

ФУНКЦИОНАЛЬНАЯ АКТИВНОСТЬ ГЛИКОПРОТЕИНА-Р У КРОЛИКОВ ПОРОДЫ «СОВЕТСКАЯ ШИНШИЛЛА» ПРИ БЕРЕМЕННОСТИ

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Гликопротеин-Р (Pgr, ABCB1-белок) – мембранный белок-транспортер, играющий ключевую роль в фармакокинетике широкого спектра лекарственных веществ. Субстратами данного транспортера является ряд препаратов (антибактериальные, антиретровирусные, гипотензивные), которые требуется назначать беременным женщинам длительными курсами, иногда на протяжении всего срока гестации. **Цель.** Изучить активность белка-транспортера Pgr на уровне целостного организма у самок-кроликов породы «Советская Шиншилла» во время беременности. **Материалы и методы.** Исследование выполнено на 21 кролике-самке породы «Советская Шиншилла» массой 3000-3500 г. Животные были разделены на 3 серии. Первая серия (n=6) – кролики на 7 сут. беременности; вторая серия (n=5) – животные на 14 сут. беременности; третья серия (n=10) – кролики на 21 сут. беременности. За 7 сут. до начала исследования и в указанные сроки гестации проводили оценку функциональной активности Pgr по фармакокинетике маркерного субстрата транспортера – фексофенадина после его однократного перорального введения в дозе 67,5 мг/кг массы и определение сывороточных концентраций прогестерона, эстрадиола, тестостерона и пролактина радиоиммунным методом. **Результаты.** Во все изучаемые сроки беременности сывороточная концентрация эстрадиола, тестостерона и пролактина у самок кроликов статистически значимо не отличалась от показателей до беременности, а уровень прогестерона в сыворотке крови значимо повышался по сравнению с уровнем нормы. На 7 сут. беременности фармакокинетические параметры фексофенадина достоверно не изменялись по сравнению с исходными значениями. На 14 сут. беременности отмечалось достоверное повышение C_{max} , AUC_{0-t} , $T_{1/2}$ фексофенадина по сравнению с параметрами до беременности, что свидетельствует о снижении функциональной активности Pgr на уровне целостного организма. На 21 сут. беременности оставалась повышенной C_{max} фексофенадина. Остальные фармакокинетические параметры достоверно не изменялись. **Вывод.** Установлено снижение функциональной активности гликопротеина-Р, определяемой по фармакокинетике его маркерного субстрата – фексофенадина, у кроликов породы «Советская Шиншилла» на 14 и 21 сутки беременности на фоне значительного повышения уровня прогестерона.

Ключевые слова: гликопротеин-Р, ABCB1-белок, функциональная активность, беременность, прогестерон.



P-GLYCOPROTEIN FUNCTIONAL ACTIVITY IN «SOVIET CHINCHILLA» RABBITS DURING PREGNANCY

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P-glycoprotein (Pgp, ABCB1-protein) is a membrane transporter protein that plays the key role in pharmacokinetics of drugs with a broad spectrum of action. Substrates of this transporter are some medical drugs (antibacterial, antiretroviral, hypotensive) that are prescribed to pregnant women for long-term intake, sometimes throughout the whole gestation period. **Aim** to study the activity of Pgp on the organism level in rabbits of Soviet Chinchilla breed in pregnancy. **Materials and Methods.** The study was performed on 21 Soviet Chinchilla female rabbits (3000-3500 g). The animals were divided into 3 series. The first series (n=6) included rabbits with 7 days of pregnancy; the second series (n=5) – animals with 14 days of pregnancy; the third series (n=10) – rabbits with 21 days of pregnancy. 7 Days before the study and in the indicated gestation periods, functional activity of Pgp was assessed by the pharmacokinetics of marker transporter substrate – fexofenadine, after its single oral introduction (67.5 mg/kg). Besides, serum concentrations of progesterone, estradiol, testosterone and prolactin were determined by radio immune method. **Results.** In all the studied gestational periods, serum concentrations of estradiol, testosterone and prolactin did not significantly differ from those before pregnancy, but the level of progesterone in blood serum was significantly elevated above the norm. On the 7th day of pregnancy pharmacokinetic parameters of fexofenadine did not show any reliable changes as compared to the initial values. On the 14th day of pregnancy a reliable increase in C_{max} , AUC_{0-t} , $T_{1/2}$ of fexofenadine was noted as compared to the parameters before pregnancy, which indicates a decrease in Pgp functional activity on the organism level. On the 21st day of pregnancy C_{max} of fexofenadine remained elevated. Other pharmacokinetic parameters of fexofenadine did not show reliable changes. **Conclusion.** Reduction in Pgp functional activity, determined by the pharmacokinetics of its marker substrate (fexofenadine), was noted in rabbits of Soviet Chinchilla breed on the 14th and 21st days of pregnancy with the underlying significant increase in progesterone level.

Keywords: *P-glycoprotein, ABCB1-protein, functional activity, pregnancy, progesterone.*

One of most important issues of clinical pharmacology is pharmacotherapy in pregnancy. By the data of international research, more than 80% of women were taking at least one medical drug in pregnancy [1].

