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LEARNING AND MEMORY

Learning through Trk-ing

One of the central aims in neuroscience is to understand the molecular mechanisms of learning. Minichiello and colleagues have now addressed this question with a novel combination of *in vivo* methods and were able to show that signalling through the TrkB receptor and its PLCγ binding site is important for associative learning and parallel long-term potentiation (LTP).

The TrkB receptor is well known for its importance in synaptic plasticity and LTP in the hippocampus. It mediates downstream signalling through the Ras/MAPK pathway through binding of Shc, or the calcium/calmodulin pathway through binding of PLCγ. Previous *in vitro* studies have shown that the PLCγ — but not the Shc — docking site of TrkB is crucial for hippocampal LTP. To investigate the question of whether learning is based on the same molecular mechanisms as LTP, the authors used an associative learning paradigm combined with direct *in vivo* recordings from the hippocampus of transgenic mice.

First, they tested transgenic mice carrying point mutations of the TrkB receptor in the Shc ($trk^{SHC/+}$) or the PLCγ ($trk^{PLC/+}$) docking site for their ability to learn. By using a classical trace-conditioning paradigm of the eyelid response, they found that $trkB^{PLC/+}$ animals learn less well than $trkB^{SHC/+}$ or control animals. When the hippocampal CA3 region was stimulated during the trace-conditioning paradigm, recording the field excitatory postsynaptic potential (fEPSP) in the CA1 region revealed an increase in synaptic strength in $trkB^{SHC/+}$ and control animals, but not in $trkB^{PLC/+}$ animals. Furthermore, the linear relationship between the acquisition of the eyelid response and potentiation at the CA3–CA1 synapses in control and $trkB^{SHC/+}$ animals was completely absent in $trkB^{PLC/+}$ animals, indicating that the PLCγ docking site of TrkB is key to both processes. Further experiments investigating short-term and long-term effects after stimulation provided evidence that the TrkB PLCγ docking site is crucial for LTP *in vivo*.

This paper shows for the first time that the same molecular mechanism forms the basis for learning a task and for changes in synaptic plasticity seen during LTP in awake animals. Future studies could apply this combination of methods to other mouse models and decipher other signalling pathways that are involved in learning and LTP.

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