norepinephrine in the synaptic cleft. Studies show it takes 2–3 weeks for the mood-enhancing effects, which indicates other mechanisms may underlie their treatment effects. Here, we investigated the role of white matter in treatment and pathogenesis of depression using an unpredictable chronic mild stress (UCMS) mouse model.

Methods: Desvenlafaxine (DVS) was orally administrated to UCMS mice at the dose of 10mg/kg/day one week before they went through 7 weeks stress procedure and lasted for over 8 weeks before the mice being sacrificed.

Results: No significant changes were found for protein markers of neurons and astrocytes in UCMS mice. However, myelin and oligodendrocyte related proteins were significantly reduced in UCMS mice. DVS prevented the stress-induced injury to white matter and the decrease of phosphorylated 5'-AMP-activated protein kinase (AMPK-α) and 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) protein expression. DVS increased open arm entries in elevated plus maze, sucrose consumption in sucrose preference test and decreased immobility in tail suspension and forced swimming tests.

Summary: These findings suggest stress induces depression-like behaviors and white matter deficits in UCMS mice. DVS may ameliorate the oligodendrocyte dysfunction by affecting cholesterol synthesis, alleviating the depression-like phenotypes in these mice.

PS118

Single administration of ketamine and Pregnenolone-Methyl-Ether (3ß-Methoxy-Pregnenolone) has antidepressant efficacy in a preclinical model of treatment resistant depression: identification of a plasma biomarker of pharmacological efficacy

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Abstract

Objective: One third of major depressive disorder (MDD) patients are unresponsive to antidepressant drugs, a sub-type known as treatment resistant depression (TRD). Acute intravenous administration of ketamine at sub-anaesthetic dosage is the only efficacious pharmacological treatment in TRD. Development of TRD preclinical assays to screen for more efficacious antidepressant drugs and identification of diagnostic biomarkers is therefore of immediate importance. The neuronal microtubule modulator Pregnenolone-Methyl-Ether (PME; also known as 3β-Methoxy-Pregnenolone) has been shown to have antidepressant efficacy.

Methods: The Wistar Kyoto (WKY) rat was used as a model of TRD to investigate the effectiveness of fluoxetine (10mg/kg, i.p.), ketamine (5mg/kg, i.p.) and PME (10mg/kg, s.c.) in the forced swimming test (FST). Hippocampal acetylated α-tubulin (Acet-Tub) was previously shown increased in preclinical models of depression and was here investigated as a potential plasma biomarker.

Results: WKY rats demonstrated depressive-like behaviour indicated by increased immobility in the FST associated with overexpression of plasma Acet-Tub compared to Sprague Dawley rats. Acute treatment with the selective serotonin inhibitor (SSRI) fluoxetine had no effect on FST immobility but increased plasma Acet-Tub in WKY rats. Acute administration of ketamine or PME demonstrated rapid antidepressant efficacy in the FST with the effects of ketamine persisting for 7 days. Ketamine and PME demonstrated long-lasting antidepressant efficacy in the FST 24h post-administration. Furthermore, both drugs decreased plasma Acet-Tub overexpression only when their antidepressant efficacy was evident.

Conclusion: WKY rats are a suitable model for screening of novel pharmacological treatments for TRD due to their sensitivity to ketamine and lack thereof to SSRIs. PME demonstrates antidepressant efficacy in this model of TRD while plasma Acet-Tub represents a potential biomarker of disease progression and pharmacological efficacy. Therefore, microtubules represent a potential target for future drug development in TRD.

PS119

Effect of pramipexole for learned helplessness behavior and cranial nerve activities

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Abstract

Purpose: In recent years, research has been reported that dopamine agonists used in the treatment of Parkinson's disease have also shown effectiveness in treating patients for depression. We treated animals with the pramipexole (PRM) and observed behavioral changes and changes in the function of the cranial nerves in animal models of learned helplessness. The purpose of the experiment is to investigate the dopamine agonist's effect as an antidepressant for depressive states as well as its role regarding the cranial nerves.

Method: The experiment included a learned helplessness behavior test, and an assessment of the cranial nerve function using c-Fos immunohistochemistry staining. The learned helplessness model involved a 5-day protocol. The drug was given for four consecutive days, and on the fifth day we measured the number of failed escape attempts using the same method as the second day. The increase or decrease in number of escape attempts was used as an indicator of the drug's effectiveness. In order to examine the effect of PRM on cranial nerve activities in learned helplessness, after completion of the test on the fifth day, the brains were collected and any changes to nerve function in the nucleus accumbens, amygdala and hippocampus were assessed using c-Fos immunohistochemistry staining.

Results and Observations: In learned helplessness models given a single dose of PRM (1.0mg/kg, i.p.), a significant decrease was observed in the number of failed escape attempts related to learned helplessness behavior. This therefore suggests that PRM, in addition to improving Parkinson's symptoms, is a drug that also has antidepressant effects. Furthermore, regarding the parts of the brain affected by PRM's antidepressant function, the nerves of the nucleus accumbens shell, central nucleus and basolateral of the amygdala, and dentate gyrus and CA3 regions of the hippocampus were shown to be affected by the antidepressant function.

