CDKL5 DEFICIENCY AUGMENTS INHIBITORY INPUT INTO THE DENTATE GYRUS THAT CAN BE REVERSED BY DEEP BRAIN STIMULATION

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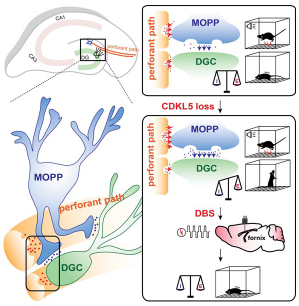
Background: CDKL5 deficiency disorder (CDD) is a neurodevelopmental disease caused by mutation of the X-linked gene cyclin-dependent kinase-like 5 (CDKL5). CDD is characterized by severe intellectual disability, gross motor impairment, early-onset epilepsy, and autistic features. Mouse models of CDD recapitulate the cognitive deficits and other characteristics of this condition. Global KO/knock-in mutation of CDKL5 or conditional CDKL5 loss in forebrain excitatory neurons impairs hippocampus-dependent memory in mice. Although loss of CDKL5 affects a number of molecular pathways, very little has been discovered about the physiological effects of these changes on the neural circuitry. Because synaptic transmission and plasticity of the perforant path (PP) to the DG play an important role in hippocampus-dependent learning and memory, we hypothesized that loss of CDKL5 causes memory deficits by specifically impairing this pathway.

Materials/Methods: We therefore assessed the hippocampus-dependent behavior, synaptic plasticity, and local circuit activity in a unique CDKL5 knockout mouse model with exon 6 deletion (B6.129(FVB)-Cdkl5tm1.1Joez/J)

Results: We found that CDKL5 haploinsufficiency in both male Cdkl5-/y and female Cdkl5+/- mice impair hippocampus-dependent learning and memory in multiple tasks including fear conditioning, passive avoidance, and Morris water maze. In vivo, loss of CDKL5 reduces long-term potentiation of the perforant path to the dentate gyrus and augments feedforward inhibition in this pathway. Ex vivo, Cdkl5-/y mice have decreased excitatory, but increased inhibitory synaptic transmission in dentate granule cells, confirming that excitatory/inhibitory input into the dentate gyrus is skewed toward inhibition after CDKL5 ablation. Furthermore, injecting the GABAergic antagonist gabazine into the dentate improved contextual fear memory in Cdkl5-/y mice. Finally, chronic forniceal deep brain stimulation rescued hippocampal memory deficits, restored synaptic plasticity, and relieved feedforward inhibition in Cdkl5+/- mice.

Conclusions: Together, our findings suggest that CDKL5 is important for maintaining proper dentate excitatory/inhibitory balance for hippocampal memory and forniceal DBS as the possible translational intervention for treating CDD.

Images / Graph / Table


CA1
CA3
DG
perforant path
MOPP
perforant path
DGC
perforant path
MOPP
DGC
CDKL5 loss
perforant path
MOPP
DGC
DBS
fornix