

P-02.040 Atypical antipsychotics with clinical antidepressant activity do not produce anti immobility effect in the mouse tail suspension test

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Objective: According to the data available so far, the second generation antipsychotics appear to be a new option for the treatment of depressive symptoms which constitute an important part of schizophrenia syndrom. This is especially true for direct antidepressant effects, i.e. antidepressant effects that are not mediated by the reduction of positive symptoms. However, this class of antipsychotic drugs cannot be treated homogeneously in the bearing of their antidepressant activity. A recent meta-analysis (Leucht et al., 2009) provides data showing that the pattern for depression represented by atypical antipsychotics was somewhat different, i.e. risperidone did not seem to be better than the first generation of antipsychotics, whereas clozapine, olanzapine, amisulpride, aripiprazole, and quetiapine were.

Methods: In the present study, we examined the potency of atypical antipsychotics (clozapine, olanzapine, amisulpride, quetiapine, aripiprazole, risperidone) to inhibit the immobility time and to increase the power of fight as well as the number of fights in the automated version of the tail suspension test in C57BL/6J mice. An antidepressant drug, citalopram was tested for comparison.

Results: Olanzapine (0.125–5 mg/kg), amisulpride (0.5–2 mg/kg), quetiapine (0.25–2 mg/kg), aripiprazole (0.25–1 mg/kg) and risperidone (0.005–0.05 mg/kg) did not produce any effect in that test. Only clozapine (0.156–2.5 mg/kg), administered at a dose of 0.312 mg/kg only, significantly increased the number of fights. As expected, citalopram (20–40 mg/kg) dose-dependently produced antidepressant-like activity in the same procedure.

Conclusion: Concluding, careful screening of potential antipsychotics for antidepressant effects is considered to be an important part of modern drug development. Our data suggest that the tail suspension test in mice may be relatively insensitive to “antidepressant-like” effects of atypical antipsychotic drugs with antidepressant properties confirmed by clinical trials.

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P-02.041 Prenatal exposure of mice to a maternal immune challenge leads to changes in expression of genes regulating white matter

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Objective: Maternal infection during pregnancy increases the risk of neuropsychiatric disorders, such as schizophrenia and autism, in the offspring. Autism and schizophrenia both involve changes to white matter systems and postmortem microarray and qPCR studies point to gene expression alterations in oligodendrocytes in these disorders. Therefore, we tested the hypothesis that maternal immune activation during pregnancy is an environmental risk factor for altered expression of genes involved in white matter development.

Methods: A conventional mouse model of maternal immune activation (MIA) was adopted with the viral mimic PolyI:C administered in early (day 9) gestation. We examined changes in myelin- or oligodendroglia-related genes reported in schizophrenia including the oligodendrocyte markers SOX10 (SRY-related HMG-box 10), MAG (myelin associated glycoprotein) and TF (transferrin). Gene expression patterns of these targets were characterized by in situ hybridization.

Results: Compared to saline-challenged sham controls, mRNA transcript expression of the myelin-related genes, MAG, SOX10 and TF was clearly altered in the brain of adult offspring exposed to poly(I:C) challenge on gestation day 9. Myelin-related gene expression in nearly all neocortical regions examined was lower compared with control mice. There was also altered level and/or spatial distribution of gene expression in limbic regions including the

hippocampus and amygdaloid nuclei. Reduction of transcript expression level was especially prominent in the left hemisphere, suggesting a loss of cerebral asymmetry of the myelin-related genes in mice exposed to prenatal immune challenge.

Conclusion: Our findings lend direct support to the hypothesis that early prenatal immune activation exerts an extensive neurodevelopmental impact in terms of white matter regulatory processes relevant to schizophrenia and related disorders. The possible causal mechanisms may involve functional variations in myelin-related genes and epigenetic regulation of chromatin.

Policy of full disclosure: None.

P-02.042 Comparison of the depression-like behavior and serotonergic system between Wistar and Wistar Kyoto strains of rats

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Objective: The present study conducted the behavioral and neurochemical comparison of the dorsal raphe nucleus (DRN) serotonin (5-HT) neurons between Wistar and Wistar Kyoto (WKY) rat strains, if whether WKY can be characterized in an animal model of a certain type of depression as previously suggested. Furthermore, the effect of the repeated escitalopram (ESCIT) administration on the depression-like behavior and on 5-HT neurotransmission in WKY was assessed.

Methods: Depression-like behavior was evaluated by using forced swim test. Extracellular 5-HT was quantified by brain microdialysis from the DRN and the prefrontal cortex (PFC). Neuronal firing activity of the DRN 5-HT neurons was assessed using extracellular single-unit in-vivo electrophysiology. Tryptophan hydroxylase and p11 protein levels were detected by western blotting.

Results: WKY exhibited remarkable longer duration of immobility in the forced swim test than Wistar did. The extracellular 5-HT level and tryptophan hydroxylase in the DRN in WKY were significantly lower; however, the inhibitory regulation of the PFC by the DRN was slightly accelerated when compared to Wistar. The 5-HT transporters in the PFC functioned weakly, and the inhibitory regulation of the DRN by the PFC was decelerated in WKY. Furthermore, an opposite effect of 5-HT_{1A/1B} autoreceptors in the DRN on 5-HT neurotransmission was revealed, in comparison with Wistar. In WKY, repeated ESCIT (5 mg/kg/day for 14 days) moderately shortened the prolonged immobility time. The 5-HT transporters in the PFC and the 5-HT_{1B} receptors localized other than the DRN 5-HT neurons, function more strongly after repeated ESCIT.

Conclusion: In conclusion, WKY apparently displayed the depression-like behavior and different regulation system of the DRN 5-HT neurons when compared to Wistar. The present data implies that WKY represent a certain type of depression that is responsive to potent serotonin reuptake-inhibiting antidepressants.

Policy of full disclosure: None.

P-02.043 Effects of chronic mild stress in bax inhibitor-1 (BI-1) gene knockout female mice

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Objective: The anti-apoptotic protein Bax inhibitor-1 (BI-1) has been recognized as a regulator of apoptosis linked to endoplasmic reticulum (ER) stress. BI-1(-/-) mice exhibit increased sensitivity to tissue damage. The purpose of the study was to investigate the role of BI-1 in the pathogenesis of depression using chronic mild stress (CMS) as a depression model.

Methods: We delivered CMS for 6 weeks in BI-1 knock out and wild type mice whereas control groups of BI-1 knock out and wild type were not exposed to CMS. The measured parameters were sucrose intake at week 1, 2, 3, 4, 5 and 6, and forced swimming test (FST) and locomotion at week 2 and 6.

Results: Starting from week 2 and throughout the experiment, significant decrease of sucrose intake and increased immobility time in FST were observed in both stress groups compared to non-stress groups. Interestingly, at week 2, stress-knock out mice showed lesser