

**PM371****Measurement of genomic copy number and DNA methylation levels of LINE-1 in the brains of poly(I:C) mouse model**

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**Abstract**

We previously reported the increased copy number of retrotransposon LINE-1 in neurons of schizophrenia as well as animal models of psychiatric disorders including poly(I:C) model. Exposure of poly(I:C), a chemical analogue of double-stranded RNA, in the prenatal stage of animal induces the behavioral impairment in its later developmental stage. Therefore, this animal model provides the opportunity to elucidate the molecular mechanism of increased LINE-1 retrotransposition during prenatal stage. Here we examined LINE-1 copy number and DNA methylation levels of brain tissues in poly(I:C) mouse. We injected poly(I:C) with various doses to pregnant mice, and found that LINE-1 copy number of pups was increased in a dose-dependent manner. Especially, pregnant mice with consecutive poly(I:C) injection showed most significant increase of LINE-1 copy number. Interestingly, DNA methylation levels of active LINE-1 subfamilies in the adult stage showed subfamily-dependent methylation changes, suggesting the distinctive functional roles among the active subfamilies.

**PM372****Functional change of serotonin 2C receptors in N-Methyl-D-aspartate (NMDA) receptor hypofunctional condition**

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**Abstract**

**Background:** N-Methyl-D-aspartate (NMDA) receptor hypofunction may contribute to the pathophysiology of schizophrenia. Clozapine, a highly effective treatment for schizophrenia, targets serotonin 2C receptors (5-HT<sub>2</sub>CR) with high affinity. 5-HT<sub>2</sub>CR modulate dopamine release. The interaction between 5-HT<sub>2</sub>CR and dopamine in an NMDA receptor hypofunctional condition, however, is not fully understood. We evaluated 5-HT<sub>2</sub>CR function for dopamine levels in an NMDA receptor antagonist-induced rat model of schizophrenia.

**Method:** Schizophrenia model rats were treated chronically the NMDA receptor antagonist MK-801. We prepared four groups: 1) Naïve rats with single administration of MK-212; 5-HT<sub>2</sub>CR agonist, 2) Naïve rats with single administration of MK-801, 3) Chronically MK-801-treated rats with single administration of MK-212, and 4) Chronically MK-801-treated rats with single administration of MK-801. Extracellular dopamine levels in the prefrontal cortex (PFC) were measured using *in vivo* microdialysis. An open field test was used for behavioral assessment

**Results:** The PFC dopamine level was significantly increased by single administration of MK-801 in naïve rats, but not in chronically MK-801-treated rats. The PFC dopamine level was not affected by single MK-212 administration in naïve rats, but was significantly increased in chronically MK-801-treated rats. Total

distance traveled in the open field test tended to be increased by single MK-801 administration in naïve rats, and was significantly increased in chronically MK-801-treated rats. It was not affected by single MK-212 administration in naïve or chronically MK-801-treated rats.

**Conclusion:** These findings indicate that function of 5-HT<sub>2</sub>CR is altered to regulate excitatory the PFC dopamine in NMDA receptor hypofunctional condition.

**PM373****Behavioral and neurochemical abnormalities in heterozygous Reelin Orleans mutant mouse model of schizophrenia**

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**Abstract**

Reelin is an extracellular matrix protein, which plays a pivotal role in embryonic neuronal migration and development of the laminar structure of cerebral cortex. In the adult brain, Reelin is produced by GABAergic interneurons and plays a role in synaptic plasticity, dendritic morphology, and cognitive function. Binding of the secreted Reelin to its receptors (VLDLR and ApoER2), induces phosphorylation of intracellular adaptor protein Disabled-1, which may be exclusively involved in Reelin signaling in the nervous system. Genetic association studies suggest that REELIN gene is associated with psychiatric disorders including schizophrenia. We have recently found novel pathogenic copy number variations (CNV) in Japanese schizophrenia patients, including deletions at 7q22.1 on which Reelin gene is located. In the present study, we carried out comprehensive behavioral and neurochemical analyses in heterozygous Reelin Orleans mutant (ROM) mice, in which a 220 nucleotide deletion exists in the 3' region of the Reelin gene, resulting in a frame shift with production of the C-terminal truncated Reelin. ROM is closely related to the CNV discovered in our schizophrenia patient. The mutant mice showed a reduction of natural aversion to illuminated open areas in the open field test, some abnormalities in 3-chambered social interaction test, and impairments in motor coordination and learning in rotarod test. Methamphetamine-induced hyperactivity was significantly reduced in ROM mice compared with WT mice, which was associated with alteration of methamphetamine-induced dopamine release in the nucleus accumbens. Region-specific alterations of GABAergic markers, including GAD67 and GABA-A receptor subunit expression levels were demonstrated in the brains of mutant mice. These results suggest that CNV of Reelin gene may lead to abnormalities in emotion, social interaction and motor learning/flexibility, which could be associated with altered dopaminergic and GABAergic neuronal systems.

