

# Review of: "Pathway-specific TNF-mediated metaplasticity in hippocampal area CA1"

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The study is from a leading expert group with extensive experience studying heterosynaptic metaplasticity. Here, they studied the LTP sensitivity of CA1 pyramidal cells to previous activities in different networks of afferent pathways and dendritic compartments. They found that priming stimulation is so inhibited LTP only in stratum radiatum (SR) of hippocampal CA1 but did not inhibit the second independent pathway of LTP in stratum oriens (SO) and lacunosum molecular layer (SLM) of hippocampal CA1. Synapses in SR are also more sensitive than SO or SLM to LTP-inhibiting effects of pharmacological TNF priming. Our results suggest that Schaffer collateral / commissural synapses in SR are particularly vulnerable to this plasticity, which may reflect the critical control of information processing in this pathway in addition to sensitivity to neuroinflammation under disease conditions. The experimental data well support the main conclusions. However, there are some points that the authors need to consider for future work.

1. Priming stimulation was given on stratum oriens in the present study; conditioning stimulation to induce plasticity was given on stratum radiatum 30 min after priming. Therefore, whether priming stimulation on stratum radiatum and conditioning stimulation on stratum radiatum will be the same effect by the TNF needs to be investigated.
2. As a cytokine, TNF is used by the immune system for cell signaling. TNFR1 signaling tends to be pro-inflammatory and apoptosis. To further confirm the inflammatory effect, it should be verified by similar agents such as Lipopolysaccharides (LPS).
3. Most of their work focus on the LTP sensitivity of CA1 in heterosynaptic metaplasticity whether the LTD sensitivity is worth further exploring.
4. The metaplasticity requires priming for later synaptic function. The present study used high-frequency stimulation and theta bursts stimulation. What will happen if the priming is low-frequency stimulation?