ASSOCIATION OF DOPAMINERGIC RECEPTORS OF PERIPHERAL BLOOD LYMPHOCYTES WITH A RISK OF DEVELOPING ANTIPSYCHOTIC EXTRAPYRAMIDAL DISEASES

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Abstract. *The pathophysiological mechanisms behind the development of schizophrenia spectrum disorder remain an unknown and little-studied problem to date. The discovery of antagonistic mechanisms of action on dopamine receptors, through which the emergence of antipsychotic effects led to the formation and subsequent development of schizophrenia dopamine theory, which raised reasonable hope within the professional community that pharmacological drugs that reduce dopaminergic neurotransmission would be a "golden blow" in the treatment of schizophrenia spectrum disorders.*

Keywords: *dopaminergic receptors, antipsychotic effects, dopamine theory schizophrenia.*

Introduction. The problem of extrapyramidal disorders (EPR), which complicate antipsychotic therapy (AP), has been the focus of researchers and practicing psychiatrists since these drugs were introduced into clinical practice. Side effects of the extrapyramidal spectrum complicate the course of mental disorders, increase the severity of negative, cognitive and affective disorders, lead to additional social stigmatization of patients, worsen the patient's quality of life and cause rejection of antipsychotic therapy. Due to these conditions, they require adequate diagnosis and additional pharmacotherapy [1-7].

Dopaminergic neurons are the main source of dopamine in the mammalian central nervous system. A number of studies have shown that dopamine is synthesized in immune cells. Lymphocytes contain the main classes of dopamine receptors on their surface-D1, D2, D3, D4, D5; the change in their expression by lymphocytes is similar to the same processes in brain neurons. An in vitro study of the model of functioning of the dopaminergic system in lymphocytes under the influence of antipsychotics allows, in our opinion, to determine the individual parameters of receptor neurotransmission, identify safety predictors and observe the antipsychotic therapy being carried out [8-12].

In their recently published works, the authors point out that patients who prescribe several antipsychotic drugs suffer from more severe forms of the disease, but at the same time better follow the therapy regimen, an indirect confirmation of the need, a polypharmaceutical approach. After more than 50 years of research and development of drugs that are dopamine receptor antagonists,

the main mechanism of action of antipsychotics remains antagonism against dopamine receptors. Almost no drug with a similar mechanism of action is discussed in terms of evidence-based medicine in the treatment of schizophrenia. In addition, it is a paradox that the only group of drugs that reliably cause psychotic disorders in healthy volunteers is dopaminergic, and amphetamine is a classic representative of this group [13-16]. Drugs that show glutamatergic (NMDA receptor) antagonism can also have antipsychotic effects. In practice, the therapeutic response when using these drugs is less important than what is currently taken. In many works of recent decades, glutamatergic strategies from the point of view of antipsychotic therapy show generally disappointing results. According to some authors, such "hopeless truths" consist mainly of the context of a weak evidence base for the use of combined and complementary strategies in therapeutic practice, such as non-compliance, severity of side effects, and drug interactions [17-20]. Such questions, which arise constantly, continue to serve as a practical link for many doctors to reject the monotherapy strategy "completely" and "partially". As part of this review, we will consider evidence of the viability of the "Golden throw" approach in the treatment of schizophrenia, both from the point of view of Neurobiology and from the point of view of Clinical Psychiatry. An approach based on the principles of "more than monotherapy" involves several directions [21-28]:

1) finding an alternative to the dopaminergic mechanisms of action of antipsychotics;
2) strategies to influence the "main" signs of schizophrenia spectrum disorder;
3) development of therapeutic effects on" shaded " Affective Disorders in schizophrenia;
4) correction of cognitive disorders along with socialization processes;
5) correction of behavioral disorders and Prevention of substance abuse.

