Complete genetic ablation of CREB in the brain impairs conditioned taste aversion but spares spatial memory and contextual fear conditioning

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Previous gene targeting studies addressing the role of the transcription factor CREB in mammalian long-term synaptic plasticity and memory were compromised by incomplete deletion of the ß-isoform of CREB. Therefore, we studied conditional knock-out lines with a deletion of all CREB-isoforms throughout the brain ($CREB^{NesCre}$), or specifically in the mature forebrain ($CREB^{CamKIICre7}$) and compared them with earlier data obtained in hypomorphic CREB mutants. It has been reported previously (Balschun et al., Soc. Neurosci. Abstr. 26, 2000) that both $CREB^{CamKIICre7}$ and $CREB^{NesCre}$ mutants show normal hippocampal late-LTP and late-LTD. To assess putative hippocampus-dependent learning, we tested both lines in the water maze and contextual fear conditioning. While contextual fear conditioning was normal in both lines, the mutants did show slightly reduced escape performance in the watermaze, reminiscent of the phenotype displayed earlier in the same paradigm by hypomorphic CREB mutants. However, the deficit in the watermaze was unrelated to spatial memory. Most strikingly, $CREB^{CamKIICre7}$ mice showed normal spatial preference during probe trials. We then tested $CREB^{NesCre}$ mice in conditioned taste aversion, a putatively hippocampus-independent behavior, and found a marked impairment, especially in female mice.

These data imply that CREB is not essential for assumedly hippocampus-dependent learning and memory in the mouse while it might be of relevance in extrahippocampal regions. This could reflect partial functional compensation in the adult brain through upregulation of the associated transcription factor CREM or other mechanisms. The more severe deficits of the earlier hypomorphic mutants might have been caused by low prenatal levels of CREB.

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