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INFLUENCE OF CHRONIC ADMINISTRATION OF ANTIPARKINSON DRUGS ON LEVELS OF SERUM AUTOANTIBODIES TO DOPAMINE AND NMDA RECEPTORS

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ВЛИЯНИЕ ХРОНИЧЕСКОГО ВВЕДЕНИЯ АНТИПАРКИНСОНИЧЕСКИХ СРЕДСТВ НА УРОВНИ СЫВОРОТОЧНЫХ АУТОАНТИТЕЛ К ДОФАМИНОВЫМ И NMDA РЕЦЕПТОРАМ

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In experiments on 108 rats, changes in the level of serum autoantibodies to NMDA receptors (subunits NR1, NR2A, NR2B) and dopamine receptors of the first and second types (DR1 and DR2) were studied during chronic intraperitoneal administration of antipsychotics, antiparkinsonian drugs and their combination. The highest values of autoantibodies to NR1 and NR2A subunits were revealed when bromocriptine was used and to NR2B – when amantadine was administered. Chronic administration of haloperidol at a dose of 0.5 mg/kg increased serum levels of autoantibodies to NMDA receptors, especially in the NR2A subunit. At a dose of 0.1 mg/kg, haloperidol increased the content of autoantibodies to DR1 dopamine receptors. The use of an antipsychotic in combination with antiparkinsonian drugs led to an even more significant increase in the levels of autoantibodies to NR1, NR2A, DR1 and DR2, especially with the combined administration of bromocriptine and haloperidol. At the same time, haloperidol prevented the increase in autoantibodies to NR2B caused by antiparkinsonian drugs. The isolated use of haloperidol or bromocriptine, as well as their joint administration, increased the level of autoantibodies to the S100B protein in the blood serum, and amantadine eliminated this increase in autoantibodies. An increase in the concentration of autoantibodies to the S100B protein correlated with a high content of autoantibodies to NR1 and NR2A, as well as low content of NR2B.

Keywords: autoantibodies, dopamine receptors, NMDA receptors, S100B protein, haloperidol, bromocriptine, amantadine, L-DOPA

В исследовании на 108 крысах было изучено изменение уровня сывороточных аутоантител к рецепторам NMDA (субъединицы NR1, NR2A, NR2B) и к дофаминовым рецепторам первого и второго типов (DR1 и DR2) при хроническом внутрибрюшинном введении нейролептиков, антипаркинсонических препаратов и их сочетании. Выявлены самые высокие значения аутоантител к NR1 и NR2A субъединицам при использовании бромокриптина, а к NR2B – при введении амантадина. Хроническое введение галоперидола в дозе 0,5 мг/кг повышало сывороточные уровни аутоантител к NMDA рецепторам, особенно к NR2A субъединице. В дозе 0,1 мг/кг галоперидол увеличивал содержание аутоантител к DR1. Применение нейролептика в сочетании с антипаркинсоническими средствами привело к еще большему повышению уровней аутоантител к NR1, NR2A, DR1 и DR2, особенно при сочетанном введении бромокриптина и галоперидола. При этом галоперидол препятствовал повышению аутоантител к NR2B, вызываемому антипаркинсоническими средствами. Изолированное применение галоперидола или бромокриптина, а также их совместное введение увеличивали уровень в сыворотке крови аутоантител к белку S100B, а амантадин устранял такое повышение аутоантител. Повышение концентрации аутоантител к белку S100B коррелировало с высоким содержанием аутоантител к NR1 и NR2A, а также с низким содержанием к NR2B.

Ключевые слова: аутоантитела, дофаминовые рецепторы, NMDA рецепторы, белок S100B, галоперидол, бромокриптин, амантадин, L-DOPA

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AAT – autoantibodies
DR1, DR2 – dopamine receptor subtypes
L-DOPA – L-3.4-dihydroxyphenylalanine
NMDA – ionotropic glutamate receptor that selectively binds N-methyl-D-aspartate
NR1, NR2A, NR2B – NMDA receptor subunits
S100B – calcium-binding protein B

The autoimmune concept of schizophrenia [1, 2] has been well articulated recently. It has been established that the level of autoantibodies to different receptor classes is increasing in patients, which is an essential pathogenetic aspect of dopaminergic hyperactivity and impairment of mental functions [3–5]. In this regard, it was logical to assume that psychotropic drugs affecting glutamatergic and dopaminergic systems may influence autoimmune processes, and dialysis and plasmapheresis methods have been pathogenetically demanded complex treatment of schizophrenia [6, 7].

