Objective: Clinical studies have shown that microduplications at 7q36.3, containing VIPR2, confer significant risk for schizophrenia. VIPR2 gene encodes the VPAC2 receptor for vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP). Lymphocytes from patients with these mutations exhibited higher VIPR2 gene expression and VIP responsiveness, but mechanisms by which overactive VPAC2 signaling may lead to these psychiatric disorders are unknown. Here we aimed to determine if the VIPR2-linkage to mental health disorders might be due to overactive VPAC2 receptor signaling during postnatal brain development by daily administration of the highly-selective VPAC2 receptor agonist Ro 25–1553 from postnatal day 1 (P1) to P14 in mice.

Results: Western blot analyses on P21 revealed significant reductions of synaptophysin and PSD-95 in the prefrontal cortex, but not in the hippocampus, in Ro 25-1553-treated mice. Furthermore, Golgi staining in adult brain revealed alterations in dendritic morphology of prefrontal cortical neurons in Ro 25-1553-treated mice. The same postnatally-restricted treatment resulted in a disruption in prepulse inhibition of the acoustic startle and cognitive impairment in the novel object recognition task in adult mice. No effects were observed in locomotor activity, sociability in the three-chamber social interaction test, or fear conditioning or extinction. In addition, Ro 25–1553 and VIP, but not PACAP, caused reductions in total numbers and length of neuronal dendrites and length of axon in mouse primary cultured cortical neurons.

Conclusions: These results suggest that overactivation of the VPAC2 receptor in the postnatal mouse leads to a reduction in synaptic proteins and alterations in dendritic morphology in the prefrontal cortex and cognitive impairments. These findings imply that the VIPR2-linkage to mental health disorders may be due in part to overactive VPAC2 receptor signaling during a critical time of neuronal maturation.

PM361

The hallucinogen D-lysergic diethylamide (LSD) decreases dopamine firing activity through 5-HT1A, D2 and TAAR1 receptors

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Abstract

D-lysergic diethylamide (LSD) is a hallucinogenic drug that interacts with the serotonin (5-HT) system binding to 5-HT1A, 5-HT2 receptors. Little is known about its potential interactions with the dopamine (DA) receptors of the ventral tegmental area (VTA). Using in-vivo electrophysiology in male adult rats, we evaluated the effects of cumulative doses of LSD on VTA DA neuronal activity, we compared these effects to those produced on 5-HT neurons in the dorsal raphe nucleus (DRN), and we attempted to identify the mechanism of action mediating the effects of LSD on VTA DA neurons. We confirmed that low doses of LSD (5–20 μg/kg, i.v.) induce a significant decrease of DRN 5-HT firing activity, but at these doses, it did not alter VTA DA neuronal activity. On the contrary, higher doses of LSD (30–120 μg/kg, i.v.) dose-dependently decreased VTA DA firing activity. The depletion of 5-HT synthesis with p-chlorophenylalanine did not modulate the effects of LSD on DA firing activity. The inhibitory effects of LSD on VTA DA firing activity were prevented by the D1 receptor antagonist haloperidol (50 μg/kg, i.v.) and by the 5-HT1A receptor antagonist WAY-100,635 (500 μg/kg, i.v.). Notably, pretreatment with the novel synthetized trace amine-associate receptor 1 (TAAR1) antagonist EPPTB (5 mg/kg, i.v.) blocked the inhibitory effect of LSD on VTA DA neurons. These results suggest that LSD at high doses strongly affects DA mesolimbic neuronal activity in a 5-HT independent manner and with a pleiotropic mechanism of action involving 5-HT1A, D1, and TAAR1 receptors.
Abstract
It was reported the unconjugated bilirubin may be associated with neurotoxicity in the developing nervous system. And it is also reported that neonatal hyperbilirubinemia might be a vulnerability factor for the development of mental disorders.

Individuals with schizophrenia show a significantly higher frequency of hyperbilirubinemia relative to patients with other psychiatric disorders and the general healthy population. We have also observed that patients with schizophrenia frequently have an elevated bilirubin plasma concentration on admission to the hospital.

There have been reports of a positive relationship between schizophrenia and hyperbilirubinemia. We assume that a high serum unconjugated bilirubin concentration has a pathogenic effect on the development of the brain and consequently the behavioral abnormalities of schizophrenia.

The Gunn rat, a mutant of the Wistar strain, which has been used in several previous studies as an animal model of bilirubin encephalopathy. The Gunn rat has a genetic deficiency in glucuronyltransferase then revealed hyperbilirubinemia. Some Gunn rats have many of the same neurological symptoms and histopathological lesions that are exhibited by hyperbilirubinemnic human newborns. It has been reported that the neural damage in Gunn rats almost always occurs in the first month after birth.

