外国語要旨

学位論文題目：

Roles of brain-expressed fatty acid binding proteins in pathogenesis of schizophrenia and autism spectrum disorder

氏名：SHIMAMOTO Chie

要旨：

Schizophrenia and autism spectrum disorder (ASD) are caused by multiple genetic factors, environmental insults and an interaction of these factors. Fatty acids have attracted much attention in the pathophysiology of these diseases. Intracellular transport of fatty acids requires chaperone molecules called fatty acid binding proteins. We have previously reported that *Fabp7* (brain-type fatty acid binding protein), one of the *Fabp* family members, plays a role in PPI (prepulse inhibition), an intermediate phenotype for mental illnesses, and that *FABP7* is genetically associated with schizophrenia and bipolar disorder. In addition to FABP7, the brain also expresses other FABP members, namely, FABP3 and FABP5. We identified and reported several rare nonsynonymous polymorphisms of the brain-expressed genes *FABP3*, *FABP5* and *FABP7* from schizophrenia and ASD, diseases known to partly share genetic architecture.

Here, we conducted further studies to better understand the contribution of these genes make to the pathogenesis of schizophrenia and ASD performing a variety of approaches including human genetics, molecular and cellular biology, biochemistry and animal studies.

First, since our previous work showed upregulation of *FABP7* transcripts in the prefrontal cortex of schizophrenic postmortem brains, we extended the transcript expression studies to *FABP3* and *FABP5* using the same sample set. We also determined the expression levels of *FABP3*, *FABP5* and *FABP7* in drug-naïve schizophrenic lymphocytes and autistic postmortem brains. We detected elevated mRNA expression levels of *FABP5* in schizophrenia, and of *FABP7* in ASD, and decreased *FABP5* in peripheral lymphocytes. The results suggest that *FABP5* is related to schizophrenia and *FABP7* may act in a disease pathway shared between schizophrenia and ASD.

Next, we performed comprehensive mutation screening using a patient cohort and identified six missense and two frameshift variants from the three *FABP* genes. When

overexpressed in cultured cells, the two frameshift proteins, FABP3 E132fs and FABP7 N89fs, formed cellular aggregates and were unstable, while the four missense mutants with predicted possible damaging outcomes showed no changes in intracellular localization. On the other hand, examining ligand binding properties of missense mutants, we found that FABP7 S86G and FABP7 V126L lost their preference for docosahexaenoic acid to linoleic acid. These findings imply that unbalanced utilization of essential fatty acids may contribute to the pathogenesis of schizophrenia and ASD.

Finally, mice deficient in *Fabp3*, *Fabp5* and *Fabp7* were evaluated in a systematic behavioral test battery. The *Fabp3* knockout (KO) mice showed decreased social memory and novelty seeking, *Fabp7* KO mice displayed decreased PPI, impaired sociability, hyperactive and anxiety-related phenotypes, while *Fabp5* KO mice showed no apparent phenotypes. Our detected behavioral alterations in *Fabp3* and *Fabp7* KO mice suggest critical roles for these genes in psychiatric illness phenotypes.

In conclusion, this study suggests that dysregulation or dysfunction of brain-expressed FABPs could represent an underlying disease mechanism involving lipid metabolic abnormality in a subset of schizophrenia and ASD sufferers.