P-glycoprotein (Pgp, ABCB1-protein) is a membrane transporter protein which plays an important role in the pharmacokinetics of a wide range of medical drugs that are its substrates. It regulates their absorption in the intestine, penetration across histohematic barriers including placental one, and its excretion by the liver and kidneys [2]. Of note, the substrates of this transporter are medical

drugs administered to pregnant women for prolonged intake and sometimes throughout the whole period of gestation. Pgp substrates used in pregnant women include some antibacterial (erythromycin, azithromycin, cefazolin, cefoperazon), antiviral (sacvinavir, ritonavir, indinavir), hypotensive (atenolol, nifedipine, amlodipine) drugs [2].

Pgp may considerably change its activity of under action of external and internal factors including hormones [3-5]. It is known that during pregnancy the organism undergoes significant hormonal restructure accompanied by buildup of serum concentrations of

sex hormones [6] which suggests a change in the functioning of Pgp in an organism of a pregnant woman.

In the literature we found only studies of activity of the transporter and of expression of *ABCB1* (*MDR1*) gene coding for Pgp, in the hemato-placental barrier in different gestation periods. Functioning of the transporter in the placenta prevents penetration of its substrates from mother to fetus, therefore its study is important for assessment of safety and effectiveness of the used medical drugs in relation to fetus. However, the general dynamics of Pgp activity in an organism of a pregnant woman may lead to a considerable alteration of pharmacokinetics of the administered substrates. Thus, reduction in the functional activity of the transporter may result in accumulation of its substrates in an organism of a pregnant woman and to development of an undesired reaction to the medical drugs both in mother and fetus, and increase in the functional activity leads to reduction in the concentration of the medical drugs and in the effectiveness of the conducted pharmacotherapy.

The aim to study the activity of Pgp transporter protein on the level of the whole organism in pregnant female rabbits of Soviet Chinchilla breed.

Materials and Methods

The work was conducted on 21 female rabbits of Soviet Chinchilla breed with 3000-3500 g mass. The animals were received from the nursery OAO Kasimov-Miacro and had the respective veterinary certificates, and were kept in standard conditions of the vivarium of Ryazan State Medical University. The animals were handled in compliance with the rules of Good Laboratory Practice (Order of HM RF №199Н of 2016 Apr 1).

All animals were divided to 3 series. The first series (n=6) were animals of 7-days pregnancy; the second series (n=5) – animals of 14-days pregnancy, the third series (n=5) – animals of 21-days pregnancy.

7 Days before the study and in the mentioned gestation periods, in all animals functional activity of Pgp and serum concentration

of hormones (progesterone, estradiol, testosterone and prolactin) were determined by a radioimmune method using standard IMMUNOTECH test-system (Czechia). The obtained results were processed on Immunotest analyzer (Russia).

The first day of pregnancy was considered to be the first day after mating with a male rabbit. Into the final analysis only those female rabbits were included whose pregnancy ended in deliveries.

Functional activity of Pgp was assessed by pharmacokinetics of fexofenadine (Allegra, Sanofy Aventis, France) after its single peroral introduction at the dose 67.5 mg/kg in aqueous suspension (5 mL/rabbit) according to the method described by us earlier [7,8].

Using non-compartmental method [9], the following pharmacokinetic parameters of fexofenadine were calculated: C_{max} – maximal concentration (ng/mL), AUC_{0-t} – area under pharmacokinetic curve concentration-time from zero to the moment of the last blood sampling (ng*h/mL); $T_{1/2}$ – half-life period, h. Concentration of hormones (progesterone, estradiol, testosterone, prolactin) in blood serum was determined in Central Scientific Research Laboratory of Ryazan State Medical University.

The obtained results were processed using Stat Soft Statistica 7.0 program (the USA). The statistical significance of differences between the parameters of hormonal status of the animals was determined using Wilcoxon test. The results were presented in the form of median (Me), upper (uq) and lower quartiles (lq). Statistical significance of differences between pharmacokinetic parameters of fexofenadine was assessed on the basis of log-normal redistribution of data. Comparison of the studied pharmacokinetic parameters was carried out using dispersion analysis (ANOVA) after taking their logarithms. The obtained results (pharmacokinetic parameters) were presented in the form of tables as the mean arithmetic and its 95% confidence interval (CI). The differences were considered statistically significant at $p < 0.05$.

Additionally, two-sided 90% CI of the ratio of geometric means of fexofenadine

pharmacokinetic parameters in the studied gestation age to the parameters of intact animals (before pregnancy) was calculated. According to U.S. Food and Drug Administration, Center for Drug Evaluation and Research, the differences between pharmacokinetic parameters were considered significant if the two-sided 90% CI of their ratio was beyond 0.8-1.25 (80-125%) range, since a change in the pharmacokinetic parameters by only more than 25% might result in changes of the pharmacodynamics of the drugs.

