ИММУНОМОДУЛИРУЮЩИЕ СВОЙСТВА КОФЕИНА И ОБРАБОТАННЫХ КОФЕИНОМ ИММУНОКОМПЕТЕНТНЫХ КЛЕТОК ПРИ ДЕПРЕССИВНО-ПОДОБНОМ СОСТОЯНИИ

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Резюме. Депрессия является одной из ведущих глобальных проблем здравоохранения во всем мире. Значительное увеличение распространенности среди трудоспособного населения, а также высокая коморбидность, частичная или полная фармакорезистентность трети пациентов определяет необходимость разработки новых подходов к терапии депрессии. Нарушение взаиморегуляции основных гомеостатических систем играет важнейшую роль в патогенезе депрессии; психо- и иммунопатология тесно взаимосвязаны: патологические изменения в функционировании обеих систем происходят одновременно и взаимообусловлены. Это определяет перспективность методов лечения депрессии, основанных на иммунологических подходах. Кофеин – препарат, известный своими психонейромодулирующими свойствами является антагонистом аденозиновых рецепторов с выраженным дозозависимым эффектом. Аденозиновые рецепторы экспрессируются как клетками ЦНС, так и клетками иммунной системы, что обуславливает его иммуномодулирующие свойства. Сходство как фенотипов, так и функций клеточных элементов иммунной и нервной систем, а также однонаправленное влияние большинства психоактивных препаратов на ЦНС и иммунную систему определяет интерес к изучению иммуномодулирующих свойств кофеина для направленного воздействия на функциональную активность иммунных клеток, с целью их последующего использования в качестве модельных объектов для нормализации нарушенных при депрессивном состоянии нейроиммунных регуляторных связей. Ранее нами впервые была продемонстрирована возможность редактирования депрессивно-подобного поведения прекультивированными с кофеином иммунокомпетентными клетками и показаны центральные механизмы этого эффекта, направленные на стимуляцию процессов нейропластичности и снижение нейровоспаления. Целью настоящего исследования было оценить функциональный фенотип иммунокомпетентных клеток депрессивно-подобных животных после обработки клеток *in vitro* кофеином, а также эффекты трансплантации прекультивированных с кофеином иммунокомпетентных клеток на параметры функциональной активности иммунной системы сингенных депрессивно-подобных реципиентов. В результате проведенного исследования было показано, что кофеин в низкой концентрации повышает спонтанную и индуцированную митогенами пролифера-

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тивную активность спленоцитов депрессивно-подобных самцов-мышей (CBA x C57BL/6)F1 *in vitro*; при этом изменяется спонтанная и митоген-стимулированная продукция этими клетками цитокинов TNFα IL-1β, IFNγ, IL-2 и IL-10. После внутривенного введения прекультивированных с кофеином спленоцитов депрессивно-подобных доноров сингенным депрессивно-подобным реципиентам у последних наблюдалась стимуляции гуморального иммунного ответа, оцененного по увеличению как относительного, так и абсолютного числа антителообразующих клеток селезенки. Была зарегистрирована также стимуляция спонтанной пролиферативной активности лимфоцитов культуре спленоцитов. Полученные данные свидетельствуют о выраженном эффекте кофеина *in vitro* на функциональную активность иммунокомпетентных клеток, равно как и о позитивном иммуномодулирующем эффекте прекультивированных с кофеином клеток при депрессивно-подобном состоянии *in vivo*.

Ключевые слова: кофеин, депрессивно-подобное состояние, иммунный ответ, иммунокомпетентные клетки, пролиферация, цитокины

