NMDA receptor subunits were determined in some brain regions of mice exposed to the stress.

Results: Acute and repeated administration of desipramine, sertraline, and aripiprazole did not attenuate deficits of social behaviors in mice exposed to stress as juveniles. Co-administration of aripiprazole with sertraline repeatedly and administration of memantine acutely showed a tendency and significant, respectively, to attenuate deficits of social behaviors. Utilization of serotonin/dopamine and the phosphorylated protein levels of NR2A were decreased and increased, respectively, in some brain regions of mice showing deficits of social behaviors.

Conclusion: These findings suggest that social defeat stress as juveniles induces the development of antidepressant-treatment-resistant deficits of social behaviors related to monoaminergic and/or glutamatergic dysfunction. Serotonergic and dopaminergic activators or glutamatergic inhibitors may be a strategy for treating to attenuate the treatment-resistant deficits.

PS135

Effects of the mineralocorticoid receptor antagonist spironolactone in a treatment-resistant model of depression in female rats

Hlavacova N.[1], Franklin M.[2], Jezova D.[1]

[1]Laboratory of Pharmacological Neuroendocrinology,Institute of ExperimentalEndocrinology, BiomedicalResearch Centre, Slovak Academy of Sciences, Bratislava, Slovakia; 2Department of Biology and Biomedical Sciences, Faculty of Life Sciences, Oxford Brookes University, Oxford, UK

Abstract

In recent studies we have shown that the tryptophan (TRP) depletion model of depression previously validated in male rats is paroxetine-resistant in females (Franklin et al. 2015). In this model, we found that secretion of the mineralocorticoid hormone aldosterone increased after 4 days of TRP depletion and surprisingly prior to corticosterone enhancement. The study aim was to investigate the effects of mineralocorticoid receptor (MR) blockade on depression-like behaviour induced by TRP depletion.

Female rats were fed a control (0.2% of TRP) or low TRP diet (0.04% of TRP) for 14 days. They were simultaneously treated with the MR antagonist spironolactone (1.2 mg/rat/day) or placebo via matrix-driven delivery pellets (Innovative Research of America, USA) for 14 days. Rats were tested in the Forced Swim Test (FST) on treatment day 14. Animals were sacrificed by decapitation on day 15.

Two-way ANOVA showed that TRP depletion resulted in an increased immobility time in the FST. Further analysis showed that TRP-depleted rats treated with spironolactone but with placebo spent a significantly shorter time immobile compared to controls. Rats exposed to TRP depletion exhibited significantly higher serum concentrations of aldosterone and corticosterone, which were slightly modified by spironolactone treatment. TRP depletion significantly enhanced serum interleukin-6 as well as gene expression of orexin A, a neuropeptide related to ghrelin, which has been shown to be altered in patients with treatment-resistant depression.

Findings show that treatment of rats with the MR antagonist spironolactone results in a mild improvement of TRP depletion-induced depression-like behaviour. Blockade of aldosterone action could represent a target for new antidepressant treatment.

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PS136

Time-dependent alteration of reward-induced dopamine release in the nucleus accumbens of the neuropathic pain model rats.

Airi Ido, Soichiro Ide, Takahiro Kato, Masabumi Minami

Hokkaido University, Japan

Abstract

Chronic pain is frequently comorbid with psychiatric disorders such as depression, suggesting the common neuroplastic changes in the central nervous system. It has been considered that chronic pain lowers the function of mesolimbic reward circuits and leads to depression-like states. Nucleus accumbens (NAc) is one of the key structures of the mesolimbic dopaminergic system, which is well known to play an important role in the reward circuits. Extracellular dopamine (DA) levels in the NAc elevate after the acquisition or prediction of rewards. In this study, we examined the reward-induced DA release in the NAc of neuropathic pain model rats. To prepare the neuropathic pain model, the spinal nerve was ligated (SNL model), and reward-induced DA release in the NAc was examined 2 and 4 weeks after SNL surgery. The animals were given with two types of rewards, 30% sucrose solution or pain relief by intrathecally injection of pregabalin (100 μg/10 μl PBS), and DA release was monitored using an *in vivo* microdialysis technique. Both rewards increased extracellular DA levels in the NAc 2 weeks after SNL surgery. In contrast, neither sucrose solution nor pain relief increased the DA release 4 weeks after SNL surgery. These results suggest that dysfunction of the mesolimbic reward circuits occurred 4 weeks, but not 2 weeks, after SNL surgery.

