ФУНКЦИОНАЛЬНАЯ АКТИВНОСТЬ ГЛИКОПРОТЕИНА-P В ГЕМАТОЭНЦЕФАЛИЧЕСКОМ БАРЬЕРЕ НА ФОНЕ ЭКСПЕРИМЕНТАЛЬНОГО ПАРКИНСОНИЧЕСКОГО СИНДРОМА

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Актuальность. Гликопротеин-P (Pgp, ABCB1-белок) – мембранный белок-транспортер с широкой субстратной специфичностью, который локализуется в гепатоцитах, энтероцитах, эпителии почечных канальцев, а также в тканевых барьерах, включая гематоэнцефалический барьер (ГЭБ). Повышение активности Pgp в ГЭБ является одной из причин фармакорезистентности ряда заболеваний ЦНС. Цель. Анализ функциональной активности Pgp в ГЭБ при экспериментальном паркинсоническом синдроме. Материалы и методы. Работа выполнена на 90 крысах-самцах вистар, разделенных на 3 серии (n=30 в каждой). Первой серии (контроль) в течение 7 сут подкожно 1 раз в сут вводили подсо лнечное масло, на 8-е сут оценивали активность Pgp в ГЭБ. Второй и третьей серии (контроль патологии) – в течение 7 и 28 сут вводили ротенон подкожно в дозе 2,5 мг/кг 1 раз в сут для моделирования синдрома паркинсонизма, а в конце эксперимента оценивали активность Pgp. Для подтверждения паркинсонического синдрома, помимо клинической картины, у животных методом иммуноферментного анализа определяли уровень дофамина в стриатуме и среднем мозге. Функциональную активность Pgp в ГЭБ оценивали по степени проникновения в кору головного мозга маркерного субстрата транспортера – фексофенадина после его внутривенного введения в дозе 10 мг/кг. Содержание фексофенадина в плазме крови и в коре больших полушарий оценивали по площади под кривой концентрация фексофенадина (в крови или ткани мозга) – время (AUC0-т(плазма) или AUC0-т(мозг)). Для оценки проницаемости ГЭБ рассчитывали соотношение AUC0-т(мозг)/AUC0-т(плазма). Результаты. Введение ротенона приводило к развитию типичной картины паркинсонизма: ригидность мышц, гипокинезия, нестабильность походки. Отмечалось снижение уровня дофамина в стриатуме на 7 сут на 69,6% (p=0,095), на 28 сут – на 93,9% (p=0,008), в среднем мозге – на 72,7% (p=0,095) и 68,7% (p=0,032) соответственно. При внутривенном введении контрольным крысам фексофенадина AUC0-т(плазма) и AUC0-т(мозг) вещества составили соответственно 266,2 (246,4; 285,6) мкт/мл*мин и 5,9 (5,8; 6,6) мкг/т*мин, AUC0-т(мозг)/AUC0-т(плазма) – 0,020 (0,019; 0,022). Введение животным ротенона в течение 7 дней приводило к возрастанию AUC0-т(мозг) фексофенадина в 2,02 раза (p=0,0163), AUC0-т(мозг)/AUC0-т(плазма) – в 2,4 раза (p=0,0283). 28-дневное введение ротенона сопровождалось возрастанием AUC0-т(мозг) фексофенадина в 1,75 раза (p=0,0283), AUC0-т(мозг)/AUC0-т(плазма) – в 2,27 раза (p=0,0163). Вывод. Развитие паркинсонического синдрома, вызванного введением ротено на, снижает функциональную активность Pgp в ГЭБ, что подтверждается накоплением в головном мозге маркерного субстрата транспортера – фексофенадина.