**PM374****Deficiency of neurogranin, a susceptible gene for schizophrenia, causes behavioral phenotypes related to schizophrenia and immaturity of the dentate gyrus in mice**

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**Abstract**

Large-scale genome-wide association studies have identified susceptibility loci for schizophrenia in the gene encoding neurogranin (NRGN). Neurogranin is a neuron-specific calmodulin binding protein abundantly expressed in brain regions implicated in schizophrenia pathophysiology, such as the hippocampus and prefrontal cortex. *Nrgn* knockout (KO) mice were previously shown to exhibit aberrant behavioral phenotypes involving deficits in cognitive functions and abnormal emotional behaviors. In this study, we examined additional behavioral and molecular traits relevant to schizophrenia in *Nrgn* KO mice. The mutant mice exhibited a series of behavioral abnormalities that resemble those of schizophrenics, including hyper-locomotor activity and impairments in working memory, social behavior and sensorimotor gating. In the DG, mRNA expressions of immature and mature granule cell (GC) markers were not significantly changed in almost all young mutant mice (<10 weeks old). On the other hand, older animals (>20 weeks old) showed increased expression of immature GC markers and decreased expression of mature GC markers. Bioinformatics analyses of transcriptome data also revealed that the gene expression patterns of the DG of older mutants are significantly similar to those of normal young mice. These results indicate that adult but not juvenile *Nrgn* KO mice show immature DG phenotype, which has been proposed as a novel endophenotype of schizophrenia, and that both genetic and undetermined (e.g., stress and aging) factors might act together to reverse matured GCs to a pseudo-immature status. *Nrgn* KO mice might be a novel animal model recapitulating the fact that typical onset of schizophrenia occurs during late adolescence or early adulthood. The late onset of the immature phenotypes would provide unique opportunities for studying molecular mechanisms of the disorder.

**PM375**

Electroconvulsive shock ameliorated the schizophrenia-like behavior and attenuated the glial activation in the hippocampus of Gunn Rat

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**ABSTRACT**

**Background:** Although electroconvulsive therapy (ECT) is regarded as one of the efficient treatments for intractable psychiatric disorders, the mechanism of therapeutic action remains unclear. Recently, many studies indicate that ECT affects the immune system, including the immune-related cells, such as microglia, astrocytes, and lymphocytes. Moreover, microglial and astrocytic activation has been implicated in postmortem brains of schizophrenia patients. We previously demonstrated that Gunn rats showed schizophrenia-like behavior and microglial activation in their brains. In this study we examined the effects of electroconvulsive shock (ECS), an animal counterpart of ECT, on schizophrenia-like behavior, microgliosis and astroglial activation in the hippocampus of Gunn rats.

**Methods:** The rats were divided into 4 groups, i.e., Wistar sham, Wistar ECS, Gunn sham and Gunn ECS. ECS groups received ECS once daily for 6 consecutive days. Subsequently, prepulse inhibition test (PPI) was performed on all animals. After PPI, immunohistochemistry analysis was carried out to determine microglial

activation and astrocytic activation, using anti-CD11b and anti-GFAP antibody, respectively.

**Results:** We found PPI deficit in Gunn rats compared to Wistar rats, and it was significantly improved by ECS. In immunohistochemistry analysis revealed that there is significant higher expression of CD11b and GFAP in Gunn rats compared to Wistar rats. ECS attenuated the expression of both CD11b and GFAP in Gunn rats. The effect of ECS on the number of microglia in the hippocampus will be shown in the poster presentation.

**Conclusion:** Our findings indicate that ECS ameliorates schizophrenia-like behavior in Gunn rats and attenuates both microglial activation and astrocytic activation in the hippocampus of Gunn rats. Accordingly, therapeutic effects of ECT may be exerted, at least in part, by inhibition of glial activation.

**PM376**

Mountain-cultivated ginseng attenuates phencyclidine (PCP)-induced schizophrenia-like psychosis in mice

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**Abstract**

**Objective:** Escalating evidence indicated that ginseng treatment protects memory deficit and psychotic behaviors. Although the underlying mechanism of schizophrenia remains elusive, oxidative stress induced by glutathione (GSH) loss might be involved in the pathogenesis of this disorder. We have selected mountain-cultivated ginseng (MG) out of various ginseng extracts to investigate firstly effect of ginsenosides on the psychosis induced by PCP

**Method:** PCP (10 mg/kg/day, s.c.) was administered for consecutive 14 days. Novel object recognition-, forced swimming-, and social interaction-tests were performed 7 days after withdrawal from PCP. In addition, behavioral sensitization to an acute challenge of PCP (3 mg/kg, s.c.) was evaluated. The parameter of oxidative stress and GSH-dependent system were examined in the prefrontal cortex (PFC). MG (200 mg/kg/day, i.p.) was administered throughout the whole experimental period.

**Result:** Repeated treatment with PCP significantly increased the immobility time in the forced swimming test and behavioral sensitization, while PCP significantly decreased the interaction time in the social interaction test and the novel object exploration in the novel object recognition test. Consistently, the oxidative stress was significantly increased, while GSH was significantly decreased in the PFC by repeated PCP treatment. MG significantly attenuated the behavioral abnormalities and oxidative damage induced by PCP.

**Conclusion:** MG attenuates PCP-induced schizophrenia-like psychosis in mice through enhancing antioxidant potentials [This study is supported by a grant (Project No.S111415L020100) of the 'Forestry Technology Projects' provided by the Korea Forest Service].