Re-evaluation of the hypothesis that LTP has two temporal phases and that the late phase is protein synthesis-dependent

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Abstract
Long-term potentiation (LTP) is an activity-dependent increase in synaptic efficacy that is most studied in the hippocampus and that is considered a cellular substrate for learning and memory. Accepting the belief that the durability (persistence in time) of LTP is analogical to long-standing store of hippocampus-dependent memories warrants the necessity for understanding the mechanisms underlying LTP stabilization. Although the great majority of neuroscientists assume that LTP induction, akin to the formation of memories triggers the synthesis of proteins that are instrumental for subsequent consolidation neither the identity of such presumed proteins nor the mechanisms by which they act to consolidate LTP are clear. Based on this notion LTP is distinguished temporally into an early phase (E-LTP), which is protein synthesis-independent and a late phase (L-LTP), which is protein synthesis-dependent. However, several behavioral and electrophysiological findings cast doubts on this notion. In the present thesis I have examined the effect of protein synthesis inhibitors (PSIs) on the stabilization of LTP in hippocampal slices obtained from young rats. Treating hippocampal slices with PSIs using a temporal window relative to the induction of LTP that has previously been used in the literature failed to block L-LTP, a result in contrast with published data. However, long-lasting pretreatment with the PSI emetine blocked LTP by LTP-unrelated mechanism as the drug showed deteriorating effect on the baseline response. In contrast, depleting the protein repertoire in the slice by long-lasting pretreatment with the PSI cycloheximide deteriorated the stabilization of LTP. Additionally, acceleration of protein degradation using hydrogen peroxide after the induction of LTP resulted in decay of LTP. Addition of cycloheximide induced additive decay of LTP stabilization. These contradictory findings have recently been replicated by other laboratories. I this thesis I present a working model that aims to explain the discrepant findings regarding PSI and LTP. The model concedes that the kinetics of protein turnover during the induction of LTP has predicts the subsequent stabilization of LTP. This can explain the wide variability in the time course of the presumed protein-synthesis independent E-LTP. The model gain support from experiments in which a low concentration of the proteasome inhibitor MG-115 improved the stability of LTP induced by a weak induction protocol. In summary, my results suggest that 1) the temporal distinction of LTP into E- and L-LTP is a false dichotomy and 2) the rate of protein degradation may explain whether PSIs would, or would not, have an effect on LTP stabilization.

Keywords: Hippocampus, Long-term potentiation, protein synthesis, memory, temporal phases

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