P.049 Antidepressant effect of ketamine in chronic unpredictable mild stress model: Involvement of nod-like protein inflammasome driven pathway

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Background: Depression is a common, life-threating psychiatric disorder associated with a social and economical burden. Current available medications for the treatment are limited on monoaminergic neurotransmission and the onset time for treatment requires few weeks. Besides, they are lacking high efficacy, which is associated with low response and remission rates. A noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine is proposed to be rapid antidepressant in resistance cases. However, latest studies indicate that uncontrolled astrocyte/microglia activity raises proinflammatory cytokines, causes changes in the amounts of neurotransmitters and so causes a lower production of neurotrophic factors in depression. Therefore, we addressed the effect of ketamine on molecular and neuroinflammatory pathway which may contribute to the activation of inflammasome forming Nod-like receptor proteins (NLRP) pathway, a member of pattern recognition receptors of the natural immune system, and histological changes in chronic unpredictable mild stress (CUMS) model.

Methods: Male Wistar Albino rats were divided into groups as Control, CUMS (0.1 ml/100 g; ip.), CUMS+Imipramine (10 mg/kg; ip.), CUMS+Acute Ketamine (10 mg/kg; ip.) and CUMS+Chronic Ketamine (10 mg/kg; ip.) groups (n=10/each). In CUMS, rats subjected to series of different mild stressors in an unpredictable manner for 6 weeks. Treatments were started at 3rd week of CUMS and continued for 21 days. Ketamine administered either on 3rd week, once a week for 3 weeks or at the end of 6th week as single dose. Anhedonia and antidepressant effect were assessed by sucrose preference (SP) in every two weeks and forced swim test (FST) at the end of the experiment respectively. Then brains were removed either with paraformaldehyde perfusion for Iba-1, CD11b and GFAP immunohistochemical examinations in hippocampus or dissected freshly for molecular analysis for mRNA gene expressions of NLRP1, NLRP3, caspase-1, ASC, NF-κB and IL-1beta in prefrontal cortex. 2-ddCT calculations were used for relative quantification method. One-way ANOVA was used for FST and PCR statistical analysis whereas two-way ANOVA was conducted for SP.

Results: SP was reduced in CUMS compared to control as a determinant of anhedonia. Both ketamine and imipramine treated group's demonstrated significantly higher SP than CUMS group. The immobility time in FST was significantly reduced in imipramine and ketamine groups compared to CUMS as a reflection of despair-like behavior. CUMS procedure caused significant elevations in mRNA levels of NLRP1, NLRP3, caspase-1, ASC, IL-1beta and NF-κB in PFC of rats. Levels of mRNA gene expression of these parameters were significantly reduced in acute and chronic ketamine groups. Iba-1, CD11b and GFAP immunoreactivity elevated in CUMS group in hippocampus, which are significantly reduced by ketamine treatment.

Conclusions: The fact that microglial activation has a fundamental role in early neuroinflammation, indicators present in microglia such as caspase-1 as it is responsible for the production and release of mature IL-1beta, NF-κB as it is a transcriptional factor for cytokines and Iba-1, CD11b and GFAP for a marker of microglial or astrocytes activation were investigated. Taken together the results of the current study suggest that the antidepressant effect of ketamine might be through modulating Nod-like protein inflammasome driven pathway.

References

[1] Haapakoski, R., Ebmeier, K.P., Alenius, H., Kivimaki, M., 2016. Innate and adaptive immunity in the development of depression: An update on current knowledge and technological advances. Prog Neuropsychopharmacol Biol Psychiatry 66, 63–72.
[2] Lang, E., Mallien, A.S., Vasilescu, A.N., Hefter, D., Luoni, A., Riva, M.A., Borgwardt, S., Sprengel, R., Lang, U.E., Gass, P., Inta, D., 2018. Molecular and cellular dissection of NMDA receptor subtypes as antidepressant targets. Neurosci Biobehav Rev 84, 352–358.
[3] Schmidt, F.M., Kirkby, K.C., Lichtblau, N., 2016. Inflammation and immune regulation as potential drug targets in antidepressant treatment. Curr Neuropharmacol 14 (7), 674–687.

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P.050 Diagnostic change in a multicenter first-psychotic episode cohort: Identifying baseline factors associated with conversion to bipolar disorder

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