



# Cyclic AMP-mediated Signaling and Neuroplasticity

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The central nervous system is capable of acquiring and storing tremendous amounts of information. In addition to the activation of ion channels and neurotransmitter receptors, other signaling molecules are also functionally involved in memory formation. Studies with invertebrates and vertebrates have established that the cAMP/PKA signaling regulates different forms of synaptic plasticity (see the figure on the top).

By using knockout (KO) mice, it was found that type 1 and type 8 adenylyl cyclases (AC1 and AC8) are the only calmodulin/ $\text{Ca}^{2+}$ -stimulated cyclases in the brain and essential for long-term memory formation. AC1 and AC8 also regulate long-term potentiation (LTP, a cellular model for studying neuroplasticity) in different areas of hippocampus (a brain region that regulates several forms of memory). Furthermore, over-expression of AC1 in mouse forebrain resulted in enhanced LTP and recognition memory. Synaptic changes and remodeling are observed during neuroplasticity. However, it is not clear how synaptic and non-synaptic signaling co-operate with each other. The regulation of neuronal plasticity by cAMP signaling may be specifically compartmentalized, because these two enzymes have distinct sub-cellular localization. AC8 is concentrated at the excitatory synapses, whereas AC1 is not.

Our current research focuses on the regulation of hippocampal neuroplasticity by AC1 and AC8 from distinct sub-cellular locations. With cell biology approaches, we are determining the targeting sequence of AC1 and AC8, which directs their sub-cellular localization. We also use biochemical and microscopy measurement to determine the role of AC1 and AC8 in neurotransmitter release. Through standard genetic manipulations in mice, we can either increase or decrease the cyclic AMP signaling in the brain, and measure neuronal activity and behavior (including memory formation). We use different paradigms, including LTP, LTD (long-term depression) and depotentiation, to measure neuroplasticity at the electrophysiology level. For behavioral examinations, we train mice for hippocampus-dependant memories, including passive avoidance, contextual memory, recognition memory (see the figure on the bottom) and spatial memory.

**Figure 1.** Calmodulin-stimulated adenylyl cyclases provide a critical cAMP signal required to support calcium activation of CRE-mediated transcription in the hippocampus. It is hypothesized that postsynaptic calcium increases generated through NMDA receptors activate several signal transduction pathways including the Erk/MAP kinase and cAMP regulatory pathways. It is proposed that either AC1 or AC8 can provide the cAMP signal necessary for activation of CRE-mediated transcription for LTP and LTM (long-term memory). Convergence of these pathways at the level of the CREB/CRE transcriptional pathway may increase expression of a family of genes required for LTM.

**Figure 2.** Help him (and us) solve the puzzle. During the training for recognition memory, mice were exposed to objects (green and blue puzzle pieces). When tested, novel objects will be presented (the ones with cAMP molecule on). If mice had memory retention for the old objects, they will show preference and spend more time with the new objects. This figure is only for illustration. The actual experiment is done differently. The background of the picture is our favorite brain region: hippocampus.

