Dendritic Spine Instability in a Mouse Model of CDKL5 Disorder is rescued by IGF-1

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CDKL5 (Cyclin-dependent kinase-like 5) is mutated in many severe neurodevelopmental disorders, including atypical Rett syndrome. CDKL5 was shown to interact with synaptic proteins important for the organization of the postsynaptic density and dendritic spine morphology. An in vivo analysis of CDKL5 role in dendritic spine dynamics and synaptic molecular organization is still lacking. *In vivo* 2-photon microscopy of the somatosensory cortex of CDKL5$^{-/y}$ mice was applied to monitor structural dynamics of dendritic spines. Synaptic function and plasticity was measured using electrophysiological recordings of excitatory post-synaptic currents and long-term potentiation (LTP) in brain slices, and assessing the expression of synaptic PSD-95 protein. Finally, we studied the impact of IGF-1 treatment on CDKL5 null mice, to restore the synaptic deficits. Adult mutant mice showed a significant reduction in spine density and PSD-95-positive synaptic puncta, a reduction of persistent spines and impaired LTP. In juvenile mutants short-term spine elimination but not formation was dramatically increased. Administration of IGF-1 rescued spine density, spine loss rate, and PSD-95 expression.

These data demonstrate that dendritic spine stabilization is strongly regulated by CDKL5. Moreover, our data suggest that IGF-1 treatment could be a promising candidate for clinical trials in CDKL5 patients.