We assumed Gunn rats as one of the schizophrenia animal models. To validate as the schizophrenia model, we examined the acute behavioral abnormalities of Gunn rats and Wistar rats, after injection of NMDA-antagonist ketamine.

The locomotor stimulatory effect of ketamine was significantly greater in Gunn rats compared with Wistar rats, and furthermore interfered PPI after ketamine injection were observed in Gunn rats.

Gunn rats were more vulnerable to ketamine than Wistar rats.

The results related to the face, predictive and construct validities.

PM364
Early risperidone exposure affects serotonin, dopamine and cannabinoid receptors binding density differently in male and female juvenile rats
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Abstract
Background: Antipsychotic drugs were developed to treat schizophrenia in adults, however they have been increasingly prescribed in children and adolescents without understanding the underlying mechanisms. The serotonin, dopamine and cannabinoid pathways are involved in antipsychotic efficacy and neurodevelopment, as well as the pathophysiology of schizophrenia. This study investigated the effects of early risperidone exposure on binding densities of serotonin 5-HT2A receptors (5-HT2A), 5-HT2C receptors (5-HT2C), dopamine D1 receptor (D1), D2 receptor (D2), receptor D2, and cannabinoids CB1 and CB2 receptors (CB1 and CB2) in the prefrontal cortex (PFC), cingulate cortex (Cg) and nucleus accumbens (NAc) and caudate putamen (CPu) of juvenile rats.

Methods: Male and female Sprague Dawley rats treated orally three times per day with risperidone (0.3 mg/kg) or vehicle (control) starting from postnatal day (PD) 23 (±1 day) for 3 weeks (a period corresponding to the childhood-adolescent period in humans). Quantitative autoradiographic methods were used to detect binding density of [3H]ketafserin (for 5-HT2A), [3H]mesulergine (for 5-HT2C), [3H]SCH23390 (for D1), [3H]raclopride (for D2), and [3H]CP55940 (binding to CB1 and CB2) and [3H]SR141716A (for CB2).

Results: Risperidone decreased [3H]ketanserin binding in the PFC of female rats (p<0.05), while it significantly attenuated the [3H]SCH23390 binding in the PFC and Cg of male rats (p<0.05). However, risperidone had no effect on [3H]mesulergine binding in both genders. Risperidone significantly increased the [3H]CP55940 bindings in the PFC, NAc (p<0.01), and CB1, CPu of male rats (p<0.05), but not in female rats. Risperidone tended to increase [3H]SR141716A binding in the PFC (p=0.055), NAc (p=0.055) and significantly enhanced it in the CPu of male rats only (p<0.05).

Discussion: These results suggested that early risperdone exposure affected serotonin, dopamine and cannabinoid neurotransmission differentially in male and female rats. Further studies are necessary to investigate whether risperidone treatment has differential long-term effects between males and females.

PM365
Effects of sulforaphane in the maternal immune activation model of schizophrenia
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Abstract
Objective: Accumulating evidence suggests the role of inflammation and oxidative stress in the pathophysiology of schizophrenia. Keap1-Nrf2 signaling plays an important role in the anti-inflammatory and anti-oxidant effects. Sulforaphane (SFN), a potent Nrf2 activator, has a potent anti-inflammatory and anti-oxidant activity. It is reported that SFN could attenuate behavioral abnormalities in mice after administration of methamphetamine or phencyclidine. The objective of this study was undertaken to examine whether glucoraphanin (a glucosinolate precursor of SFN) can prevent the onset of schizophrenia-like behavioral abnormalities in the offspring after maternal immune activation.

Methods: The synthetic double strand RNA polyriboinosinic-polyribocytidilic acid (poly I:C; 5.0 mg/kg) or saline were injected intraperitoneally on days E12 – E17 (a period corresponding to the childhood-adolescent period in humans). Quantitative autoradiographic methods were used to detect binding density of [3H]ketafserin (for 5-HT2A), [3H]mesulergine (for 5-HT2C), [3H]SCH23390 (for D1), [3H]raclopride (for D2), and [3H]CP55940 (binding to CB1 and CB2) and [3H]SR141716A (for CB2).

Results: Risperidone decreased [3H]ketafserin binding in the PFC of female rats (p<0.05), while it significantly attenuated the [3H]SCH23390 binding in the PFC and Cg of male rats (p<0.05). However, risperidone had no effect on [3H]mesulergine binding in both genders. Risperidone significantly increased the [3H]CP55940 bindings in the PFC, NAc (p<0.01), and CB1, CPu of male rats (p<0.05), but not in female rats. Risperidone tended to increase [3H]SR141716A binding in the PFC (p=0.055), NAc (p=0.055) and significantly enhanced it in the CPu of male rats only (p<0.05).

Discussion: These results suggested that early risperdone exposure affected serotonin, dopamine and cannabinoid neurotransmission differentially in male and female rats. Further studies are necessary to investigate whether risperidone treatment has differential long-term effects between males and females.