There has previously been a marked increase in levels of autoantibodies to NMDA and dopamine receptors during prolonged administration of antineuroleptics in rats [8], so it was interesting to study the influence of dopaminergic transmission enhancers – antiparkinson drugs, including in combination with haloperidol at levels of autoantibodies to these receptors, which was the purpose of this study.

Material and Methods. Experiments were carried out on 105 white rats of the Wistar line with a mass of 250–300 g. Nine animal groups were formed (11–12 rats in each). The first (control) group of rats was given intraperitoneal saline solution. The second group was injected with haloperidol at a dose of 0.1 mg/kg, the third at a dose of 0.5 mg/kg. The fourth group of rats received L-DOPA (25 mg/kg), the fifth bromocriptine (1 mg/kg) and the sixth amantadine (5 mg/kg). In addition, the effects of combined use of haloperidol (0.5 mg/kg) with L-DOPA (25 mg/kg) – seventh group, bromocriptine (1 mg/kg) – eighth group and amantadine (5 mg/kg) – ninth group were studied. Injections were performed intraperitoneally in a volume of 0.5 ml daily, totaling 30 injections.

After three days of the administration, venous blood was taken from the animals, from which the serum was obtained. In the blood serum, the concentration of autoantibodies (IgG) to dopamine receptors 1 and 2 types (DR1 and DR2), as well as to NR1, NR2A, and NR2B subunits of the NMDA receptor, was estimated. The serum content of autoantibodies to S100B was also determined. Quantitative determination of autoantibodies (AAT) vidospecific for rats in the blood serum was carried out by solid phase immunoassay (ELISA). On the solid phase of polystyrene tablets were immobilized antigen of the corresponding receptor or protein S100B (Cloud-Clone Corp. – USA, China). The research was carried out on an automatic immunoferment analyzer «Lazurit» (Dynex Technologies, USA), at a wavelength of 450 nm.

Statistical analysis of the obtained measurement results was carried out using STATISTICA 10.0(StatSoft Inc., USA). Using the Shapiro – Wilk test, the normality of distribution was assessed. If the distribution was normal, Student's t-test was used. In case of abnormal distribution of values, the Mann – Whitney test was used in a pairwise comparison of groups of animals. The differences between the groups were considered valid at $p<0.05$. A correlation analysis (for Spirman) was also conducted to determine the relationship of autoantibody levels to different neuroreceptors.

Results and Discussion. The study found that chronic use of antiparkinsonian drugs led to an increase in AAT credits to all NMDA receptor subunits – NR1, NR2A and NR2B ($p=0.000001$). However, in animals given bromocriptine, the AAT to NR1 content was markedly higher than in rats injected with L-DOPA ($p=0.0056$). The increase in AAT credits to NR2A was comparable in groups of rats receiving anti-Parkinsonic drugs. Higher AAT values to NR2B have been reported with amantadine than chronic bromocriptine ($p=0.00005$) or L-DOPA ($p=0.00021$).

High values of AAT to DR1, compared to the control group, were found in the groups of rats treated with bromocriptine ($p<0.000001$), L-DOPA ($p=0.000001$), amantadine ($p=0.000001$). At the same time, in animals injected with bromocriptine, the AAT to DR1 was reliably hi-

gher than in animals with L-DOPA (p=0.00279). Higher AAT values were noted for dopamine receptors in the control group compared to AAT levels for NMDA receptors.

The content of AAT to dopamine DR2 receptors was higher than in the control group of rats when using bromocriptine (p=0.000009), L-DOPA (p=0.000001), and amantadine (p=0.000006). However, it did not differ between groups treated with antiparkinsonian drugs. At the same time, serum AAT to DR2 was significantly lower than the content of AAT to DR1 in all groups of rats treated with antiparkinsonian drugs (p<0.01).

For the chronic administration of haloperidol in both doses used, an increase in the levels of AAT in the blood serum of rats to the NR1 subunits and to the NR2A NMDA receptors was also observed (p=0.000001) (Table 1). At the same time, the use of haloperidol at a dose of 0.5 mg/kg, compared with the group of rats receiving a dose of 0.1 mg/kg, gave the most significant increase in the concentration of AAT to subunits NR2A (p=0.024) and NR2B (p=0.00027). In rats treated with antiparkinsonian agents, the levels of anti-NR2B AAT were significantly higher than in animals given the haloperidol.

