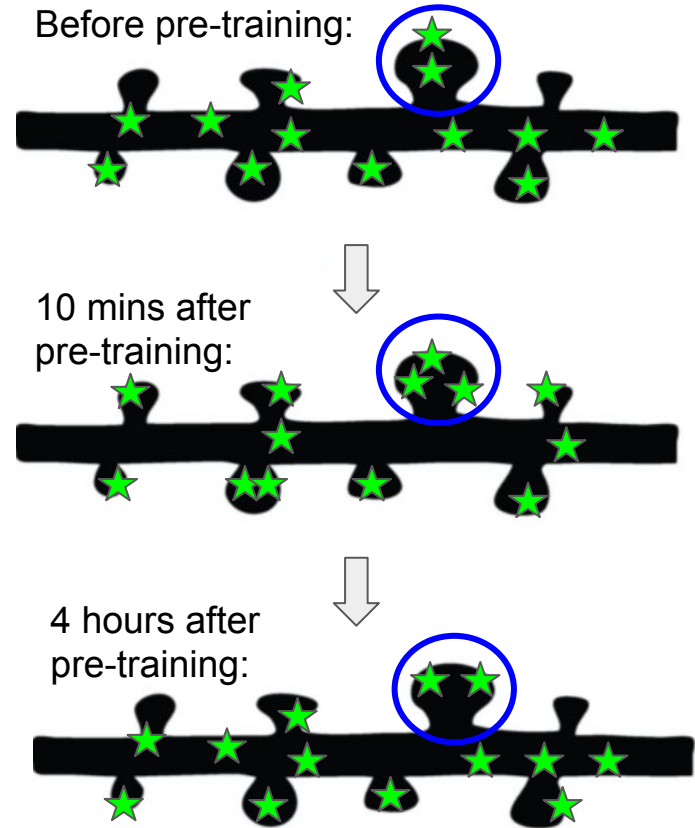
Part II - Tracking and Analyzing DHHC5 Localization

- Transfect hippocampal slice with GFP-DHHC5
- Using two-photon microscopy, obtain images of transfected dendrite in region of interest
 - 1) Before pre-training
 - 2) 10 minutes after pre-training
 - 3) 4 hours after pre-training
- Compare integrated density of DHHC5 in spine

Expected Outcomes

Pre-training activity should lead to transient increase (higher IntDen) in DHHC5 localization in the spine.

Increase in plasticity modification threshold due to stabilization of DHHC5 at dendritic spine.



Significance

Various neurological disorders show evidence of improper regulation of synaptic plasticity¹

Our study may provide insight into disease mechanisms and potential treatment options

Future directions: Mechanism of DHHC5 retention at dendritic spine and relationship with other proteins.

References

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