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PS140
Suppression of reward-induced dopamine release in the nucleus accumbens of the chronic mild stress model rats
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Abstract
One of the main symptoms of major depressive disorder is an inability to experience pleasure, anhedonia. Dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) constitute the brain reward system. Various kinds of rewards and drugs of abuse elevate the dopamine (DA) release in the NAc, which is considered to be important to generate pleasant emotion. In the animal models of depression, sucrose preference is reported to be reduced, and this reduction is thought to be due to the suppression of VTA dopaminergic neurons. In this study, using a chronic mild stress (CMS) model which is one of the animal models of depression, we examined the influence of CMS on reward-induced DA release in the NAc and the effect of SSRI treatment on the alteration of DA release induced by CMS. Male Sprague-Dawley rats (4 week old at the start of CMS) were exposed to CMS for 4 weeks. Then, escitalopram (10mg/kg/day) or vehicle was intraperitoneally administrated for 3 weeks. Extracellular DA levels in the NAc were measured using an in vivo microdialysis technique, and reward (30% sucrose water)-induced DA release was examined. In the non-CMS groups, the reward elevated extracellular DA levels regardless of presence or absence of SSRI treatment. In the CMS group without SSRI treatment, the reward-induced DA release disappeared. Chronic treatment with escitalopram recovered the reward-induced DA release in the CMS group. These results suggest the possibility that the reward-induced DA release in the NAc is useful for an index to quantitatively evaluate the anhedonic condition and the effect of SSRI treatment.

PS141
Depressive Symptoms, as a side effect of Interferon-α therapy induced by induction of indoleamine 2,3-dioxygenase 1
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Abstract
Objective of Study: To investigate whether indoleamine 2,3-dioxygenase 1 (IDO1) mediated L-tryptophan (TRP)-kynurenine (KYN) pathway metabolism plays a critical role in depressive symptoms occurring as a side effect of interferon (IFN)-α therapy. We measured the levels of TRP metabolites in serum of hepatitis C virus (HCV) patients. To investigate whether depression-like behavior is affected by IFN-γ treatment, we transfected pCpG-Muγ plasmid, continuously expressing murine IFN-γ, to normal mice and IDO1 gene deficient (KO) mice.

Methods: We measured the levels of TRP metabolites in serum of HCV patients with and without depression symptom during IFN-α therapy using HPLC. For the animal model, C57BL/6J mice and IDO1 KO mice were transfected with murine IFN-γ expressing plasmid by a hydrodynamic tail vein injection.

Summary of results: In serum of HCV patients, the levels of TRP metabolites were significantly changed. Especially, the increase in serum 3-hydroxykynurenine (3-HK) concentration in depressive HCV patients was much larger than that in HCV patients without depressive symptoms. The ratios of serum KYN/TRP, reflecting IDO1 activity, and 3-HK/kynurenic acid (KA) were increased in depressive and non-depressed HCV patients with therapy but the increases in serum KYN/TRP and 3-HK/KA ratios in depressive patients disappeared completely after the end of the therapy. When pCpG-Muγ was transfected to normal mice, depression-like behavior was significantly increased. Additionally, IFN-γ gene transfer to mice caused a dramatically changes of TRP metabolites concentrations in serum, as same as HCV patients. On the other hand, genetic deletion of IDO1 abrogated the increase depression-like behavior after IFN-γ gene transfer.

Conclusions: Our results indicate that the KYN pathway of IDO1-mediated TRP metabolism plays a critical role in depressive symptoms associated with IFN.

PS142
Ketamine is effective in an animal model of treatment resistant depression
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Abstract
Background: Clinical studies show that ketamine, an NMDA receptor antagonist, produces a rapid and sustained antidepressant response, while classical antidepressants require repeated treatment for up to four weeks to produce similar effects. Due to the high number of individuals with affective disorders, which are resistant to the established monoaminergic drug therapies, there is a great need to develop novel and more effective antidepressants. Ketamine has a potential to be applied as an alternative intervention to patients with treatment resistant depression, but given methodological difficulties there are only few studies evaluating its effects in adequate animal models.
**Aims:** This project aims to assess whether systemic treatment with ketamine may improve the behavioral response in an animal model of a treatment-resistant condition.

