The role of mTOR complex 1 in synapse function and plasticity

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Changes in synaptic function are the basis of learning and memory. Several lines of evidence indicate that local protein synthesis is required for the long-lasting changes in synaptic function. A candidate signaling pathway that might control local protein translation in postsynaptic structures is the mTORC1 (mammalian target of rapamycin complex 1) pathway. The central component of mTORC1 is the highly conserved kinase mTOR. Like mTOR, the other mTORC1-associated proteins are conserved from yeast to humans. Here we investigated the role of raptor, an obligatory component of mTORC1, in adult hippocampal neurons using the Cre/loxP technology. Cre expression was driven by the promoter of the calcium/calmodulin-dependent protein kinase 2 (CamK2). Recombination of the floxed raptor allele in those Raptor-KO mice was detected in forebrain neurons. Learning and memory was affected in adult Raptor-KO mice when tested in a Morris water maze using only 2 training sessions per day. In such paradigm, Raptor-KO mice showed deficits during the learning phase and in the memory test. Interestingly, no deficit in learning and memory was observed with the standard protocol in which mice were trained 6 times per day. When we tested synaptic function using electrophysiological methods, we found a reduction in the amplitude of excitatory currents in hippocampal CA1 neurons in the Raptor-KO mice. Interestingly, lysates from the hippocampus of Raptor-KO mice also showed a reduced amount of AMPA receptors, which is consistent with the reduction in amplitude of miniature excitatory postsynaptic currents (mEPSCs). Measurement of L-LTP using extracellular recordings in hippocampal slices furthermore showed a deficit in the maintenance of L-LTP in the CA1 area. However, this effect was not as pronounced as previously reported using the mTORC1 inhibitor rapamycin (Cammalleri et al. 2003) This difference in L-LTP between the Raptor-KO mice and acute inhibition by rapamycin could be based on the strong increase in phosphorylation of Akt/PKB and increased ERK-activity as detected by Western blot analysis. Such hyperactivation may compensate for the loss of mTORC1 activity. Alternatively, some of the effect of rapamycin might be due to its inhibitory function on mTORC2. In summary, our data demonstrate that mTORC1 plays an important role at excitatory synapses and they suggest that mTORC1 signaling is required for the generation of a long-term trace at synapses that are only weakly activated. Moreover, our data show that acute inhibition of mTOR by rapamycin affects synapse function differently than the selective deletion of mTORC1 in forebrain neurons.

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