IMMUNOMODULATORY PROPERTIES OF CAFFEINE AND CAFFEINE-TREATED IMMUNE CELLS IN DEPRESSION-LIKE STATE

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Abstract. Depression is one of the leading global health problems worldwide. A significant increase in prevalence among the working-age population, as well as high comorbidity, partial or complete drug resistance in a third of patients determines the need to develop new approaches to the treatment of depression. Violation of mutual regulation of the main homeostatic systems plays an important role in the pathogenesis of depression. Psycho- and immunopathology are closely interrelated: pathological changes in the functioning of both systems occur simultaneously and are interdependent. This determines the prospects for the treatment of depression based on immunological approaches. Caffeine, a drug known for its psychoneuromodulatory properties, is an adenosine receptor antagonist with a pronounced dose-dependent effect. Adenosine receptors are expressed by both CNS cells and cells of the immune system, which determines its immunomodulatory properties. The similarity of both phenotypes and functions of the cellular elements of the immune and nervous systems, as well as the unidirectional effect of most psychoactive drugs on the central nervous system and the immune system, determines the interest in studying the immunomodulatory properties of caffeine for a targeted effect on the functional activity of immune cells, with a view to their subsequent use as model objects for the normalization of neuroimmune regulatory connections disturbed in a depressive state. Previously, we first demonstrated the possibility of editing depression-like behavior by immune cells precultivated with caffeine and showed the central mechanisms of this effect aimed at stimulating neuroplasticity processes and reducing neuroinflammation. The aim of this study was to evaluate the functional phenotype of immune cells in depressive-like animals after *in vitro* treatment of cells with caffeine, as well as the effects of transplantation of caffeine-precultured immune cells on the parameters of the functional activity of the immune system of syngeneic depressive-like recipients. As a result of the study, it was shown that low concentrations of caffeine increase the spontaneous and mitogen-induced proliferative activity of splenocytes of depression-like male mice (CBA x C57BL/6)F1 *in vitro*; this changes the spontaneous and mitogen-stimulated production of cytokines TNFα IL-1β, IFNγ, IL-2, and IL-10 by these cells. After intravenous administration of the precultured with caffeine depression-like donor's splenocytes to syngeneic depression-like recipients, stimulation of the humoral immune response was observed in the latter, assessed by an increase in both the relative and absolute number of antibody-forming spleen cells. Stimulation of spontaneous proliferative activity of lymphocytes in splenocyte culture was also registered. The data obtained indicate a positive effect of caffeine *in vitro* on the immune cell's functional activity, as well as a positive immunomodulatory effect of the immune cells precultured with caffeine in a depression-like state *in vivo*.

Keywords: caffeine, depression-like state, immune response, immune cells, proliferation, cytokines

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Introduction

Depression is one of the urgent medical and social problems of our time due to its wide prevalence among various contingents, including among the working population throughout the world. There is still no consensus on the contribution of genetic, environmental, social factors to the etiology and pathogenesis of this disease. The heterogeneous nature, high comorbidity, and pronounced drug resistance of major depressive disorder (MDD) determine the search and development of new highly effective treatment approaches. In patients with major depressive disorder (MDD), a violation of the functional activity of the immune system and its cellular elements was found, which prevents a favorable prognosis, including the response to antidepressants. Altered innate and adaptive immunity involving a pronounced increase in the number of neutrophils, alterations in the numbers of monocytes, in the relative abundance of T cell subtypes, reduced numbers of the regulatory T (Treg) and B (Breg) cells, increased Th1/Th2 ratio and the Th17 cells, a decrease in the number of B-cells, decrease in the proliferative activity of lymphocytes and the intensity of the immune response has been found in depressed patients and in stress-induced depression-like behavior in animal models [2, 4, 9]. There is also evidence of changes in the levels of cytokines IL-1β, IL-2, IL-4, IL-6, IL-12, IL-18, IL-8, IL-13, TNFα, IFNγ, TGF-β1, and IL-10 [6, 7, 8, 9].

Among the known molecular pathways activated in MDD are JAK-STAT and PI3K/Akt/RAS/MAPK [3, 5, 15]. The main pharmacological agents for the treatment of depression include drugs aimed at the monoamine and melatonin systems. Positive effects are also provided anti-cytokine treatment [7, 14], but the issue of toxicity and safety of the use of such drugs is not well understood.

Caffeine, a drug known for its psychoneuromodulatory properties, is an adenosine receptor (AR) antagonist with a pronounced dose-dependent effect [1, 13, 15]. Adenosine receptors are not only expressed by CNS cells, they are also present in most immune cells and are involved in the regulation of various cell functions. The similarity of both phenotypes and functions of the cellular elements of the immune and nervous systems, as well as the unidirectional effect of most psychoactive drugs on the central nervous system and the immune system, determines the interest in studying the immunomodulatory properties of caffeine for a targeted effect on the functional activity of immune cells, with a view to their subsequent use as model objects for the normalization of neuroimmune regulatory connections disturbed in a depressive state and alleviation of depressive symptoms. Previously, we first demonstrated the possibility of editing depression-like behavior by immune cells precultured with caffeine and showed the central mechanisms of this effect aimed at stimulating neuroplasticity processes and reducing neuroinflammation [10, 11, 12].

In connection with the above, **the aim of this study** was to evaluate the functional phenotype of immune cells in depressive-like animals after *in vitro* treatment of cells with caffeine, as well as the effects of transplantation of caffeine-precultured immune cells on the parameters of the functional activity of the immune system of syngeneic depressive-like recipients.

