Conditional deletion of CC2D1A reduces hippocampal synaptic plasticity and impairs cognitive function

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Background: Coiled-coil and C2 domain containing 1A (CC2D1A) is a recently cloned protein, originally identified as a nuclear factor-kappa B activator through a large-scale screen of human genes. Human studies have shown that CC2D1A dysregulation may contribute to the development of major depression and nonsyndromic intellectual disability. However, the precise mechanisms by which CC2D1A regulates intellectual and psychological functions remain elusive. Because CC2D1A is highly expressed in the hippocampus, we undertook this study to examine its role in the regulation of hippocampal neuronal structure and function.

Methods: We have taken advantage of Cre/loxP recombinase-based strategy to delete CC2D1A exclusively from excitatory neurons of the mouse forebrain in a conditional manner to examine its *in vivo* relevance. Double immunofluorescent staining was used to characterize its expression. Extracellular field potential recordings were used to measure the induction of long-term potentiation (LTP). Novel object location recognition test was used to assess hippocampus-dependent memory. Golgi-Cox staining was used to visualize the morphology of individual CA1 pyramidal neurons.

Results: We have confirmed the expression pattern of CC2D1A protein and mRNA in the developing and adult mouse hippocampus. The expression levels of CC2D1A protein and mRNA in mouse hippocampal tissue lysates were relatively high during the embryonic stage and the first postnatal week, and remained constant in adulthood. Double immunofluorescent staining with the mature neuronal marker NeuN revealed that nearly all of the CC2D1A-expressing cells were positive for neuronal nuclear antigen in hippocampal CA1 region. Conditional deletion of *cc2d1a* (*cc2d1a*^{-/-}) from excitatory neurons leads to impaired performance in novel object location recognition test. Consistently, *cc2d1a*^{-/-} mice displayed a deficit in the maintenance of LTP in the CA1 region of hippocampal slices. An increase of Rac1 activity was observed following *cc2d1a* deletion. Conditional deletion of *cc2d1a* also led to decreased complexity of apical and basal dendritic arbors of hippocampal CA1 pyramidal neurons.

Conclusions: Our results implicate Rac1 hyperactivity in the cognitive deficits observed in *cc2d1a*^{-/-} mice and demonstrate a novel role for CC2D1A in regulating hippocampal long-term synaptic plasticity and cognitive function.