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Extracellular potassium accumulation may contribute to long-term potentiation induced with long 100 Hz stimulus trains

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Long-term potentiation is often induced by high-frequency stimulation (100 Hz) for 1 second. However, in hippocampal CA1 pyramidal cells we observe that EPSPs quickly become depressed in such trains and it is rare to see action potentials in the pyramidal cell after 200 ms into the train. Because LTP induction depends on postsynaptic depolarization and there appeared to be little depolarization after 200 ms, we predicted that lengthening the train from 200 ms to 1600 ms should produce little additional LTP. However we found that LTP magnitude progressively increased with train length. Further investigation revealed that fiber volley amplitude decreased and latency increased during a long train and that these changes could be reproduced by raising extracellular potassium concentration in the bath. In addition NMDA receptor mediated field EPSPs were increased with elevated extracellular potassium. These experimental findings strongly suggest that decreased afferent excitability and decreased glutamate release during a train are more than compensated by increases in extracellular potassium which enhances the NMDA receptor response and allows long trains to produce additional LTP.

We have constructed computational models to test this idea and gain insight into how elevated extracellular potassium might be produced by long high-frequency trains and how this might affect LTP. If extracellular potassium concentration is raised from 3.4 mM to 13 mM, we note that: i) the NMDA reversal potential changes only 1.5 mV, ii) the potassium reversal potential depolarizes by 35 mV, and iii) resting potential depolarizes by 20 mV. The effect of these changes is to double the amount of calcium coming into a dendritic spine through NMDA receptor channels, but these changes also make the neuron fire action potentials even when input is depressed, in contradiction to the experimental results. This suggests that changes in extracellular potassium are likely to be restricted to regions around the afferent axons and the sites of synaptic contact. We are currently investigating this hypothesis and are seeking parameter conditions that reproduce the experimental findings.

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