Materials and methods

Male mice (CBA × C57BL/6)F1 at the age of 4 months, weighing 25-30 g, obtained from the animal facility of the E.D. Goldberg Scientific Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center of the Russian Academy of Sciences (Tomsk, Russia) were used. The animals were housed in groups of ten per cage in a laboratory vivarium, at least two weeks prior the start of the experiment under standard conditions on a standard diet, with free access to water and a natural light regime. All experimental procedures were in compliance with the European Communities Council Directive (Strasburg, 1986) and were approved by the Institutional Animal Care and Use Committees of the Scientific Research Institute of Fundamental and Clinical Immunology. Every effort was made to minimize the number of animals used and their suffering.

A depression-like state was formed in passive mice (n = 36) as a result of repeated experience of defeat in agonistic interactions with an aggressive partner during 20 days, as described earlier [10, 11]. The depression-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). Then depression-like mice were isolated into individual cages to avoid agonistic interaction and were used as donors and recipients of immune cells.

Immune cells were obtained under sterile conditions from a suspension of splenocytes, precultured *in vitro* with caffeine at the dose of 100 μg per 15×10^6 cells with 3% FCS (Hyclone) for 25 minutes,

as we described earlier [10, 11], with subsequent assessment of the cells spontaneous and mitogen-induced proliferative activity by a standard method for the inclusion of a radioactive label in nucleoprotein fractions (H^3-thymidine), as well as the production of a number of cytokines by splenocytes by determining their quantitative content in samples of culture supernatants by ELISA, using specific test-systems for the determination of IFNγ, IL-6 (eBioscience, BenderMedSystems, Austria) and for the determination of IL-1β, IL-10, TNFα (R&D Systems Inc, UK) in accordance with the manufacturer's instructions.

At the second stage of the study, splenocytes precultured with caffeine were administered intravenously to syngeneic depression-like recipients. Splenocytes precultured under similar experimental conditions, but without caffeine, as well as a group of depressed recipients who were transplanted with these cells served as controls. In syngeneic depression-like recipients, the intensity of the humoral immune response was assessed by the relative and absolute number of antibody-forming spleen cells in response to the T-dependent antigen (sheep erythrocytes). The intensity of the cellular immune response was assessed by the severity of the delayed-type hypersensitivity reaction (DTH).

The results were statistically processed using the Mann–Whitney paired test (Statistica for Windows 10.0 software). Results are presented as the mean ± SEM. Differences were considered significant at $p \le 0.05$.

Results and discussion

As a result of the study, it was found that caffeine *in vitro* stimulates the proliferative activity of depression-like mice splenocytes, which is expressed in an increase in spontaneous and Con-A-induced proliferation of lymphocytes within splenocytes (Table 1), apparently through the direct action of caffeine on A1AR and A2AR receptors present on spleen immune cells. The binding of caffeine to these receptors leads to a change in the chain of intracellular events that affect, among other things, the synthesis and production of cytokines [1, 3, 13, 15]; therefore, the production of a number of cytokines by caffeine-treated depression-like mouse splenocytes was evaluated.

It has been shown that after *in vitro* treatment with caffeine at a low concentration, the spontaneous production of IL-1β, IFNγ and TNFα decreases with a significant increase in the production of IL-2 and IL-10. In the study of mitogen-stimulated production of cytokines, a decrease in the production of IL-1β, IFNγ and an increase in IL-10 was found (Table 2). The obtained results are consistent with the data of other researchers, in particular, on the negative regulation of TNFα secretion by caffeine in various cells, including splenocytes, peripheral blood mononuclear cells, and mast cells [13, 15]. A likely mechanism for changing the proliferative activity of splenocytes and the production of a number of pro- and anti-inflammatory cytokines by cells is an increase in cAMP accumulation as a result of *in vitro* binding of caffeine at a low concentration used to A1AR and A2AR, followed by prevention of NF-κB activation through the cAMP/PKA pathways [1, 3, 15]. It is assumed that activated A2AR promotes the differentiation of $CD4^+$T cells towards regulatory T cells, due to an increase in the level of IL-2 and a decrease in the level of IL-6, which is one of the activators of the JAK-STAT signaling pathway [4, 5].