As everyone knows, Arrows are removed from the rifle one by one, that is, with one arrow. Any goal that can be lively or inanimate should be in front of the eye, along with moving slowly or being inactive. The weapon is aimed at the target before pulling the trigger. In cases where a shotgun is used, the latter is charged with a special type of cartridge, inside which there are many small metal balls (fractions). After the shot is fired, the bullet will spread as the rifle moves away from the bullet.

In the context of this review, the analogy we have chosen with schizophrenia spectrum disorders is that, instead of relying on the "single-axis effect", a large number of fractional particles, viz. various potential mechanisms of the therapeutic effect of drugs give patients more chances to have some of them still "hit" the target. "In the latter case, the" scattering effect "works in much larger parts of the central nervous system than in the «single axis" [29-36].

The technical characteristics of hunting rifles make this type of weapon an "ideal tool" for shooting at small targets that appear from a place where they move quickly in space (pigeons and other feathered game). There is no time to target a hunting rifle for a long time, so in everyday life they often say that the weapon is "directed". The trigger is pressed when the weapon is directed to the point where the shooter thinks it will be a target at a certain time interval. In this case, the projectile will fly from the rifle to the intended position of the target. In our opinion, this similarity is fully applicable for a violation of the spectrum of schizophrenia: the existing therapeutic arsenal of psychotropic drugs, according to the practitioner, affects pathophysiological mechanisms. Unfortunately, the "external trust" of clinicians is now largely based on unproven hypotheses. Unlike the" classic "rifle, the rifle should" fit " the shooter. Of great importance is how it is fixed on the shoulder and how accurately it is directed to the projected trajectory of the target. If the

shotgun is too long or vice versa short and its muzzle is narrow or too deep, as well as the position of the shooter in the body is not adjusted according to the position of the eye, the weapon is not directed exactly where the shooter wants [37-42].

This similarity is best applied to medications for the treatment of schizophrenia. Although clozapine exhibits several affinities to different types of receptors and is capable of antagonistic effects against dopamine, none of these properties explain its high clinical efficacy. Until now, the exact mechanism of action of the drug is not known [43-46].

The purpose of the study is to assess the correlation between dopamine receptor expression levels (D1R, d5r) in peripheral blood lymphocytes and AP Generation II (Olanzapine) with early EPR development.

Materials and methods. The study included male Caucasian individuals between the ages of 18 and 45 who were diagnosed with schizophrenia spectrum disorder (F2 heading on ICD-10) - F20.0, F20.1, F20.2, F20. 3, F20. 6, F20.8, F23. 1, F23. 1, F23.2, F23.3, F23.8, F23.9. Patients had not previously received antipsychotic therapy at all or had not matched each other for at least 3 months before joining the study.

Patients were given Olanzapine in monotherapy mode. AP doses were selected individually, taking into account the mental state of patients and its dynamics, and could change in the course of therapy.

Olanzapine doses range from 5-20 mg per day. (the average dose is 10 mg / day.). In this study, the use of combined psychotropic drugs, with the exception of benzodiazepines, was prohibited. To prevent arousal conditions and sleep problems, the use of phenazepam at a dose of up to 4 mg per day was allowed. Given a significant decrease in quality of life during EPR development, the study allowed the use of correctors from the group of anticholinergic drugs (trihexyphenidyl). Correctors were appointed only when there were indications indicated in the survey and neurological examination, and the dosages changed only when there were clinically defined inefficiencies prescribed earlier.

A prospective assessment of the condition was carried out in three visits: initially when included in the study (before the start of therapy) (visit 1), 14±2 days (visit 2) and 28±2 days after the start of antipsychotic therapy (visit 3). Clinical and neurological studies were carried out according to the standard method (Gusev E. I. etc. 2000). Standardized scales have been used to objectify the clinical picture of side effects of the extrapyramidal spectrum: drug-induced akathisia assessment scale-BARS, Simpson - Angus scale-SAS to assess extrapyramidal side effects; esrs extrapyramidal symptom scale, abnormal involuntary movement assessment scale-AIMS.

