mice. Male ddY mice were treated with nicotine (1 mg/kg, i.p.), and the intensity and duration of nicotine-induced tremor was evaluated over 10 min. Anti-essential tremor agents were given 15 min before the nicotine injection. The medications for human essential tremor, propranolol (a β receptor antagonist), diazepam (benzodiazepine receptor agonist) and phenobarbital (a GABA A receptor stimulant), all significantly reduced the duration and intensity of nicotine-induced tremor. In contrast, neither medication for parkinsonian tremor, trihexyphenidyl (a muscarinic receptor antagonist), L-DOPA (a dopamine precursor) nor bromocriptine (a D 2 receptor agonist) affected nicotine-induced tremor. These results show that nicotine-induced tremor mimics essential tremor not only for the causative site (inferior olive), but also for the responses to anti-tremor agents, suggesting both tremor types share the common tremorgenic mechanisms.

**Abstract**

**Objective:** Recently, the number of patients suffered from mental disorders has been increased with increase of stress. The two hit hypothesis proposed that mental disorders, such as schizophrenia, bipolar and depression, may be caused by the damage in both of developmental and adult stage. VGF nerve growth factor inducible (VGF) is a neuropeptide induced by nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and so on. It is also known that this peptide is related to brain function in both of developmental and adult stages. Additionally, the expression of VGF is changed in patients with these diseases. However, detailed mechanism of VGF action in brain is still unknown. In the present study, we generated mice in which VGF expression is increased and investigated the roles of VGF in the central nervous system.

**Methods:** To investigate the role of VGF, we investigated several behavioral phenotypes using several behavioral tests, such as locomotor activity test, open field test, Y-maze test, tail suspension test, forced swimming test, and social interaction test and organization of the brain.

**Results:** These adult VGF overexpression mice showed (a) hyperactivity in home cage and novel environment, working memory impairment, lower sociality, higher depressive state compared with age-matched wildtype mice, (b) decreased the brain weight without the change of body weight, and (c) increased the lateral ventricle volume compared with wild-type mice.

**Conclusion:** These results suggest that VGF is implicated in several mental behaviors and the formation of the brain, and this transgenic mice provide good insight to research of mental disorders.

**Policy of Full Disclosure:** None.

**PT674**

**VGF overexpression mice exhibited several behavioral abnormalities with disruption of brain organization: implication in mental disorders.**

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**Abstract**

**Objective:** The present study to clarify the role of cerebellar D 2 receptors in modulating D 1 agonist SKF-38393-induced dyskinesia in rats. In normal SD rats, the D 2 agonist SKF-38393 dose-dependently elicited vacuous chewing movements (VCM), which was blocked by SCH-23390 (D 1 antagonist) and haloperidol (antipsychotic drug). Microinjection of the preferential D 2 agonist 7-OH-DPAT into lobe 9 of the cerebellum significantly inhibited SKF-38393-induced VCM. The inhibition of VCM by 7-OH-DPAT occurred in a dose-dependent manner and was blocked by simultaneous treatment with U-99194A (D 3 antagonist). In the unilateral 6-OHDA lesioned hemiparkinsonian rat model, chronic L-DOPA treatment elicited intensive dyskinesia including axial, forelimb and orolingual dyskinesia. However, microinjection of 7-OH-DPAT into lobe 9 of the cerebellum failed to alleviate L-DOPA-induced dyskinesia. The present results illustrate the important role of cerebellar D 2 receptors in modulating D 1 receptor-mediated dyskinesia, implying that stimulation of cerebellar D 2 receptors can ameliorate tardive dyskinesia in the treatment of schizophrenia.

**PT676**

**Empathic deficits in a mouse model of autism spectrum disorder**

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**Abstract**

Empathy, a high-level cognitive process, is believed to exist exclusively in humans; however, recent evidence has demonstrated empathy-like behaviors in rodents. The rodent models provide experimental platforms to investigate the neural basis for empathy and help elucidating the mechanisms underlying pathological conditions, such as autism spectrum disorders (ASDs). People with ASD have social impairments and often lack the ability to fully understand emotions in others, however, the neural substrates for the deficits remain largely unknown. In this study, we developed a fear observational system in which a mouse (observer) exhibits freezing behavior, a form of fear responses, through observation of another freezing mouse (demonstrator) that receives repetitive electrical foot shocks. We found that observers showed higher freezing responses when they had received a priming foot shock, suggesting that empathy-based behavior of mice is enhanced by a previous similar experience. Next, we investigated the relationship between neuronal populations that were active during the direct shock experience and observation of the other’s shocks in neocortical regions involved in pain coding. To detect neural activities with cellular resolution, we used a biochemical technique called catFISH. The neuronal populations that were active during the priming shock were significantly overlapped with those engaged in the fear observation, indicating that neural networks involved in firsthand and vicarious experiences are shared at the single-cell level. We then examined empathetic behaviors in ASD model mice. The ASD model was produced by intraperitoneal injection of poly(I:C) into pregnant females. In ASD model mice, observational fear was not enhanced by a priming foot shock, and this behavioral deficit was rescued by sub-chronic injection
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 hypokinesia, it has been reported that PD patients can induce kinesia paradoxa, a condition where patients can perform complex motor movements efficiently, regardless of their depleted DA. The mechanism of kinesia paradoxa 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 (Su2a(L174Q))
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Abstract

SV2A is a prototype synaptic vesicle protein and regulates action potential-dependent synaptic release of neurotransmitter. We previously reported that SV2A mutant rats, carrying a missense mutation (L174Q) in the Su2a 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 Su2a 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 Su2a gene mutation. Haloperidol (0.5 mg/kg, i.p.) completely suppressed MAP-induced hyperlocomotion both in SV2A mutant and control (F344) rats. In addition, development of locomotor sensitization (reverse tolerance) to repeated MAP treatments (0.3 mg/kg/day, 12 days) was significant enhanced in SV2A mutant rats as compared to F344 rats. The present results suggest that dysfunction of SV2A by the above 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 diphtheria 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 diphtheria 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 resulted in a transient decrease in the instrumental motivation, strengthening the evidence that VLS D2-MSNs mediate 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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