外国語要約

Thesis title: A role of PPARα in the pathogenesis of schizophrenia and its potential as a novel therapeutic target molecule

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The pathophysiology of schizophrenia, a major psychiatric disorder, remains elusive. We have previously reported that dietary deprivation of polyunsaturated fatty acid (PUFA) during a neurodevelopmental stage in mice elicited schizophrenia-like phenotypes in the offspring at adulthood, and that the nuclear receptor peroxisome proliferator-activated receptor (PPAR)/retinoid X receptor (RXR) system acts as an upstream mechanism linking PUFA deficiency and the behavioral phenotypes. In the current study, we examined whether the PPAR/RXR system is associated with the pathophysiology of schizophrenia. Firstly, we screened for genomic variants using molecular inversion probe-based targeted next-generation sequencing using the samples of 1,200 Japanese patients with schizophrenia. By referring to the whole genome sequencing databases of the Japanese cohort (ToMMo) (n = 3,554), we focused on four potentially functional and schizophrenia-specific variants, namely c.209-2delA, His117Gln, Arg141Cys, and Arg226Trp, of the *PPARA* gene that encodes the PPARα subtype. The c.209-2delA variant caused skipping of exon 4, thereby generating a premature termination codon. All the three missense variants significantly decreased the activity of PPARα as a transcription factor *in vitro*. Next, we evaluated the *in vivo* effects of PPARα deficiency, by preparing *Ppara* KO mice with the CRISPR/Cas9n technology. The *Ppara* KO mice exhibited schizophrenia-relevant phenotypes, including behavioral abnormality, and decreased spine density in the dendrites of pyramidal neurons in the prefrontal cortex. Finally, we revealed that oral administration of fenofibrate, a clinically used PPARα agonist, alleviated spine pathology induced by phencyclidine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, and that pre-treatment with fenofibrate suppressed the sensitivity of mice to another NMDA receptor antagonist, MK-801. Collectively, these results demonstrate a role of PPARα in schizophrenia pathophysiology, and support the idea that PPARα can serve as a novel therapeutic target for schizophrenia.