TABLE 1. PROLIFERATIVE ACTIVITY OF DEPRESSION-LIKE MALES (CBA × C57BL/6) F1 SPLENOCYTES AFTER *IN VITRO* TREATMENT WITH CAFFEINE AND DEPRESSION-LIKE RECIPIENT'S SPLEEN CELLS AFTER TRANSPLANTATION OF SYNGENEIC CAFFEINE-TREATED SPLENOCYTES, M±SD

Cell group	Splenocyte proliferative activity (cpm)		
	spontaneous	Con A	LPS
Splenocytes of depression-like mice precultured without caffeine (control)	372.7±73.2	30854.4±3095.8	3848.7±491.4
Splenocytes of depression-like mice precultured with caffeine (experimental)	861.4±104.1**	50437.1±7237.8*	4117.0±342.1
Depression-like recipient's splenocytes (control)	401.2±75.6	32589.2±4161.7	4198.7±396.8
Depression-like recipient's splenocytes (experimental)	623.4±71.6**	43964.3±6172.8	4569.3±281.5

Note. Control cell's group – splenocytes of depression-like mice precultured without caffeine or splenocytes of depression-like recipients after transplantation of these cells. Experimental cell's group – splenocytes of depression-like mice precultured with caffeine or splenocytes of depression-like recipients after transplantation of these cells. *, $p < 0.05$; **, $p < 0.01$ relative to the corresponding indicator in the control group.

TABLE 2. CYTOKINE PRODUCTION (pg/mL) BY *IN VITRO* CAFFEINE-TREATED SPLENOCYTES OF DEPRESSION-LIKE MALES (CBA × C57BL/6)F1, M±SD

Cell group	IL-1β	IL-4	IL-6	IL-10	IL-2	IFNγ	TNFα
	Spontaneous production						
Splenocytes of depression-like mice precultured without caffeine (control)	11.3±1.5	6.4±1.5	201.0±8.1	13.1±7.3	10.8±2.3	28.0±5.8	32.5±3.8
Splenocytes of depression-like mice precultured with caffeine	7.5±2.7*	5.3±1.4	191.0±7.1	31.9±4.1**	34.2±6.5*	12.2±4.2**	24.5±2.4**
Mitogen-stimulated production							
Splenocytes of depression-like mice precultured without caffeine (control)	192.1±5.6	31.3±5.9	1081.0±108.3	52.9±10.2	48.3±3.4	115.1±10.4	159.4±8.9
Splenocytes of depression-like mice precultured with caffeine	61.1±7.5**	32.2±2.3	971.0±95.1	91.0±14.1**	57.1±2.2*	42.2±7.1**	148.9±5.4

Note. *, $p < 0.05$; **, $p < 0.01$ compared with the corresponding indicator in the control group of cells.

TABLE 3. INTENSITY OF THE HUMORAL AND CELLULAR IMMUNE RESPONSE IN DEPRESSION-LIKE RECIPIENTS (CBA × C57BL/6)F1 AFTER TRANSPLANTATION OF SYNGENEIC SPLENOCYTES MODULATED *EX VIVO* BY CAFFEINE, M±SD

Parameter	Recipient group	
	Control group	Experimental group
Relative number of antibody-forming spleen cells /10^6	332.2±74.7	553.6±57.1*
Absolute number of antibody-forming spleen cells	69515.4±7678.6	87821.2±6118.6*
DTH reaction (%)	10.2±2.3	12.1±1.4

Note. Control group of recipients – depression-like recipients after transplantation of syngeneic splenocytes precultured without caffeine. Experimental group of recipients – depression-like recipients after transplantation of syngeneic splenocytes precultured with caffeine. *, $p < 0.01$ relative to the corresponding indicator in the control group.

Previously, we demonstrated the depression-like behavior editing by the transplantation of caffeine-treated immune cells [10, 11]. Taking into account the above-mentioned important role of disturbances in the functional state of the immune system and its cells in the pathogenesis of depression, including the formation of depression-like behavior, in this study, the intensity of the main components of the immune response and the proliferative activity of lymphocytes of depression-like recipients were assessed after transplantation of syngeneic splenocytes treated *in vitro* with caffeine. As a result of the studies, stimulation of the humoral immune response was registered in depressive-like recipients, which was assessed by an increase in both the relative and absolute number of antibody-forming spleen cells (Table 1). At the same time, a significant stimulation of the spontaneous proliferative activity of splenocytes was also shown (Table 3).

There were no significant changes in the DTH response in depressive-like recipients. The demonstrated stimulation of the functional activity of the immune system of depression-like recipients occurs along with the modulation of the structural and functional parameters of their nervous system, including editing depression-like behavior, reduction of neuroinflammation and stimulation of neuroplasticity [11]. Taking into account the fact that si-

milar effects are also observed during antidepressant therapy [4, 9, 14], adoptive immunotherapy with *in vitro* caffeine-modulated immune cells should be considered as a possible promising method in the treatment of depression, excluding the negative side effects observed with the direct use of this psychoactive drug substances.

Conclusion

Thus, the data obtained indicate a pronounced effect of caffeine *in vitro* on the functional activity of immune cells, as well as a positive immunomodulatory effect of the immune cells precultured with caffeine *in vivo* in a depression-like state.

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