PS137

Evidence that Cannabidiol Induces Acute Antidepressant-Like Efects in Different Animal Models

Samia Joca[1], Amanda J. Sales[2], Ariandra G. Sartim[1], Vitor S. Pereira[3], Gregers Wegener[3], Francisco S. Guimaraes[2]*

*[1]School of Pharmaceutical Sciences of Ribeirao Preto, University of São Paulo (FCFRP-USP), Brazil. *samia@usp.br [2] School of Medicine of Ribeirao Preto, University of Sao Paulo (FMRP-USP), Brazil [3] Department of Clinical Medicine, Translational Neuropsychiatric Unit, Aarhus University, Denmark*

Abstract

Objectives: Cannabidiol (CBD), a non-psychotomimetic compound of *Cannabis sativa*, induced antidepressant like-effects in rodents tested in the forced swimming and olfactory bulbectomy models (Zanelati et al., 2010, Linge et al., Neuropharmacology, 2015). However, no study so far has investigated CBD effects in animal models with greater construct validity for depression, such as the learned helplessness and the Flinders Sensitive and Flinders Resistent Line (FSL/FRL). The present work aimed at investigating the acute effects of CBD in these models.

Methods and Results: *Experiment 1*. For the learned helplessness (LH) paradigm male Wistar rats were submitted to the pre-test (inescapable footshocks) and test (escapable shocks) sessions with a seven days interval. A single injection of CBD (10, 30 mg/Kg, ip), imipramine (15 mg/Kg, ip) or vehicle was given to rats either after pre-test or 1h before test. Another group received daily injections of imipramine (15 mg/Kg/day, ip), between the pre-test and test, as a positive control for the antidepressant effect.

Experiment 2. FSL and FRL animals received single injections of CBD (10 or 30 mg/Kg, ip), ketamine (10 mg/Kg, ip) or vehicle and were submitted to the forced swimming test (FST) 1h later.
Results: *Experiment 1*. Acute treatment with CBD (30 mg/Kg) immediately after the pretest, but not with imipramine, significantly reduced the number of escape failures during the test, an antidepressant-like effect similar to chronic treatment with imipramine (ANOVA, $p<0.05$). *Experiment 2*. Single injection of CBD (30 mg/Kg, ip) reduced the immobility in FSL and FRL animals, similarly to ketamine (10 mg/Kg, ip) (ANOVA, $p<0.05$).
Conclusion: Acute treatment with CBD is able to induce antidepressant-like effect in the learned helplessness and FSL/FRL models. These results reinforce the proposal that CBD could induce acute antidepressant effects in humans.
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PS138

Early life stress increases stress vulnerability through BDNF gene epigenetic changes in the rat hippocampus

Mi Kyoung Seo [1], Nguyen Ngoc Ly [2], Chan Hong Lee [1], Hye Yeon Cho [1], Cheol Min Choi [2], Le Hoa Nhu [2], Jung Goo Lee [1,2,3], Bong Ju Lee [3], Gyung-Mee Kim [3], Baik Seok Kee [4], Sung Woo Park [1,2], and Young Hoon Kim [1,2,3*]*

[1] Paik Institute for Clinical Research, [2] Department of health science and technology, Graduate School of Inje University, [3] Department of Psychiatry, School of Medicine, Haeundae Paik Hospital, Inje University, Busan, Republic of Korea and [4] Department of Psychiatry, School of Medicine, Chungang University, Seoul, Republic of Korea.

