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Psychoneuroimmunomodulating effect of immune cells in depressive-like mice

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Motivation and Aim: Immune and neuroendocrine systems play an important role in maintaining homeostasis in normal and in mental maladaptation Depression is a prime example of a pathology characterized by impaired neuroimmune interactions There is a sufficient amount of data on the leading role of immune cells and their biologically active products in the pathogenesis of depression [1, 5]. Unidirectional influence of the majority of psychoactive drugs on the CNS and the immune system allows to consider immune cells as model objects for influencing the intersystem functional relationship. We demonstrated the possibility of animal's behavior directed regulation by the transplantation of immune cells with definite functional characteristics [3]. It was shown also the ability of splenocytes with *in vitro* caffeine modulated functional activity to stimulate passive behavior in animals in a dose dependent manner. Based on the previous results we investigated the effect of the transplantation of *in vitro* caffeine-modulated immune cells in depressive like recipients.
Materials and Methods: Experiments were held on 3 month old male (CBAxC57 Bl/6)F1 mice. Given individual behavioral differences, the groups were gathered after preliminary behavioral phenotyping to collect animals with uniform behavioral responses and stress reactivity. We performed the Open Field test to select mice with passive behavior, which are the least resistant to stress. Depressive-like state was formed in passive mice as a result of repeated experience of defeat in agonistic interactions with aggressive partner during 20 days (the sensory contact model) [2]. The depressive-like phenotype was characterized in the Forced swimming test, Open Field and Plus Maze using a modern hardware and software complex EthoVision XT (Noldus, Netherlands); anhedonia was assessed by the sucrose preference test using an automated system for behavioral and cognitive phenotyping IntelliCage (TSE systems, Germany). Splenocytes from depressive- like mice were received aseptically, treated *in vitro* with caffeine for 25 minutes, then, after a 3-fold washing, cells were collected and intravenously injected to syngeneic depressive- like recipients (15 million cells per animal). Mice-recipients of control group were undergoing the transplantation of immune cells treated without caffeine. Recipient's behavior, parameters of nervous and immune systems functional activities were estimated.
Results: Anhedonia is considered one of the main symptoms of major depression in humans. Anhedonia is also the main sign of depression in experimental models and is estimated by the decrease in animal's consumption of sucrose solution. In assessing the mice behavior in IntelliCage we found that depressive -like mice after the transplantation of caffeine-modulated immune cells in a free choice demonstrated increased consumption and preference of 1 % sucrose solution, as compared with the control group of animals. Behavioral despair in mice is a primary screening test for antidepressants.

Porsolt swimming test revealed in depressive-like mice after the transplantation of caffeine-modulated immune cells a significant increase in the time periods of mobility with the disappearance of periods of immobility in the water. We have shown also that transplantation of *in vitro* caffeine- modulated immune cells caused in depressive like recipients stimulation of motor and exploratory activities in the Open Field test [4].
In the scientific world widely discussed phenomenon of "cytokine induced depression" [1, 5]. We have shown that behavioral changes after the transplantation of the caffeine-treated immune cells were accompanied by decreased levels of several pathogenic significance pro-inflammatory cytokines TNF-α, IL-1β, IL-6, INF-γ in some brain regions (hippocampus striatum, hypothalamus, frontal cortex and increase of IL-4I and L -10 in hippocampus of mice- recipients. The results suggested the reduction of neuroinflammation in depressive-like recipients. In depressive disorders is decreasing the volume of the hippocampus, due to a decrease in the density of pyramidal neurons in the CA 1 and CA 3 fields. Apoptosis of neurons in these zones is one of the pathogenetic mechanisms of cognitive impairment in depression [5]. We found also that after the transplantation of caffeine-modulated immune cells in the brain of depressive-like mice the number of neurons in the CA 1 CA 3 fields of the hippocampus substantially increases on the background of increasing level of brain-derived neurotrophic factor. Cell transplantation also led to modulation of the functional activity of recipient's immune system, expressed in stimulating the humoral immune response and the proliferative activity of splenocytes, modulating the production of some cytokines by splenocytes and reducing the catabolism of tryptophan in these cells.
Conclusion: The presented results indicate that modulated ex vivo with caffeine immune cells in depressive-like animals, affecting the main pathogenetic mechanisms of depression, have a positive psychoneuroimmunomodulating effect, which determines the possibility and prospects of immunotherapy of this disease by autologous immune cells with modulated *in vitro* functional activity.
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