Synaptic basis of intellectual disability

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A series of synaptic proteins are related to the mild intellectual disability. Cereblon is one of mild mental retardation related factor of which nonsense multation (R419X) is thought to cause the intellectual disability in the patients with IQ 50-70. However the detailed mechanism of cereblon in synapse is mostly unclear yet. Here we studied the role of Cereblon in the synaptic structure and function using multiple model systems including mouse hippocampal slices and Drosophila neuromuscular junction. The knockout mouse lacking the expression of cereblon shows generally normal gross brain anatomy as well as spine density and length. However cereblon KO animal shows clear impairment in cognitive function analyzed by Y-maze test, passive avoidance test and novel object recognition test. The synaptic function in cereblon KO animal are intact in Schaffer-collateral synapse in hippocampus with normal input-output relationship, LTP, LTD, long-lasting LTP, and mGluR-induced LTD. Interestingly the paired-pulse ratio was altered in KO animal, implying the changes in presynaptic release function. To further confirm the function of cereblon and to identify its signaling mechanism, we monitored the synaptic function of Drosophila cereblon KO animal. The changes in paired-pulse ratio were also monitored in KO animal. Interestingly the mutants also showed the increased evoked excitatory postsynatpic currents and size of releasable neurotransmitter pool as well. These results suggest that the changes in presynaptic neurotransmitter release could be involved in the pathology of mild mental retardation in the patients with cereblon mutation. In addition, we studied the effect of thalidomide on synaptic functions and cognitive behaviors using a mouse model. Thalidomide led to cognitive deficits in learning behavior in a passive avoidance test and in a novel object recognition test, increased anxiety in an elevated plus maze test, and increased depressive behaviors in a tail suspension test. Interestingly, thalidomide elevated BK channel expression in the plasma membrane and BK channel activity in the hippocampus. Thalidomide also increased the paired pulse ratio of excitatory postsynaptic current, which suggests a decreased probability of glutamate release. Furthermore, the changes in the paired pulse ratio and in BK channel activity were blocked by paxilline, a BK channel blocker. Finally, we found that thalidomide-induced cognitive dysfunctions were restored by paxilline treatment. These results suggest that thalidomide-mediated BK channel hyperfunction is responsible for the pathological mechanism of thalidomide-associated reversible memory loss.