Abstract

The risk of antidepressant treatment versus the risk of major depression itself on the development of the fetus is a long-term subject of debates. Particularly important are possible delayed consequences on mental well-being which can occur later in life. The aim of the present studies was to verify the hypothesis that perinatal exposure to venlafaxine has impact on hormones involved in stress coping as well as on anxiety and depression-like behaviour of adult offspring.

Dams were treated orally with one of three doses of venlafaxine or placebo starting on day 15 of gestation until day 21 post partum. At that time, pups were weaned and caged in groups according to gender. As adult, both male and female offspring were subjected to behavioural tests to measure anxiety and depression-like behaviours. Concentrations of corticosterone and aldosterone were analysed by radioimmunoassay in blood obtained by decapitation under non-stress conditions in the morning.

Plasma corticosterone concentrations were higher in females than in males and they were enhanced in offspring of both genders exposed perinatally to venlafaxine (significant main factors gender and treatment by two-way ANOVA). Post-hoc analysis showed that venlafaxine exposure-induced enhancement of plasma corticosterone was particularly strong in females exposed to the lowest (7.5mg/kg) and the highest (75mg/kg) dose. Exposure to venlafaxine resulted also in a mild increase in plasma aldosterone (main factor treatment), particularly in males from the highest dose group. On the other hand, exposure to venlafaxine led to reduced anxiety and depression-like behaviour as shown by several variables in elevated plus maze, light-dark box and forced swim tests.

In conclusion, treatment with venlafaxine during pregnancy and lactation may result in positive consequences on signs of anxiety and depression in adult offspring associated with only mild increase in stress hormone levels. *Supported by grants VEGA2/0168/15, VEGA2/0057/15 and partly by APVV-14-0840*

PS114

Effects of Tianeptine on mTOR Signaling in Rat Hippocampal Neurons

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Abstract

Objective: Recent studies have demonstrated that mTOR activation may be related to the antidepressant action. However, the relation between mTOR signaling activation and currently prescribed antidepressants have not been well elucidated. The aim of the present study was to find out whether alterations in mTOR signaling could be observed following treatment with tianeptine under toxic conditions induced by B27 deprivation in rat hippocampal neuronal cultures. Additionally, we investigate whether this drug affect the synaptic proteins, neurite outgrowth and spine density via mTOR signaling.

Methods: Using Western blotting, we measured the phosphorylation levels of mTOR, 4E-BP-1, p70S6K, Akt, and ERK. Changes in BDNF, dendritic outgrowth, spine density, and synaptic proteins (PSD-95, synaptophysin, and GluR1) were measured.

Results: Tianeptine significantly increased the phosphorylation of mTOR, 4E-BP-1, p70S6K, Akt, and ERK. The increase in mTOR phosphorylation was blocked by the PI3K, MEK, and mTOR inhibitors. Tianeptine increased BDNF, dendritic outgrowth, spine density, and synaptic proteins, which were blocked by the mTOR inhibitor. **Conclusions:** In this study, we demonstrated that tianeptine activates the mTOR signaling pathway and increases dendritic outgrowth, spine density, and synaptic proteins through mTOR signaling, suggesting that mTOR signaling activation may be related to the antidepressant effects of tianeptine.

Keywords: Depression, Antidepressant drugs, Tianeptine, mTOR signaling, Neuroplasticity

PS115

The Effect of Fluoxetine on Behaviors in Transient Forebrain Ischemic Gerbil

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Abstract

Objective: This study aims to explore the effect of fluoxetine on memory, locomotor and depressive behavior in transient forebrain ischemic model of gerbil.

Methods: The two doses of fluoxetine (10, 40mg/kg) or vehicle were intraperitoneally administered once 30min before ischemic surgery in gerbil. Novel object recognition test, spontaneous motor activity, learned helplessness test were performed 4 days, 8 days, or 9 days, respectively, after sham or ischemic surgery.

Results: Fluoxetine treatment (40mg/kg) significantly reduced recognition memory in sham operated gerbil. However, fluoxetine (10, 40mg/kg) did not affect ischemia-induced impairment in recognition memory. The treatment of fluoxetine (10, 40mg/kg) significantly inhibited locomotor hyperactivity induced by transient ischemia even though fluoxetine (40mg/kg) did not affect spontaneous motor activity in the sham operated gerbils. Fluoxetine did not affect depressive behavior in sham and ischemic gerbils.

Conclusion: The treatment of fluoxetine inhibited ischemia-induced hyperactivity, but did not affect memory and depressive behavior in transient forebrain ischemic gerbils.

Key Words: transient forebrain ischemia, fluoxetine, novel object recognition test, spontaneous motor activity, learned helplessness test

PS116

Desvenlafaxine prevents white matter injury and improves the decreased phosphorylation of rate-limiting enzyme of cholesterol synthesis in a chronic mouse model of depression.

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Abstract

Objective: Serotonin/norepinephrine reuptake inhibitors antidepressants exert their effects by increasing serotonin and

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 administered 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 (3 β -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 3 β -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