of oxytocin. Moreover, the degree of neural overlap was significantly low in ASD model mice. These findings offer insight into our understanding of the neural mechanisms of empathy and the development of therapeutic treatment of ASD.

PT677

c-Fos immunoreactivity in hypoactive and hyperactive Dopamine-deficient mice
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Abstract
Objectives: Parkinson’s Disease (PD) is a neurodegenerative disorder with the loss of dopaminergic neurons, having severe difficulties in performing normal motor movements due to the decreased dopamine (DA) concentration. Although PD is known primarily for its hypoactive mobility, it has been reported that PD patients can induce kinesia paradox, a condition where patients can perform complex motor movements efficiently, regardless of their depleted DA. The mechanism of kinesia paradox is still unclear, not knowing whether this phenomenon is DA-related. Here we observe and analyze the biological mechanism and its cell activation patterns that explain the ameliorated motor movements while the DA is depleted.

Method: As a model of PD, Dopamine-deficient (DD) mice were utilized. In DD mice, their tyrosine hydroxylase (TH) gene is inactivated, disabling them from synthesizing L-Dopa from tyrosine, and ultimately having no DA since there is no L-Dopa to synthesize. We injected L-Dopa onto DD mice to let them acquire DA; 72 hours after their last L-Dopa injection, the DA in their brain get heavily depleted, however becoming hyperactive when they were put under a novel environment. To monitor their cell activation patterns, we observed their c-Fos immunoreactivity in the striatum and hippocampus.

Result: We find that comparing to Wild-type (WT) mice, the hypoactive non-habituated DD mice have significantly low c-fos immunoreactivity in the striatum and hippocampus. In addition, when DD mice were put into a novel environment for 4 hours, making them hyperactive, their c-fos immunoreactivity were strikingly high in both areas.

Conclusion: These results indicate how the increase of c-Fos immunoreactivity in the striatum and hippocampus is heavily linked to the hyperactivity in the DA-deprived mice. From above, this supports the notion that for the hyperactivity during the DA-deprived state, high neuronal cell activities in the striatum and hippocampus could induce the hyperactivity.

PT678

Enhancement of the accumbal dopamine release by the gene mutation of synaptic vesicle protein 2A (Sv2aL174Q)
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Abstract
SV2A is a prototype synaptic vesicles protein and regulates action potential-dependent synaptic release of neurotransmitter. We previously reported that SV2A mutant rats, carrying a missense mutation (L174Q) in the Suv2a gene, showed impaired hippocampal GABA release and enhanced seizure susceptibility. Since recent studies reported a significant association of genetic SV2A polymorphism with schizophrenia (Schizophr. Res., 141, 262, 2012), we performed in vivo microdialysis and behavioral studies using the SV2A mutant rats to evaluate the role of SV2A in controlling accumbal dopaminergic neurotransmission. In vivo microdialysis studies showed that the sv2a gene mutation significantly increased both depolarization (100 mM K⁺)- and methamphetamine (MAP, 100 µM)-induced dopamine release in the nucleus accumbens (NAc) without affecting basal dopamine release and dopamine contents. In behavioral studies, MAP (1 mg/kg, i.p.)-induced hyperlocomotion was significantly augmented by the sv2a gene mutation. Haloperidol (0.5 mg/kg, i.p.) completely suppressed MAP-induced hyperlocomotion both in SV2A mutant and control (F344) rats. The present results suggest that dysfunction of SV2A by the missense mutation (L174Q) enhances synaptic dopamine release in the NAc, which may be linked to vulnerability to psychotic disorders.

PT679

Apathy and striatal dopamine receptor type 2-expressing medium spiny neurons
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Abstract
Apathy is defined as the quantitative reduction of voluntary, goal-directed behaviors. It often coincides with lesions or dysfunction of the cortico-striatal system. However, the underlying neural substrate of apathy is largely unknown. Based on the coincidence of apathy with bilateral striatal lesions or the pre-diagnosis phase of Huntington’s disease in which striatal dopamine receptor type 2-expressing medium spiny neurons (D2-MSNs) are particularly degenerated, we hypothesized that bilateral loss-of-function of D2-MSNs cause apathy.