Ключевые слова: болезнь Паркинсона; паркинсонический синдром; гликопротеин-P; функциональная активность; гематоэнцефалический барьер.
FUNCTIONAL ACTIVITY OF P-GLYCOPROTEIN IN BLOOD-BRAIN BARRIER DURING EXPERIMENTAL PARKINSON'S SYNDROME


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Background. P-glycoprotein (Pgp, ABCB1-protein) is a membrane transporter with broad substrate specificity that is localized in hepatocytes, enterocytes, epithelial renal tubules, and also in tissue barriers, including blood-brain barrier (BBB). Increased Pgp activity in BBB is one of the reasons for the pharmacoresistance of a number of CNS diseases. Aim. Analysis of Pgp functional activity in BBB during experimental Parkinson's syndrome. Materials and Methods. The work was performed on 90 Wistar rats, divided into 3 series (n=30 in each). The 1 series (control) was subcutaneously injected sunflower oil once a day for 7 days, and Pgp activity in BBB was assessed on the 8th day. The 2 and 3 series (pathology control) – were administered rotenone at a dose of 2.5 mg/kg once a day for 7 and 28 days respectively to simulate parkinsonism. At the end of the experiment Pgp activity was estimated. To confirm Parkinson's syndrome, in addition to the clinical picture, level of dopamine in midbrain and striatum was determined using enzyme-linked immunosorbent assay. Pgp functional activity in BBB was assessed by the degree of penetration of its marker substrate fexofenadine into the brain after its intravenous administration at a dose of 10 mg/kg. The content of fexofenadine in the blood plasma and in brain tissue was estimated by the area under pharmacokinetic curve of the substance (in the blood or brain tissues) − AUC0−t(plasma) or AUC0−t(brain) respectively. To assess the BBB permeability the ratio AUC0−t(brain)/AUC0−t(plasma) was calculated. Results. Rotenone administration led to the development of parkinsonism typical picture: muscle stiffness, hypokinesia, gait instability. There was a decrease in dopamine level in the striatum after 7 days by 69.6% (p=0.095), after 28 days – by 93.9% (p=0.008), in midbrain – by 72.7% (p=0.095) and 68.7% (p=0.032) respectively. Fexofenadine AUC0−t(plasma) and AUC0−t(brain) after its intravenous administration to control rats were 266.2 (246.4; 285.6) μg/ml*min and 5.9 (5.8;6.6) μg/g*min respectively, AUC0−t(brain)/AUC0−t(plasma) − 0.020 (0.019; 0.022). When rotenone was for 7 days administered − fexofenadine AUC0−t(brain) increased 2.02 times (p=0.0163), AUC0−t(brain)/AUC0−t(plasma) − 2.4 times (p=0.0283). 28 days administration of rotenone led to augmentation of AUC0−t(brain) of fexofenadine by 1.75 times (p=0.0283), AUC0−t(brain)/AUC0−t(plasma) − by 2.27 times (p=0.0163). Conclusions. The development of Parkinson’s syndrome, caused by the administration of rotenone, inhibits Pgp functional activity in BBB, which is confirmed by the accumulation in the brain marker substrate of the transporter − fexofenadine. Keywords: Parkinson's disease; Parkinson's syndrome; P-glycoprotein; functional activity; blood-brain barrier.

Parkinson’s disease is a socially significant chronic progressive neurodegenerative disease of the central nervous system, with the pathogenesis based on death of neurons of substantia nigra of the midbrain and of other parts of the brain where the main neurotransmitter is dopamine. The disease is characterized by a wide spectrum of motor, neuro-psychic and sensory disorders [1]. The etiology of Parkinson’s disease is generally unknown, but is believed to involve genetic, constitutional, age-related and toxic factors and mechanisms. Chemical agents include many pesticides, insecticides and other neurotoxins, the molecu-
lar basis of whose action consists in alteration of the confirmation of a molecule of α-synuclein presynaptic protein and in the ability to considerably accelerate the rate of formation of α-synuclein fibrils and of Lewy bodies in neurons [2].

Of certain significance in development of parkinsonism is the ability of pesticides to change the function of mitochondria through inhibition of I complex of the respiratory chain, stimulation of oxidative stress and of reactions of apoptosis, and through reduction in the activity of ubiquitin-proteasome system [3].

