P.237 Ketamine improves depressive symptoms caused by stress and induces c-Fos expression in the brain resembling some effects of stress

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Purpose: Optogenetic stimulation of the hippocampal pyramidal glutamatergic neurons resulted in a depressive-like behavior [1] which was accompanied by activation of neurons in the hippocampal CA1 region and prefrontal cortex [2]. In the present study, using expression of c-Fos, we examined which changes in neuronal activity could be associated with antidepressant effects of ketamine, an antagonist of glutamate NMDA receptors.
Methods: Adult male Wistar rats were injected with ketamine (15 mg/kg, i.p.) or saline. Two hours later, half of the animals of each treatment group were subjected to the tail suspension test for 6 minutes (stress) and their behavioral responses were evaluated. One hour after the test, brains and samples of the brain tissue of these animals and unexposed to stress rats of both groups were harvested for immunofluorescence analysis of c-Fos, Satb2 and Calretinin proteins and measurement of c-fos mRNA levels by RT real-time PCR. Plasma corticosterone levels were determined by ELISA. Statistical analysis was made using one- and two-way ANOVA.
Results: Stress of the tail suspension test significantly ($p<0.001$) increased c-fos mRNA levels in all brain regions studied: in the cortex [for example: $F(1, 9)=69.364$, $p<0.001$], hippocampus, amygdala, midbrain and the brain stem. Ketamine also increased ($p<0.01$) c-fos mRNA levels in the cortex [for example: $F(1, 9)=15.950$, $p<0.002$] and in the brain stem of the non-stressed animals and attenuated ($p<0.05$) activation of this early gene by stress in the cortex [for example, ketamine X stress interaction: $F(1, 18)=12.293$, $p<0.002$], hippocampus, amygdala and the brainstem. The pattern of ketamine-induced changes in c-fos mRNA matched the increased number of cells expressing c-Fos protein in the prefrontal cortex in the basal state and weakened response of these cells to stress in result of ketamine pretreatment [ketamine X stress interaction: $F(1, 10)=5.077$, $p<0.048$]. These effects of ketamine were found in entire population of prefrontal cortical cells, as well as in subpopulation of glutamatergic neurons labeled with the transcription factor Satb2 [ketamine X stress interaction: $F(1, 10)=9.176$, $p<0.013$], but not in calretinin-positive interneurons of this brain region. Though stress increased c-Fos expression in calretinin-positive interneurons also [$F(1, 10)=5.026$, $p<0.049$], ketamine had no effect on this activation of early gene expression [ketamine X stress interaction: $F(1, 10)=0.135$, $p=0.721$]. Ketamine attenuated the depressive-like behavior [$F(1, 14)=7.670$, $p<0.015$] and decreased adrenocortical response to acute stress caused by the tail suspension test, as assessed by corticosterone levels [ketamine X stress interaction: $F(1, 14)=44.323$, $p<0.001$].
Conclusion: Pretreatment with ketamine improves depressive symptoms caused by acute stress and induces changes in c-Fos expression in the brain that resemble some effects of stress. In general, the results indicate that the neurons of the prefrontal cortex and the brain stem involved in the antidepressant effects of ketamine. It looks like stress-induced activation of at least some neuronal populations in the brain acts against symptoms of depression and stimulation of these neurons by pretreatment with ketamine may confer resilience to stress-related mood disorders.

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P.238 The 5-HT7 receptor antagonist SB 269970 reverses prenatal stress-induced changes in synaptic transmission in the rat dorsal raphe nucleus

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Background: Pathophysiology of mood disorders remains poorly understood. Currently used drugs require prolonged administration and often cause burdensome side-effects. The serotonin 5-HT7 receptor has been implicated in the pathophysiology of depression. The 5-HT7 receptor antagonist SB 269970 shows antidepressant properties in animal models of depression. Moreover, blockade of 5-HT7 receptors reverses some effects of repeated stress, for example the enhancement of glutamatergic transmission in the rat frontal cortex [1]. The dorsal raphe nucleus (DRN), a major source of 5-HT in the mammalian forebrain, regulates the stress response and is involved in the development of stress-related psychiatric disorders. 5-HT7 receptors in the DRN modulate GABAergic [2] and glutamatergic transmission. A growing body of evidence indicates that prenatal maternal stress (PS) may be an important risk factor for the pathogenesis of affective disorders. Little is known of the effects of the prenatal stress on the activity of the DRN neuronal