**Methods:** Male Sprague-Dawley rats received subcutaneous injections of ACTH (100ug/ra/day) or vehicle during 14 days. On the 14th day the animals were exposed to the pre-test session of forced swim (FST) and after 24h they were exposed to the open-field test (OFT) followed by the FST test session. The animals received an intraperitoneal injection of ketamine (15mg/kg) or vehicle or imipramine (3 injections of 15mg/kg) 1h before the test session.

**Results:** The immobility time during the pre-test was increased on the group treated with ACTH (F(14,37)=3.464; *p<0.05; Dunnett). Ketamine, but not imipramine, reduced the immobility time when exposed to the test session (F(14,37)=4.002; *p<0.05; Dunnett). The OFT showed that the drugs did not increase the locomotor activity.

**Conclusion:** The data suggest that ACTH treatment can induce a pro-depressive-like effect, which highlights its role as an inducer of a treatment-resistant condition. The results reinforce the potential antidepressant-like effects of ketamine in a treatment-resistant condition, thus corroborating the literature findings. Further studies are necessary to investigate the mechanisms which ketamine induces its effects on treatment-resistant rats.

**Keywords:** depression, antidepressants, ketamine, treatment-resistant.

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**PS143**

**Resetting of neuronal maturation in the adult brain: a novel candidate cellular mechanism of electroconvulsive treatment**

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**Abstract**

Despite a long history of clinical use and well-known high efficacy for depression, the mechanism of action of electroconvulsive therapy (ECT) remains poorly understood. Accumulating evidence suggests that the regulatory mechanism of neuronal maturation could be a promising target for treating psychiatric disorders. In the present study, to explore the cellular mechanism of ECT, we examined the effect of electroconvulsive stimulation (ECS), an animal model of ECT, on the maturation status of granule neurons in the hippocampal dentate gyrus of adult mice. Single or a few times of ECS immediately reduced expression of mature neuronal markers in almost entire population of granule neurons and induced immature neuron-like functional properties such as higher excitability. The phenotypes of the ECS-treated neurons resembled those of the intermediate developmental stage. Repeated ECS stabilized such immature-like phenotypes without causing further phenotypic changes toward the younger stage. This stabilization process required NMDA receptor activation likely supported by an excitatory shift of synaptic excitation/inhibition balance in the ECS-treated neurons. These results demonstrate that brief neuronal activation by ECS and subsequent enhancement of excitability can consistently reset mature hippocampal neurons to the particular immature state. The global increase in neuronal excitability accompanying this resetting could improve perturbed neuronal activity in pathological conditions and thus may be relevant to highly effective antidepressant action of ECT.

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**PS144**

**Dopamine D1 receptor in the medial prefrontal cortex mediates behavioral resilience under stress in mice**

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**Abstract**

Physical and psychological stress can cause not only emotional and cognitive disturbance, but also behavioral resilience to stress, depending on the duration and severity of stress. Whereas rodent studies have extensively examined neural mechanisms about how stress induces harmful behavioral consequences, mechanisms that underlie stress-induced behavioral resilience remains poorly understood. Using social defeat stress in mice, we previously reported that social defeat stress preferentially activates the dopaminergic pathway to the medial prefrontal cortex (mPFC), and that repetition of social defeat stress attenuates this activation, leading to social avoidance. Here we show a role of dopamine D1 receptor in mPFC excitatory neurons for stress-induced behavioral resilience. Repeated social defeat stress reduced mRNA expression of dopamine D1 receptor in mPFC only in mice susceptible to social defeat stress. Knockdown of D1 receptor in whole neuronal populations in mPFC by viral delivery of artificial miRNA enabled single social defeat stress to induce social avoidance. Simultaneous expression of miRNA-resistant D1 receptor mutants in mPFC neurons abolished the effect of D1 knockdown. These data indicate that D1 receptor in mPFC neurons is critical for stress-induced behavioral resilience. Neuron type-specific knockdown of D1 receptor in mPFC revealed that excitatory neurons, but not GABAergic neurons, are the site of action of D1 receptor for stress-induced behavioral resilience. Furthermore, morphometric analyses showed that single stress induces dendritic growth of apical dendrites of mPFC layer 2/3 pyramidal neurons and increases spine density on these dendrites through D1 receptor. Collectively, our findings show that short-term stress induces dendritic remodeling of mPFC pyramidal neurons and behavioral resilience through dopamine D1 receptor.

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**PS145**

**Anxiety-like and depressive-like behaviors in rats administered ACTH during early postnatal period**

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**Abstract**

**Objective:** Negative life experience such as chronic neglect and maltreatment in the early postnatal period can lead to...