Characteristic of Parkinson’s disease and of other kinds of chronic neurodegeneration (Alzheimer disease, schizophrenia, autism) is dysfunction of the blood-brain barrier (BBB) with derangement of close contact structures and with dysregulation of transporter proteins. In parkinsonism, permeability of BBB in the substantia nigra of the midbrain and striatum may increase which is associated with alteration of expression of transport proteins and proteins of intercellular contacts, with damage to vessels, accumulation of activated microglia with release of proinflammatory cytokines and with alteration of expression of close contact proteins ZO-1 and occludin. Inflammatory hyperexpression of intercellular adhesion proteins facilitates migration of immune cells into the damaged region increasing permeability of BBB [4].

Glycoprotein-P (Pgp, ABCB1-protein) is one of transporters localized in endo heliocytes of BBB, an efflux ATP-dependent transmembrane protein with molecular mass 170 kDa that prevents penetration of numerous endogenous and exogenous substances of different chemical structures – its substrates – from blood to the brain [5].

Functional activity of Pgp may increase or decrease under influence of external and internal factors, and also of medical drugs [6]. In case of inhibition of the function of Pgp, permeability of BBB for its substrates increases with increase in their contents in the brain tissue, while induction of the activity of the transporter, on the contrary, leads to reduction in the concentration of its substrates in the brain [7].

Pharmacoresistant epilepsy, ineffectiveness of medicinal treatment of acute disorder in cerebral circulation and of Alzheimer disease are supposed to be associated with increase in the activity of Pgp in BBB [8]. On the other hand, some authors believe that one of leading pathogenetic factors of Parkinson’s disease is reduced activity of the transporter [9], and a pharmacological induction of Pgp is a probable strategy to prevent this pathology.

The aim of work was assessment of the functional activity of Pgp in BBB of the cerebral cortex in rats with the underlying experimental parkinsonian syndrome.

Materials and Methods
The work was conducted on 90 male rats of Wistar line with 280-320 g mass in accordance with the Rules of good laboratory practice (Order of HM of Russia of 2016 April 1).

The functional activity of Pgp in BBB was evaluated by the extent of penetration into the cortex of the marker substrate of the transporter protein – fexofenadine – introduced intravenously (i/v) at a dose 10 mg/kg of body mass.

The animals were divided into 3 series (n=30 in each). The animals of the 1st series (control group) were subcutaneously intradermally introduced sunflower oil once a day for 7 days and on the 8th day were introduced fexofenadine into the tail vein. The animals of the 2nd and 3rd series (control of pathology) were subcutaneously introduced rotenone within 7 and 28 days, respectively, at a dose of 2.5 mg/kg once a day [10] for modeling Parkinson’s syndrome, and on the 8th day were intravenously introduced fexofenadine.

Because of unavailability of a pharmaceutical form of fexofenadine for injections, the medical substance was extracted from Allegra, Sanofi pills (France) 180 mg by the following method: one pill was ground and suspended in 20 ml of acetonitrile (ACROSORGANICS, Belgium) of ‘for High-Efficiency Liquid Chromatography (HELC)’ category, the contents were shaken for 15 minutes on Shaker device with subsequent centrifugation at 1750 g within 15 min. The supernatant fluid was evaporated on a rotor-
vacuum evaporator, the dry residue was diluted in 10 ml of water for injections. The concentration of fexofenadine for calculation of the dose was determined by HELC method.

Rats of all series were withdrawn from the experiment under zoletile narcosis in 5, 10, 15, 30, 45 and 60 minutes after introduction of fexofenadine, taking 5 animals for each time point for construction of pharma-
cokineti c curve. For analysis 4 ml of blood were taken from the abdominal aorta in the quantity of 4 ml, and also cerebral cortex tissue where concentration of fexofenadine was determined by HELC with UV detection by the earlier described method, after appropriate preparation of samples [7,12].

