Signaling mechanisms underlying hippocampal long-term depression

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One biochemical event hypothesized to contribute to the expression of NMDA recepor-dependent long-term depression (NMDAR-LTD) in the hippocampus is decreased protein phosphorylation, caused by a decrease in protein kinase activity and/or an increase in protein phosphatase activity. We have shown that NMDAR-LTD in the hippocampus *in vivo* is associated with both transient and persistent increases in phosphatase activity (*Neuroscience* 86: 1023). In addition, we have shown that LTD is associated with phosphatase-dependent decreases in the phosphorylation and activity of protein kinase C (*J. Neurosci.* 20: 7199). We also have investigated the role of extracellular signal-regulated kinase (ERK) in NMDAR-LTD. Surprisingly, we found that LTD was associated with a transient *increase* in the phosphorylation and activation of ERK2 and that NMDAR-LTD was blocked by the MEK inhibitor SL327 (*J. Neurosci*. 22: 2054). Taken together these findings indicate that the activation of ERK2 is necessary for NMDAR-LTD. Recent studies from our laboratory have focused on signaling pathways involved in metabotropic glutamate receptor-dependent LTD (mGluR-LTD), a form of LTD that has been shown to require dendritic protein synthesis. We have found that mGluR-LTD requires the activation of several protein kinase signaling pathways, including a phosphoinositide 3-kinase (PI3K)/Akt/mTOR cascade and an ERK/Mnk1/eIF4E cascade, both of which are critical for the regulation of translation initiation. The activation of the PI3K/Akt/mTOR cascade is required for the phosphorylation and inactivation of the translation repressor 4E-BP2 and for enhancing S6-directed translation during mGluR-LTD. Overall, our findings suggest that a diverse and complex set of signaling cascades underlie the various forms hippocampal LTD.

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