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ROLES OF CREB SIGNALING PATHWAY IN REGULATION OF FEAR MEMORY

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Activity-dependent gene expression through activation of Ca^{2+}-CREB signal transduction pathways has been thought to play a central role in fear memory formation. On the other hand, retrieval of fear memory triggers two time-dependent phases of reactivated memory; reconsolidation and extinction. To understand the mechanisms for determining the fate of the reactivated fear memory, we investigated roles of CREB in reconsolidation and extinction of contextual fear memory and then analyzed the brain-regions regulating reconsolidation and extinction by identifying regions where CREB-mediated gene expression is activated and then examining the role of protein synthesis in those regions on reconsolidation and extinction. We first showed that activation of CREB-mediated transcription is required for reconsolidation and long-term extinction of contextual fear memory. Using immunocytochemical analyses, we demonstrated that CREB is activated in the hippocampus/amygdala and amygdala/medial prefrontal cortex (mPFC) in the reconsolidation and extinction phases, respectively. Similar results were observed by analyzing the expression of a CREB-dependent gene, Arc. We finally showed that reconsolidation and long-term extinction of the contextual fear memory depended on new gene expression in the hippocampus/amygdala and amygdala/mPFC, respectively. Thus reactivated contextual fear memory is reconsolidated or extinguished through distinct CREB-mediated gene expression regulation in the hippocampus, amygdala and mPFC.

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