Research results and discussion. The material for the study was peripheral venous blood. The separation of lymphocytic mRNA was carried out using Qiagen bundles. The IBM SPSS Statistics 20.0 software package was used to process statistics. The total number of patients included in the study was 25 people. Development of early EPR has been reported in 60% of cases (n=12).

The spectrum of clinical manifestations of extrapyramidal symptoms has been characterized by the development of neuroleptic tremor (n=4; 16%), Parkinsonism (n=3; 12%), and akathisia (n=5; 20%).

The average initial score on the BARS scale, SAS scale, AIMS scale, and ESRS scale (0.00; 0.04; 0.00 and 0.00, respectively) indicates that not all patients had significant extrapyramidal symptoms during the study's entry period. By Visit 2, it was found that the average

overall score on the sas scale would increase significantly by 1,65±3,35 points (p<0,003), and on the ESRS scale by 5,30±9,94 points (p<0,003). At the same time, the increase in acation installed on the Bars scale, up to 0,22±0,52 points (p<0,059), was not statistically significant. Visit 3 recorded an increase in the severity of akathisia compared to visit 2 (an increase in the total score on the BARS scale to 0,36±0,90 points (p<0,655), which was also not statistically significant. However, the overall score on the sas scale and ESRS scale was observed to decrease only at the trend level: up to 1,14 ± 1,70 points (p<0,316) on the sas scale and up to 4,55 ± 5,94 points (p<0,753) on the esrs scale. There is no difference between visits on average in the number of Aims scores, as no cases of dyskinetic reactions have been recorded, but it cannot be ruled out that an acute dystonic reaction has occurred and is temporary.

Cases of development of extrapyramidal disorders are relatively rare when taking AP Generation II (Olanzapine), but as shown, drug Parkinsonism and other motor disorders occur with this AP therapy, which does not allow us to talk about its absolute safety about the risk of developing side effects of the extrapyramidal spectrum.

The following correlations were obtained by analyzing the level of expression of d1r and D5R dopamine receptors mRNA in peripheral blood lymphocytes of live patients In vitro and in vivo. In lymphocytes grown in vitro with AP participation, d1r expression levels were positively correlated with the sas total score in Visit 2 (r=0,898; p=0,015). The reliability trend is derived in correlation with the d1r expression level in Visit 1 with the ESRS total score in visits 2 and 3 (r=0,821; p=0,08 and r=0,821; p=0,08, respectively) and the sas total score in Visit 3 (R=0,821; p = 0,08, respectively).=0,08).

In lymphocytes grown without AP, the d5r mRNA expression level was positively correlated with the overall score on the BARS scale in Area 3 (r=0,878, p=0,021), while the expression level of the given receptor correlating with the total score in Area 2 was only susceptible to reliability (R=0,741; p=0,092).. In lymphocytes cultured with AP participation, d5r expression levels were significantly correlated with the sas total score in Visit 2 (r=0,899; p=0,015), but only had the 3rd visitor trend rate (r=0,736; p=0,096). The d5r expression level in Visit 1 was positively correlated with the sas total score in Visit 2 (r=0,975; p=0,005).

Conclusions. Thus, the high expression levels of the receptors under study coincided with higher scores on the sas, BARS and ESRS scale and, accordingly, with more specific clinical manifestations of EPR, implying poor tolerance of antipsychotic therapy.

Thus, a study conducted showed that the initial level of expression of d1r and D5R receptors mRNA in peripheral blood lymphocytes of patients is significantly associated with EPR severity against the background of antipsychotic therapy.

The findings show the predictive importance of lymphocyte dopaminergic neurotransmission reactivity to assess the risk of developing early EPR with AP Generation II (Olanzapine). Preliminary results suggest that the in vitro lymphocyte receptor neurotransmission model can be used to predict the safety of antipsychotic therapy at risk of developing EPR.

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