To address this question, we combined time-controllable diptheria toxin-mediated D2-MSN-specific loss-of-function with food-reinforced instrumental tasks in mice. Loss-of-function always started in the ventrolateral striatum (VLS) and expanded concentrically day-by-day, enabling our search for the responsible region underlying apathy appearance according to behavioral onset. We found that a loss-of-function of only 17% of a specific cell type (D2-MSN) within a restricted region (VLS) was sufficient to trigger apathy. Termination of diptheria toxin expression induced a restriction of cell ablation within the VLS, producing a chronic apathy model. We further demonstrated that acute optogenetic inhibition of VLS D2-MSNs cause apathy.

Taken together, our data demonstrate a key role of VLS D2-MSNs in apathy pathogenesis.

PT680

Distribution and brain function of Hyaluronan Binding Protein Involved in Hyaluronan Depolymerization (HYBID, KIAA1199) in mouse central nerve system.
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Abstract

Objective: HYBID (Hyaluronan Binding Protein involved in HA depolymerization, KIAA1199) is a hyaluronan (HA) binding protein, which involves in depolymerization of HA. It is reported that HYBID mRNA is expressed in the lung, heart, skin and brain in murine and human. However, the role of HYBID in the brain remains unclear. In this study, we have made HYBID KO mice and evaluated its function in the central nervous system.

Methods: To investigate the role of HYBID in brain, behavioral tests were performed by using HYBID KO mice. In situ hybridization was performed to investigate the localization of HYBID mRNA in mouse brain.

Results: HYBID mRNA was expressed in the brain, especially hippocampus and cerebellum in wild-type mice, but not KO. HYBID KO mice showed decreased memory ability in a novel object recognition test. The expression of Hya1 and Hyal2 mRNAs was not changed in the HYBID KO mouse brain. These results suggest that HYBID plays a key role in memory function in the brain.

Conclusion: HYBID may be involved in brain function, such as memory and learning.

Policy of Full Disclosure: None.

PT682

A novel mutation associated autism in Neuroligin1

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Abstract

Neuroligins (Nlgs) are postsynaptic adherent molecules consisting of five family members (Nlg1, 2, 3, 4X and 4Y). A number of genetic studies showed that the mutations of Nlgn2, 3 and 4 have been associated with neuropsychiatric disorders including autism spectrum disorder (ASD). However, only few genetic and functional analyses have been reported in Nlgn1.

In this study, we introduced whole-exome sequencing technique to find mutations in ASD siblings and identified a novel mutation predicted as damaging by in silico analysis. To uncover its functional significance, we performed comprehensive analyses both in vitro and in vivo.

We introduced this NlgN1 mutation into the mouse primary hippocampal neurons. The Nlgn1 mutation altered not only subcellular localization from cytoplasm to endoplasmic reticulum (ER) but also dendritic spine induction.

To address how this mutation affects behavioral phenotypes, we generated knock-in mice with Nlgn1 mutation by direct injection of CRISPR/Cas9 RNA with guide RNA. In a series of behavioral tests, we found several autistic traits, such as impaired social communication, in addition to hippocampal dependent spatial memory deficit. Furthermore, our biochemical studies revealed that Nlgn1 protein was significantly decreased in the forebrain of mutant mice (both whole lysate and synaptosomal fraction). These results suggest that this novel Nlgn1 mutation is involved in ASD traits in a haploinsufficient manner and reinforce the significant association between mutations in Nlgs and neuropsychiatric disorders.

PT683

Effects of acute administration of moderate and high caffeine doses on the spatial memory and motor coordination in mice.

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Abstract

Caffeine is the most widely consumed psycho-stimulant substances known to man. Caffeine has important effects on alertness. While moderate caffeine use is “generally recognized as safe” but heavy caffeine consumption has been associated with serious adverse health effects. The aim of this study was to evaluate the effects of moderate (0.1 gm/L) and high (1 gm/L) doses of caffeine administered mixed with drinking water on the learning and memory and motor coordination in mice. BLC57 mice were divided into 3 groups: control group (n=8 males, no caffeine), moderate dose group (n=8 males) and high dose group (n=8, males) were tested for spatial memory by the Morris-water