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Correction of the aggressive behavior by immune cells modulated *ex vivo* by psychoactive drug

Serenko E.V.*, Markova E.V.
Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russia
** serenko.evgeniy@mail.ru*

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Motivation and Aim: Increasing evidence shows that there is an important relationship between aggression traits and the immune system, including immune cells function activity. Psychological stress can trigger cytokine release, and growing evidence has shown an important role for the immune system in regulating negative emotional states as well as personality. To produce deleterious behavioral effects in response to stress, peripheral cytokines must enter and act upon brain circuitry controlling mood and emotion. Within the CNS, activated microglial cells, astrocytes, neurons, and endothelial cells have all been shown to produce several cytokines and express many cytokine receptors. Thus, brain cytokines have important roles beyond inflammatory processes and can act as neuromodulators to regulate neuronal transmission and plasticity [5]. Earlier we demonstrated the influence of immune cells with certain functional phenotype on behavioral parameters and cytokine gene expression in the brain of experimental animals [4]. Findings from studies using animal models of social stress have uncovered numerous mechanisms of the immune cells functional impairment and immune-brain interactions that have opened up new avenues in novel drug targets for the treatment of psychiatric conditions with high aggression using syngeneic immune cells with modulated with psychoactive drugs functional activity. Objective of this study was to investigate the effect of the *in vitro* chlorpromazine-modulated immune cells on the behavioral patterns and brain cytokines in aggressive mice.
Methods and Methods: Adult male (CBA×C57Bl/6)F1 were tested in the open field; active animals were used for aggressive behavior generate with consecutive experience of 20- fold victories in daily agonistic confrontations with passive mice of approximately the same weight under the sensory contact model [2]. Aggressive mice immune cells were obtained in sterile conditions from splenocytes suspension, cultured *in vitro* with chlorpromazinee (15×10^6 cells/150 μg drug) for 25 minutes, and intravenously administered to syngeneic aggressive recipients [3]. In the control group of recipients, the immune cells preparation and transplantation was carried out under similar experimental conditions, except that the cells were cultivated without the presence of chlorpromazine. The behavioral parameters (level of aggressive motivation, attacking behavior using Partition Test and behavior in the Open Field Test) were registered in the experimental and control recipient's group. In all aggressive recipients cytokines content in the pathogenetically significant for stress-induced forms of behavior brain structures (frontal cortex, striatum, hypothalamus, hippocampus) were determined by ELISA. Statistical data analysis was performed using an analytics software portfolio Statistica 10.0 for Windows (StatSoft, Tulsa, OK, USA). Mann–Whitney U test was applied; $p \leq 0.05$ was considered statistically significant.

Results: The features of the aggressive mice immune cells functional activity after the treatment *in vitro* with chlorpromazine were described earlier [3]. It was found that transplantation of chlorpromazine-modulated immune cells change the recipient's behavior. In particular, total time (seconds) spent near the partition, when mice touch the partition with their fore parts (nose, paws) reacting to the control partner in the neighboring compartment was less ($p < 0.05$); the number of approaches did not differ significantly in experimental and control recipient's group. After removal of the partition total time of attacks (seconds) and number of attacks registered in recipients after the transplantation of chlorpromazine-treated immune cells were significantly decrease ($p < 0.01$). Transplantation of chlorpromazine-modulated splenocytes in aggressive mice-recipient was accompanied also by changed behavior parameters in the Open Field Test, manifested as decreased horizontal motor activity parameters ($p < 0.01$), reflecting the behavioral motor component and vertical motor activity ($p < 0.01$), reflecting the exploratory component of the behavior. As mentioned above, cytokines are involved in the central mechanisms of aggression. The aggressive behavior strategy formation correlates with changes in cytokine profile in some brain structures, such as the hypothalamus, hippocampus, striatum and frontal cortex; particularly increased levels of IL-1β, IL-2, and IL-6 has been shown in mice dominating in intermale collisions [1]. It was shown that the above-mentioned behavioral changes in aggressive recipients after the transplantation of chlorpromazine -modulated immune cells were accompanied by cytokines changes in the brain: in the hippocampus IL-1β, IL-2, IL-6, IFN-γ levels were decreased ($p < 0.01$); in the hypothalamus IL-4 level was increased ($p < 0.01$) and IFN-γ – decreased ($p < 0.01$); in the frontal cortex IL-1β level was decreased ($p < 0.01$). So, opposite changes in the brain cytokines during formation of behavioral aggressive strategy and its correction by chlorpromazine-modulated immune cells suppose its involved in the mechanisms underlying the development of aggressive reactions.

Conclusion: Thus, the present study demonstrated that immune cells with *in vitro* chlorpromazine-modulated function activity have a cytokine-mediated aggressive behavior corrective effect.

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