Table 1

The content of autoantibodies to neuroreceptors in blood serum in rats (Me [Q 25–75 %], U/ml) with isolated use of antiparkinsonian drugs and haloperidol

Neuroreceptors	Control group	Bromocriptine 1 mg/kg	L-DOPA 25 mg/kg	Amantadine 5 mg/kg	Haloperidol 0.1 mg/kg	Haloperidol 0.5 mg/kg
NR1	1.8 [1.6–1.9]	192.9 [172.9–283.2]	157.2 [155–166.3]	166.6 [155–215]	173.8 [163.8–192.9]	176.9 [167.7–213.8]
NR2A	1.5 [1.4–1.8]	155.2 [141.2–173]	142 [137.8–149.2]	141 [137–156]	189.5 159.9–249.4]	251.0 [232–288.7]
NR2B	2.2 [2.0–3.8]	150.3 [139.7–158.3]	147.4 [144.6–160]	176.8 [163–223]	22.6 [20.8–38.9]	69.9 [65.5–81]
DR1	17.1 [16.3–31.9]	173.5 [154.8–257.9]	146.3 [144.1–158.5]	156.3 [151–190.4]	200.7 [176.3–225.5]	160.4 152.2–208]
DR2	21.2 [19–24.3]	46.7 [33.2–56.4]	41.8 [38.4–45]	41.1 [39.1–49]	40 [31.4–42.7]	43.5 [39.4–61.2]

Chronic use of haloperidol at both doses increased serum concentrations of AAT to dopamine receptors DR1 (p=0.000001). Higher values of AAT to DR1 were found in animals treated with haloperidol at a dose of 0.1 mg/kg compared with rats given a dose of 0.5 mg/kg (p=0.0387). At the same time, the content of serum AAT was higher than when using antiparkinsonian drugs: L-DOPA (p=0.0004) and amantadine (p=0.014).

AAT levels to DR2 were twice as high as control levels (p=0.000005 for a dose of 0.1 mg/kg and p=0.000003 for a dose of 0.5 mg/kg), the same for both doses of neuroleptic and were comparable to AAT to DR2 when using antiparkinson agents.

The combined use of antiparkinsonian drugs and haloperidol at a dose of 0.5 mg/kg also, in comparison with the control group of rats, led to an increase in the concentration of AAT to NMDA receptors (p=0.000001). The highest values of AAT to the NR1 subunit were registered when bromocriptine was administered with haloperidol (Table 2). They were significantly higher than the levels of AAT alone and bromocriptine (p=0.0317) or haloperidol (p=0.00279).

The combination of L-DOPA and amantadine with haloperidol slightly increased the level of AAT to NR1 level compared to the groups of rats treated with antiparkinsonian drugs. However, no difference was found in comparison with rats given one haloperidol.

The level of AAT to NR2A was the highest in the group of rats given bromocriptine with haloperidol. It was higher than in rats treated with bromocriptine (p=0.0002) or haloperidol (p=0.00029) alone. The concentration of AAT to NR2A with the combined administration of L-DOPA and haloperidol was higher than with L-DOPA alone (p=0.001). When using amantadine with haloperidol, the level of AAT was the same as with the introduction of amantadine alone but significantly lower than with the isolated administration of haloperidol (p=0.000001).

While antiparkinson drugs showed a significant increase in AAT to NR2B and haloperidol moderately increased it in isolated use, antiparkinson drugs combined with haloperidol (0.5 mg/kg) were used in animals with haloperidol serum AAT concentrations have been significantly reduced. In rats treated with bromocriptine and haloperidol, the level of AAT to the NR2B subunit was more than three times lower than in the group of isolated animals injected with bromocriptine (p=0.000001). Compared with the isolated use of haloperidol (0.5 mg/kg), the content of serum AATs was also lower (p=0.0374). At the same time, the levels of AAT to the NR2B subunit of the NMDA receptor were the lowest when L-DOPA was administered with haloperidol. However, they significantly exceeded the values in the control group of rats (p=0.000001). Compared to rats that received only L-DOPA, the amount of AAT to NR2B was five times lower (p=0.000003), and those that received haloperidol were 2.4 times lower (p=0.000006).

