Behavioral and neurochemical analyses in the Piccolo knockdown mice as a new animal model for schizophrenia

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[Background] Schizophrenia is a serious mental disorder and is characterized by the positive symptom, negative symptom and cognitive dysfunction. Several risk factors such as genetic and environmental factors are generally involved in contributing to the onset of schizophrenia. Previous reports revealed that the expression levels of PCLO mRNA enhanced in the postmortem brain of the patients with schizophrenia and in the SH-SY5Y cells after treatment with atypical antipsychotics. The PCLO gene encodes Piccolo, a presynaptic cytomatrix protein, which serves in synaptic vesicle trafficking in the presynaptic active zone. We reconfirmed that the expression levels of PCLO mRNA and Piccolo protein were increased in the prefrontal cortex (PFC), of mice subchronically treated with risperidone and clozapine. Accordingly, we tried to investigate the behavioral and neurochemical phenotypes in the Piccolo knockdown mice.

[Methods] Male C57BL/6J mice were injected the AAV-miPCLO or AAV-Mock vectors into the PFC, and were assessed by various behavioral tests 4 weeks after the AAV vector injection. For in vivo microdialysis combined with optogenetical methods, the AAV-ChIEF vectors were injected additionally into the PFC with the above vectors, and the neuronal activation by optical stimulation and the measurement of extracellular neurotransmitters were performed in the dorsal striatum (dSTR).

[Results] The Piccolo knockdown mice showed hyperlocomotion in the novel environment, impaired acoustic prepulse inhibition and cognitive deficits. Furthermore, the Piccolo knockdown mice exposed to mild social defeat stress exhibited behavioral despair and social withdrawal. Although the control mice showed increased glutamate and decreased dopamine in extracellular levels by the optical activation of the PFC projections in the dSTR, these responses in the Piccolo knockdown mice were blunted. To support with these results, the depolarization-evoked glutamate and GABA levels reduced in the dSTR of the Piccolo knockdown mice. In contrast, the depolarization-evoked dopamine levels in the same brain region enhanced.

[Conclusions] Our observations suggest that Piccolo in the PFC plays an important role in neurotransmission in the projective region from the PFC, the dSTR, and its malfunction induces psychiatric phenotypes similar to schizophrenia symptom. Thus, enhanced PCLO mRNA expression in the patients with schizophrenia could be due to the therapeutic efficacy.