The total content of fexofenadine that got into the systemic circulation and the cortex was evaluated by the area of the curve of fex-
ofenadine concentration (in blood or cortex tissue) – time (AUC0-t(plasma) or AUC0-t(brain)) that were calculated by trapezoidal method. Because of the fact that AUC0-t(brain) parameter may increase both in result of reduction in the functional activity of Pgp locally in the BBB, and in result of increase in the concentration of marker substrate of transporter in blood plasma, it was reasonable to additionally evaluate the ratio AUC0-t(brain)/AUC0-t(plasma), the change in which would characterize the activity of Pgp particularly in BBB [11].

To confirm development of parkinsonian syndrome in animals, besides evaluation of its clinical presentation, the level of dopamine was determined in striatum and the midbrain selectively in 5 rats in each of 3 series by ELISA method on StatFax-2100 analyzer (USA) (reagents: CEA851Ge 96 Tests, Cloud-Clone Corp., IIIA).

Statistical processing of the results was carried out using Statssoft Statistica 7.0 program (USA). The character of distribution of data was determined using Shapiro-Wilk test. With normal distribution of data, the statistic-
al significance of differences was determined by ANOVA test, for pairwise comparison Fisher’s test was used. With other than nor-
mal distribution of data, differences between series were evaluated by Kruskal-Wallis test. With the level of significance less than 0.05, pairwise comparison of parameters was car-
ried out using Mann-Whitney test with Bonferroni correction. The data with normal distri-
bution were presented in the form of arithmetic mean ± standard error of the mean, the data with other than normal distribution – in the form of median, lower and upper quartiles.

Results and Discussion

Introduction of rotenone within 7 and 28 days led to a typical presentation of par-
kinsonism: rigidity of muscles, hypokinesia and unsteady gait. On the 7th day dopamine level in striatum decreased by 69.6% (p=0.095), and on the 28th day – by 93.9% (p=0.008), in the midbrain – by 72.7% (p=0.095) and by 68.7% (p=0.032), respective-
ly (Table 1). No reliable differences between the content of dopamine in the midbrain on the 7th and 28th days of introduction of rotenone were found (p>0.05), however, in the striatum concentration of dopamine on the 28th day was 80.0% lower that on the 7th day (p=0.056).

Alteration of concentration of fexofenadine in plasma and its content in homogenate of the rats’ brain after its single intravenous introduction in different experimental series is given in Figures 1, 2, respectively.

Table 1

<table>
<thead>
<tr>
<th>Series of Experiment</th>
<th>Dopamine Level: striatum</th>
<th>Dopamine Level: midbrain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=5)</td>
<td>14.8 (13.1; 16.5)</td>
<td>9.9 (6.6; 15.1)</td>
</tr>
<tr>
<td>Rotenone 7 days (n=5)</td>
<td>4.5 (1.6; 11.3), p=0.095</td>
<td>2.7 (1.5; 8.5), p=0.095</td>
</tr>
<tr>
<td>Rotenone 28 days (n=5)</td>
<td>0.9 (0.5; 1.7), p=0.008</td>
<td>3.1 (1.7; 6.5), p=0.032</td>
</tr>
</tbody>
</table>
Fig. 1. Dynamics of concentration of fexofenadine in plasma after its intravenous introduction, in series of control and of introduction of rotenone for 7 and 28 days (medians of values)

Fig. 2. Dynamics of concentration of fexofenadine in homogenate of cerebral cortex after its intravenous introduction in series of control and of introduction of rotenone for 7 and 28 days (medians of values)

The dynamics of concentrations of fexofenadine in plasma did not show any reliable differences in all experimental series (p>0.05). With this, maximal concentration of the substance was determined in 5 minutes after introduction with a gradual reduction by the 60th minute. To note, in the series with 28-day introduction of rotenone, the content of fexofenadine in blood plasma of animals in 15 minutes was 1.82 times lower (p=0.0472) as compared to control.