Table 2

The content of autoantibodies to neuroreceptors in the blood serum of rats (Me [Q 25–75 %], units/ml) with the combined administration of antiparkinsonian drugs and haloperidol

Subunits of neuroreceptors	Control group	Bromocriptine 1 mg/kg + haloperidol 0.5 mg/kg	L-DOPA 25 mg/kg + haloperidol 0.5 mg/kg	Amantadine 5mg/kg + haloperidol 0.5 mg/kg
NR1	1.8 [1.6–1.9]	310.4 [246.9–369.7]	165.2 [162.5–188.4]	180.3 [168–273.4]
NR2A	1.5 [1.4–1.8]	341 [296.3–524]	213.6 [174.5–326.5]	145.4 [137.3–156.7]
NR2B	2.2 [2.0–3.8]	47.3 [41.6–71.1]	29.1 [25.1–37.4]	59.0 [51.2–70.5]
DR1	17.1 [16.3–31.9]	304.2 [269.8–650.9]	254.5 [190.1–288.1]	165.5 [151.1–189.6]
DR2	21.2 [19–24.3]	71.4 [59.6–80.6]	38 [32.5–40]	37.8 [32.6–72.7]

The content of AAT to DR1 was the highest when bromocriptine was combined with haloperidol, 1.9 times more increased than the values in the isolated use of haloperidol (p=0.0013) and 1.7 times higher than when

using bromocriptine alone (p=0.0156)). Administration of L-DOPA and haloperidol also increased AAT levels compared to those alone. The combination of amantadine with haloperidol did not significantly affect autoantibody levels compared with amantadine or antipsychotic alone. However, the content of AAT to DR1 was many times higher than in control rats (p=0.000001). At the same time, in rats treated with bromocriptine and haloperidol, the content of AAT to DR1 was higher than in animals treated with L-DOPA with haloperidol (p=0.047) or amantadine with haloperidol (p=0.0022).

When using bromocriptine and haloperidol, the level of AAT to DR2 was significantly higher than when using an antipsychotic (p=0.0022) or bromocriptine (p=0.0056). The combination of L-DOPA or amantadine with haloperidol increased the level of AAT compared with the control group of rats (p=0.000022). Still, it did not change the values compared with groups of animals treated in isolation.

The levels of AAT to the S100B protein significantly increased with chronic administration of haloperidol (0.1 and 0.5 mg/kg) and bromocriptine in rats, as well as with the combined use of bromocriptine and L-DOPA with haloperidol (Table 3). At the same time, in the group of rats treated with amantadine with haloperidol, the content of AAT to S100B was significantly lower than in animals treated with haloperidol using a dose of 0.5 mg/kg. When conducting a correlation analysis (for the entire array of animals but without the control group), it was found that the concentration of serum AATs to the S100B protein is associated with the level of autoantibodies to NMDA receptors NR1 (r=0.4; p<0.05) and NR2A (r=0.57; p<0.05). There was a weak negative association with NR2B (r=–0.25; p<0.05). There was also a weak positive relationship between the blood levels of AAT to DR1 (r=0.39; p<0.05) and DR2 (r=0.29; p<0.05). A correlation was also found between the level of AAT to NMDA and to dopamine receptors. In particular, high content of AAT to the NR1 subunit of the NMDA receptor correlated with a high level of AAT to DR1 (r=0.62; p<0.05) and to DR2 (r=0.56; p<0.05), to NR2A – with a high level of AAT to DR1 (r=0.62; p<0.05) and to DR2 (r=0.44; p<0.05). There was a negative relationship between the content of AAT to the NR2B subunit and to DR1 (r=–0.32; p<0.05). Between the levels of AAT to NR2A and NR1, a positive average relationship was revealed (r=0.54; p<0.05), and with the content of AAT to NR2B – a weak negative relationship (r=–0.26; p<0.05).

Autoimmune changes in the chronic use of neurotropic drugs should probably be seen from the point of view of an adaptation of the organism to the introduction of xenobiotics aimed at attenuating their action and providing adjustment to the state caused by pharmacological agents. It was previously found that the blockade of dopamine receptors using haloperidol causes an increase in the number of dopamine receptors (DR1) and NMDA receptors (NR2A) in the forebrain tissue [9, 10], which coincides with an increase in AAT levels to these receptors. Chronic administration of antiparkinsonian drugs (bromocriptine, L-DOPA, and amantadine) leads to a pronounced increase in the amount of AAT to dopamine and NMDA receptors in the blood serum. The question remains as to what extent this autoimmune response to chronic administration of dopaminergic and glutamatergic mechanisms affects dopamine and NMDA receptor activity in the brain, given the presence of the blood-brain barrier. Immunoglobulins pass through the intact blood-brain barrier only slightly, and the IgG content in the cerebrospinal fluid is age-dependent [11]. However, recent work has shown that neurospecific AAT in the cerebral cortex (IgG) is found in both schizophrenic patients and healthy people. Therefore, it is assumed that IgGs are normally present in the brain and are actively eliminated from it [12].