PS120

Effects of linalool on chronic stress-induced depressive-like behaviour and BDNF protein in the hippocampus of rats

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Abstract

Linalool, one of the major components of essential oils extracted from many aromatic plants, has shown sedative, anticonvulsant

and anxiolytic properties in several studies. However there is limited data showing the beneficial effect of linalool following exposure to chronic stress. The aim of the present study was to investigate the effect of linalool in chronic stress rats on behaviour related depressive disorder and BDNF protein in hippocampus. Male Wistar rats were randomly divided into 5 groups, 1) Tween 80 + home cage (HC) 2) Tween 80 + restrain stress (RS) 3) linalool 50 mg/kg + RS 4) linalool 160 mg/kg + RS and 5) linalool 500 mg/kg + RS. Either Tween 80 or linalool was intraperitoneally injected to rats daily for two weeks. Some rats were housed in home cage but the others induced chronic restrained stress (15 min daily) for two weeks. At the end of the treatment, rats were assessed for depressive-like behavior using the forced swimming test. Then, the rats were immediately decapitated and hippocampus was removed for the measurement of BDNF protein by ELISA. Restrained rats injected with linalool 500 mg/kg for two weeks significantly reduced immobility time ($p<0.05$) but increased climbing time ($p<0.05$) compared their controls, suggesting that this dose produced antidepressant activity. Linalool had no effect on the level of BDNF protein in hippocampus. Therefore, these findings suggest that linalool decreases behaviour related depressive disorder but has no effect on hippocampal BDNF in chronic restrained stress.

PS121

Evaluation of extrapyramidal side effects in the treatment of behavioral and psychological symptoms of dementia (BPSD): Interactions between anti-Alzheimer drugs and antidepressants

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Abstract

Background/Objectives: Antidepressants are often used in conjunction with anti-Alzheimer drugs to treat the behavioral and psychological symptoms of dementia (BPSD). Here, we studied the interactions between anti-Alzheimer drugs, cholinesterase inhibitors (ChEIs), and antidepressants in inducing extrapyramidal side effects (EPS).

Methods: Male ddY mice were used. Using the pole test, we examined the actions of serotonin reuptake inhibitors (SSRIs), fluoxetine and paroxetine, a serotonin and noradrenaline reuptake inhibitor (SNRI) milnacipran, a noradrenergic and specific serotonergic **antidepressant (NaSSA)** mirtazapine in modulating the ChEIs (galantamine and donepezil)-induced bradykinesia.

Results: Both fluoxetine and paroxetine significantly potentiated galantamine-induced bradykinesia in a synergistic manner. The EPS augmentation by fluoxetine was antagonized by ketanserin (5-HT_2 antagonist) and SB-258585 (5-HT_6 antagonist), but not by ondansetron (5-HT_3 antagonist). In contrast to SSRIs, milnacipran and mirtazapine failed to augment galantamine-induced EPS. In addition, combined treatment of prazosin (α_1 antagonist), but not yohimbine (α_2 antagonist), with milnacipran significantly potentiated galantamine-induced EPS.

Conclusion: The present results indicate that SSRIs and ChEIs synergistically facilitate the EPS induction, via the activation of 5-HT_2 and 5-HT_6 receptors, in the treatment of BPSD. The combination of ChEIs with SNRIs (or **NaSSA)** is recommended in terms of EPS liability for the BPSD therapy, where the activation of α_1 receptors by SNRIs seems to reduce EPS.

PS122

Overexpression of *N*-acetyltransferase Shati/Nat8l in the dorsal striatum induces depression-like behaviors in mice.

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Abstract

Depression is one of the most serious psychological disorders, but its pathogenesis remains unclear and the current medical treatment is mainly restrictive effect. We have identified Shati/Nat8l, which is containing a well-conserved *N*-acetyltransferase sequence, in the brain of psychosis animal model. Shati/Nat8l synthesizes *N*-acetylaspartate (NAA) from L-aspartate and acetyl-CoA, and NAA is subsequently converted into *N*-acetylaspartylglutamate (NAAG) by being condensed with glutamate. It is reported that NAA and NAAG abundantly exist in human brains and those both or one quantity change in the postmortem brain of patients with psychological disorders including depression. In the present study, to clarify the functional roles of Shati/Nat8l in depression, we investigated various behavioral analyses in Shati/Nat8l-overexpressed mice.

Firstly, the expression levels of Shati/Nat8l mRNA were assessed in the brain of depressed C57BL6J mouse model, which was exposed repeated social defeat stress for 10 days following procedure as physical stress for 10 min and sensory stress for 24 hrs by aggressor ICR mice. And, Shati/Nat8l mRNA in the dorsal striatum of the depression mice significantly increased compared with that of control mice. Therefore, mice were microinjected Shati/Nat8l-inserted or non-inserted (Mock) adeno-associated virus vectors into the dorsal striatum. The Shati/Nat8l-overexpressed mice exhibited decreased social interaction and sucrose preference after subthreshold social defeat stress as the exposure to aggressor ICR mice for 5 min×3 on only one day,which showed normal behaviors in the Mock mice. These two phenotypical impairments in the Shati/Nat8l-overexpressed mice were ameliorated by treatment with a selective serotonin reuptake inhibitor fluvoxamine at the dose of 10 mg/kg i.p., which has no effect in the Mock mice.

These findings suggest that Shati/Nat8l in the striatum play an important role in depression-like behaviors including diminished sociability and pleasure by regulating the serotonergic neuronal system.

PS123

Altered peptide ligands of myelin basic protein produce persistent antidepressant-like effects

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Abstract

Cytokine levels were generally changed in both depressed patients and animal models. Altered peptide ligand (APL) of myelin basic protein (MBP) regulates levels of various cytokines,