Concentration of fexofenadine in homogenate of cerebral cortex of rats after 7-day introduction of rotenone in 10 and 45 minutes was 3.91 and 3.53 times higher than control values, respectively, on level of the tendency (p=0.0758). After introduction of rotenone for 28 days, the content of fexofenadine in the brain in 10 minutes increased 3.02 times, and in 15 minutes – 4.85 times (trend: p=0.0758).
In intravenous introduction of fexofenadine to control rats, \( \text{AUC}_{0-t(\text{brain})} \) and \( \text{AUC}_{0-t(\text{plasma})} \) of the substance made 266.2 \((246.4; 285.6)\) \(\mu g/ml\times\text{min}\) and 5.9 \((5.8; 6.6)\) \(\mu g/g\times\text{min}\), respectively, with the ratio of these parameters \( \text{AUC}_{0-t(\text{brain})}/\text{AUC}_{0-t(\text{plasma})} \) equaling 0.020 \((0.019; 0.022)\). Introduction of rotenone within 7 days led to 2.02 times increase in \( \text{AUC}_{0-t(\text{brain})} \) of fexofenadine \((p=0.0163)\), and to 2.4 times increase in the ratio \( \text{AUC}_{0-t(\text{brain})}/\text{AUC}_{0-t(\text{plasma})} \) \((p=0.0283)\). Introduction of rotenone for 28 days caused increase in \( \text{AUC}_{0-t(\text{brain})} \) of fexofenadine 1.75 times \((p=0.0283)\), and of \( \text{AUC}_{0-t(\text{brain})}/\text{AUC}_{0-t(\text{plasma})} \) ratio – 2.27 times \((p=0.0163)\). With this, no differences between parameters of series with 7-day and 28-day introduction of rotenone were found.

The identified changes of pharmacokinetics of the marker substrate of Pg — fexofenadine — evidence reduction of the functional activity of the transporter protein in BBB with the underlying introduction of rotenone — pesticide inducing parkinsonian syndrome.

Table 2

<table>
<thead>
<tr>
<th>Series/Parameter</th>
<th>( \text{AUC}_{0-t(\text{brain})} ), ( \mu g/g\times\text{min} )</th>
<th>( \text{AUC}_{0-t(\text{plasma})} ), ( \mu g/ml\times\text{min} )</th>
<th>( \text{AUC}<em>{0-t(\text{brain})}/\text{AUC}</em>{0-t(\text{plasma})} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5915.8 ((5783.2; 6645.2))</td>
<td>266181.6 ((246356.3; 285630.8))</td>
<td>0.020 ((0.0199; 0.0222))</td>
</tr>
<tr>
<td>Rothenone 7 days</td>
<td>11940.8 ((9237.8; 24989.4))*</td>
<td>206994.0 ((195394.7; 292076.2))</td>
<td>0.048 ((0.0396; 0.0856))*</td>
</tr>
<tr>
<td>Rothenone 28 days</td>
<td>10343.9 ((8448.6; 10770.3))*</td>
<td>235258.6 ((231383.8; 267335.3))</td>
<td>0.0458 ((0.0447; 0.0569))*</td>
</tr>
</tbody>
</table>

*Note: * — reliable differences as compared to control series; the data are presented in the form of median, lower and upper quartiles

A number of research works devoted to study of correlation between polymorphisms of \( MDR1 \) gene coding for Pg, show existence of dependence between the function of the transporter and Parkinson’s disease. Correlation of polymorphism of \( MDR1 \) \( C3435T \) gene with the risk for development of the disease was studied in 606 patients of Japanese population. Patients with \( TT \) genotype associated with reduced activity of Pg, exhibited a higher risk for development of Parkinson’s disease in comparison with patients with \( CC \) genotype [13].

Patients with Parkinson’s disease of Swedish population showed correlation dependence between \( C1236T \) polymorphous marker of \( MDR1 \) gene and the disease, however, polymorphisms \( 2677G/T/A \) and \( 3435C/T \) were non-significant for development of the disease [14].