Table 3

Changes in the level of autoantibodies to the S100B protein in the blood serum of rats (u/ml)

Groups of rats	Me	Q 25–75 %	p values compared with the control group (Mann – Whitney test)
Control	15.3	14.5–16.1	–
Haloperidol 0.1 mg/kg	17.1	15.8–19.1	0.0268
Haloperidol 0.5 mg/kg	18.7	17.7–19.9	0.00001
Bromocriptine 1 mg/kg	16.5	16.3–22.1	0.00356
L-DOPA 25 mg/kg	15.0	14.1–16.3	0.525
Amantadine 5 mg/kg	15.9	14.5–16.9	0.74
Bromocriptine 1 mg/kg + haloperidol 0.5 mg/kg	22.9	18.2–26.3	0.000003
L-DOPA 25 mg/kg + haloperidol 0.5 mg/kg	17.3	16.0–20.0	0.00562
Amantadine 5 mg/kg + haloperidol 0.5 mg/kg	15.4	14.9–16.0	0.69

In addition, it should be taken into account that dopamine and NMDA receptors are found on the membranes of cells of the immune system. These findings were combined in detailed literature reviews. It has been shown that DR1 (similar) is present on naive T-lymphocytes and DR2 (similar) on memory T-lymphocytes, which is considered a manifestation of the relationship between the peripheral immune system, neuroinflammation, and neurodegeneration [13]. At the same time, it was found that antipsychotics cause a change in the activity of lymphocytes, and dopamine receptor agonists modulate the expression of receptors on lymphocytes in patients with parkinsonism [14].

The chronic use of antiparkinsonian drugs, antipsychotics, and their combined use may cause an autoimmune response due to effects on the peripheral immune system. Moreover, this effect may be due to a direct effect on the corresponding receptors of lymphocytes and through a change in the activity of autonomic regulation associated with the major effects of drugs.

Of course, what is interesting is the fact of autoimmune response to the long-term use of drugs affecting neuroreceptors. High levels of AAT to neuroreceptors are correlated with an increase in autoantibodies to S100B. The most significant increase in AAT levels to S100B was observed in isolated chronic use of haloperidol, or bromocriptine, and their combined use. However, for the NR2B subunit, the AAT increase was achieved with the introduction of antiparkinson drugs, and when combined with haloperidol, this effect was reduced. Indeed, high levels of AAT to NR1 and NR2A are correlated with an increase in AAT to S100B, suggesting exeytoxicity. The shift of AAT to NR2A with AAT to NR2B may coincide with a low AAT to S100B, suggesting neuroprotective action. This occurs when using amantadine, L-DOPA, and amantadine in combination with haloperidol (the latter,

on the contrary, significantly increased AAT levels to S100B when used in isolation). It is possible that haloperidol, combined with antiparkinson drugs, prevented an increase in AAT to NR2B in response to dopaminergic stimulation.

Conclusions

1. Chronic administration of antiparkinsonian drugs (bromocriptine, L-DOPA, amantadine) and the antipsychotic haloperidol to rats leads to an increase in the serum level of AAT to NMDA and DR receptors.

2. Long-term use of antiparkinsonian drugs in combination with haloperidol also causes an increase in the concentration of AAT to neuroreceptors. In contrast, the administration of bromocriptine combined with haloperidol achieves the highest levels of AAT to NR1, NR2A, and DR1.

3. Haloperidol reduces the increase in AAT in the blood against NR2B caused by antiparkinsonian drugs.

4. Chronic administration of haloperidol and bromocriptine, as well as the combination of haloperidol with bromocriptine and L-DOPA, led to an increase in AAT levels to the S100B protein. Amantadine eliminated the increase in serum AAT to the S100B protein.

5. Increased AAT concentrations to S100B were correlated with high AAT content to NR1 and NR2A, as well as low to NR2B.

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Informed consent: The experimental study was conducted in full compliance with the requirements of good laboratory practice (set out in the national standard «Principles of good laboratory practice» GOST R 53434-2009), in compliance with the International Principles of the European Convention on «Protection of vertebrate animals used for experiments and other scientific purposes» (Strasbourg, 1986), following the international recommendations for biomedical research using animals» (1985), «General ethical principles of experiments on animals» (Russia, 2011), the rules of laboratory practice in the Russian Federation (order of the Ministry of Health of the Russian Federation No 267 from 19.06.2003) and a positive conclusion of the local ethical committee.

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