Abstract
Objective: Early life stress (ELS) exerts long-lasting epigenetic influences on the brain and makes an individual susceptible to later depression. It is poorly understood whether ELS and subsequent adult chronic stress modulate epigenetic mechanisms. We examined the epigenetic mechanisms of the BDNF gene in the hippocampus, which may underlie stress vulnerability to postnatal maternal separation (MS) and adult restraint stress (RS).
Methods: Rat pups were separated from their dams (3 h/day from P1-P21). When the pups reached adulthood (8 weeks old), we introduced RS (2 h/day for 3 weeks) followed by escitalopram treatment.
Results: We showed that both the MS and RS groups expressed reduced levels of total and exon IV BDNF mRNA. Furthermore, RS potentiated MS-induced decreases in these expression levels. Similarly, both the MS and RS groups showed decreased levels of acetylated histone H3 and H4 at BDNF promoter IV, and RS exacerbated MS-induced decreases of H3 and H4 acetylation. Both the MS and RS groups had increased MeCP2 levels at BDNF promoter IV, as well as increased HDAC5 mRNA, and the combination of MS and RS exerted a greater effect on these parameters than did RS alone. In the forced swimming test, the immobility time of the MS+RS group was significantly higher than that of the RS group. Additionally, chronic escitalopram treatment recovered these alterations.
Conclusion: Our results suggest that postnatal MS and subsequent adult RS modulate epigenetic changes in the BDNF gene, and that these changes may be related to behavioral phenotype. These epigenetic mechanisms are involved in escitalopram action.
Keywords: Epigenetic mechanism; Maternal separation; Restraint stress; BDNF; Escitalopram.

PS139

Neuroprotective effect of multifunctional drug M30 against depressive-like behavior induced by hypercortisolemia in rats

Chun-Sing Lam[1], George Lim Tipoe[1, 2], Johnny Kong-Ching Wong[3], Man-Lung Fung[1,2]*

[1]School of Biomedical Sciences, The University of Hong Kong, Hong Kong SAR [2]Research Centre of Heart, Brain, Hormone & Healthy Aging, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR [3]Department of Pharmacology & Pharmacy, The University of Hong Kong, Hong Kong SAR

Abstract
Hypercortisolemia is suggested to associate with the onset of depressive symptoms in clinical patients [1–2]. Monoamine oxidases (MAO), the enzymes maintaining the turnover and homeostasis of monoamine neurotransmitter, is up-regulated upon exposure to glucocorticoid in *in vitro* studies [3–4]. However, the mechanistic involvement of MAO in monoamine deficiency, oxidative stress and neuroinflammation in rodent model of hypercortisolemia is not fully understood. Drug M30 comprises brain selective MAO inhibition and iron-chelating free radical scavenging moieties, and has been demonstrated protective in various neurodegernative disease models [5–6]. This study aims to investigate the neuroprotective effect of M30 against depressive-like behavior induced by chronic corticosterone (CORT) treatment. Adult male Sprague-Dawley rats (220-250g) were given subcutaneous CORT injections with or without concurrent M30 application for 14 days. CORT-treated rats showed significant depressive-like behavior with remarkable increases in plasma corticosterone level. Chronic CORT treatment elicited the increases in MAO activities, serotonin turnover, oxidative stress, neuroinflammation and apoptosis in the hippocampus when compared with the control group. In addition, the cytokine-responsive serotonin and tryptophan catabolic enzyme indoleamine 2,3-dioxygenase (IDO-1) was significantly elevated in the CORT-treated group resulting in serotonin deficiency. Moreover, CORT-treatment impaired the neuroarchitecture of pyramidal CA1 and CA3 neurons. M30 application promisingly abrogated the adverse alterations in the hippocampus and protected the rat against depressive-like behavior provoked by CORT. Therefore, our results provide a strong support that M30 is neuroprotective against depressive-like behavior resulting induced by CORT by antagonizing overactivation of MAO-A that trigger oxidative stress, neuroinflammation, IDO-1 activation, serotonin deficiency and neurodegeneration.

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