In European and Asian populations, absence of correlation between the existence of \( C3435T \) polymorphous marker of \( MDR1 \) gene and development of Parkinson’s disease was identified on allelic, homozygous, recessive and dominant models; here, a statistically significant influence of \( C1236T \) polymorphism was found on recessive model [15].

Thus, in works studying interrelation between polymorphism of \( MDR1 \) gene and development of Parkinson’s disease, contradictory results were obtained, which requires further study of this matter and does not exclude participation of Pg in the pathogenesis of the disease.

Today the results of some research works evidence changes in the functional activity of Pg in parkinsonism. For example, a method of photon emission computed tomography permitted to identify increased pene-
tration of tagged $^{11}$C verapamil (Pgp substrate) into the brain of patients with Parkinson’s disease [16].

In experiments on rats with parkinsonism modeled by a session of subcutaneous introduction of rotenone, 3-fold increase in the amount of Pgp-positive cells in BBB of the midbrain was found [17].

Thus, the data about functioning of Pgp with the underlying parkinsonism are also ambiguous.

In the given work the activity of Pgp in BBB of the cerebral cortex of rats was studied in experimental parkinsonian syndrome modeled by subcutaneous introduction of rotenone at a dose 2.5 mg/day within 7 and 28 days.

With recognition of the role of neurotoxins in Parkinson’s disease, some of such substances are used to model parkinsonism in vivo experiments (6-hydroxydopamine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, rotenone, etc.) [4]. Here, in the opinion of many authors, the optimal model is obtained by subcutaneous introduction of rotenone to rats according to the scheme used by us [4,18]. An advantage of rotenone model is the ability of the neurotoxin to provoke dopaminergic neurodegeneration with symptoms and molecular-biological signs similar to those in Parkinson’s disease. Thus, introduction of rotenone leads to selective progressive degeneration of nigrostriatal pathway, similar to that in Parkinson’s disease[19], and also to formation of ubiquitin- and α-synuclein-positive inclusions in nigral cells similar to Lewy bodies.

Activity of Pgp in BBB was evaluated by penetration of the marker substrate of the transporter – fexofenadine – into the brain. Marker substrate is a substance of exogenous and endogenous origin, whose pharmacokinetics largely depends on functioning of Pgp, that is, it does not undergo biotransformation and is not a substrate of other transporter proteins [11].

Introduction of rotenone led to a typical picture of parkinsonism (rigidity of muscles, hypokinesia, unsteady gait) and decreased the level of dopamine in the striatum and in the midbrain of animals. Besides, increased penetration of fexofenadine into the cerebral cortex was detected which indicated reduction in the activity of Pgp in BBB.

Inhibition of the activity of Pgp in BBB may lead to accumulation of neurotoxins – substrates of transporter protein in the brain tissues, and in result may promote neurodegenerative processes and manifestation of pathology.

So, one of promising trends of prevention of initiation and progression of parkinsonism especially in individuals whose occupation suggests contact with toxic substances, is probably application of Pgp inducers. Recently, some medical drugs (dexamethasone, carbamazepine, rifampicin, morphine, retinoic acid, phenothiazine, etc.), have been found to have inducing influence on the transporter protein [20]. However, besides their effect on Pgp, they also possess a wide spectrum of basic and side effects. At present, there have been not synthesized any safe substances possessing the ability to selectively activate the transporter, and such ability is not found in any of the known drugs, for example, in drugs of the neuroprotector group.

Thus, the hypothesis of reasonability of induction of Pgp in BBB for prevention of parkinsonism associated with action of neurotoxic substances, requires further verification.

**Conclusion**

Development of parkinsonian syndrome induced by subcutaneous introduction of rotenone at a dose of 2.5 mg/kg of body mass once a day within 7 and 28 days leads to reduction of the activity of glycoprotein-P in the blood-brain barrier of the cerebral cortex of rats that is confirmed by accumulation of the marker substrate of the transporter protein – fexofenadine.

References


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Информация об авторах [Authors Info]

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