



New Players in the Molecular Basis of Memory and Learning

Background: During learning and memory formation, the connections between neurons, called synapses, change in strength. An increase in the strength of a synapse is called long term potentiation (LTP), while a decrease in the strength of a synapse is called long term depression (LTD). Both LTP and LTD have an early and late phase. The early phase is believed to correspond to short-term memory, which involves temporary, or transient, changes in the proteins located at the synapse. However, in the late phase, believed to correspond to long-term memory, the molecular changes call for the production of new proteins, which requires gene expression – the process of copying, or transcribing, information from DNA to ultimately produce a new protein – and this process is modulated by specific other proteins, called transcription factors.

The switch from early to late phase LTP or LTD is an important step in the formation of long-term memories and has been intensively investigated. Many of these studies have shown that the activation of a particular transcription factor, CREB (an abbreviation for cyclic AMP response element-binding protein), is involved in the switch from the early to late phases of LTP. However, it has not been clear whether CREB-regulated gene expression is necessary for LTD as well.

Advance: Using both a pharmacological approach and a powerful new technique, called particle-mediated gene transfer, in a nerve cell culture system, NIH-funded investigators examined the role of CREB in LTD. This study showed that the late phase of LTD, like the late phase of LTP, is indeed dependent on CREB activation. As an extension of this work, the researchers looked further upstream in this biochemical pathway to see what activated CREB in LTD. In testing proteins known to activate CREB under other conditions, they found a specific protein called CaMKIV (short for Ca²⁺/calmodulin-dependent protein kinase IV) was also needed for LTD.

Implications: This study adds two new and important pieces to our knowledge of how memories are formed. Understanding the molecular basis of learning and memory may help elucidate the causes and treatments of both learning disorders and disease such as Alzheimer's. [Area of Emphasis: Biology of Brain Disorders, Genetic Medicine; GPRA performance goals: add to body of knowledge about normal and abnormal biological functions: develop new or improved instruments and technologies for use in research and medicine]

Ahn, S., Ginty, D.D., and Linden, D.J.: A late phase of cerebellar long-term depression requires activation of CaMKIV and CREB. *Neuron* 23: 559-568, 1999.

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