Results and Discussion

In all the studied gestation periods, the

serum concentration of estradiol, testosterone, and prolactin in female rabbits of Soviet Chinchilla breed did not show statistically significant differences from the parameters before pregnancy.

At the same time the level of progesterone in blood serum increased on the 7th day of pregnancy 6.06 times ($p=0.017$), on the 14th day – 11 times ($p=0.001$), and on 21st day – 18.8 times ($p=0.001$) as compared to the norm (Tab. 1).

Throughout pregnancy changes in the pharmacokinetic of Pgp marker substrate – fexofenadine – were noted (Tab. 2).

Table 1

Serum Concentrations of Hormones in Female Rabbits in Different Gestation Age (Med, Iq, uq)

Parameters	Studied Periods of Experiment					
	7 th day		14 th day		21 st day	
	norm	n=6	norm	n=5	norm	n=10
Progesterone, ng/mL	0.675 (0.383; 1.29)	4.09 (3.35; 5.09)*	0.79 (0.47; 1.96)	8.69 (8.19; 9.65)*	0.39 (0.17; 1.02)	7.33 (6.2; 8.55)*
Estradiol, pg/mL	256.0 (247.25; 434.0)	352.7 (312.9; 473.1)	295.9 (254.1; 483.1)	314.83 (247.2; 406.7)	253.46 (241.04; 335.93)	208.08 (183.13; 251.75)
Testosterone, nmol/L	0.8 (0.69; 1.74)	1.28 (0.99; 1.74)	0.78 (0.66; 1.74)	1.08 (0.95; 1.78)	0.76 (0.62; 0.8)	1.35 (0.62; 1.35)
Prolactin, mIU/mL	24.55 (17.88; 26.21)	20.91 (15.61; 22.43)	22.58 (16.5; 25.23)	19.1 (18.4; 23.4)	20.6 (15.15; 24.55)	19.7 (16.36; 24.54)

Note: * – statistically significant differences from the initial parameters (norm), $p<0.05$

Table 2

Pharmacological Parameters of Fexofenadine in Female Rabbits in Different Gestation Age (the geometric mean and its 90% CI)

Parameters	Studied Periods of Experiment					
	7 th day		14 th day		21 st day	
	norm	n=6	norm	n=5	norm	n=10
C_{max} , ng/mL	198.18 (121.89; 322.20)	233.32 (109.88; 495.44)	139.04 (89.13; 216.88)	329.13 (161.68; 670.02)*	216.58 (141.64; 331.15)	424.47 (247.02; 729.39)*
AUC_{0-t} , ng/mL*h	2054.97 (1127.67; 3744.82)	2085.94 (1230.51; 3536.06)	1107.11 (570.18; 2149.65)	2777.07 (840.69; 9173.43)*	1841.29 (1162.62; 2916.11)	2499.49 (1594.07; 3919.17)
$T_{1/2}$, h	9.17 (2.34; 35.89)	18.24 (5.28; 62.96)	8.45 (4.14; 17.24)	25.70 (10.62; 62.22)*	5.44 (2.48; 11.96)	9.72 (4.94; 19.12)

Note: * – statistically significant differences from the initial parameters (norm), $p<0.05$

On the 7th day of pregnancy pharmacokinetic parameters of fexofenadine did not show any reliable changes compared to the initial value.

On the 14th day of pregnancy C_{max} increased 2.37 times (90% CI 1.38; 4.05, $p=0.027$), AUC_{0-t} – 2.51 times (90% CI 1.48; 4.24, $p=0.02$), $T_{1/2}$ – 3.04 times (90% CI 1.56; 5.91, $p=0.023$) as compared to the values before pregnancy.

On the 21st day of pregnancy C_{max} of fexofenadine remained elevated and 1.96 times exceeded the parameters before pregnancy (90% CI 1.22; 3.14, $p=0.029$). All the rest pharmacokinetic parameters did not show any reliable changes.

Since pregnancy in rabbits lasts 28-35 days [10], the hormonal status and activity of Pgp transporter protein were assessed on the 7th, 14th and 21st days.

Fexofenadine is a marker substrate of Pgp therefore its pharmacokinetics is mostly determined by functioning of this transporter protein. Absence of changes in the pharmacokinetic parameters of fexofenadine on the 7th day of gestation indicates preservation of the initial activity of Pgp. Increase in C_{max} , AUC_{0-t} , $T_{1/2}$ of fexofenadine on the 14th day of pregnancy and increase in C_{max} on the 21st day indicate increase in the concentration of the drug in rabbits' organism, and, consequently, reduction in the activity of the transporter in the given gestation periods.

Since concentration of estradiol, testosterone, prolactin in blood serum of pregnant rabbits did not undergo any reliable changes, inhibition of the activity of Pgp was probably due to a considerable increase in the concentration of progesterone in pregnancy.

In some *in vitro* experiments progesterone showed dose-dependent influence on expression of *MDR1* gene coding for Pgp, and on activity of the transporter: in high concentrations it inhibited Pgp activity, and in low concentrations induced expression of *MDR1* gene and activity of the transporter [11-13].

In research on rabbits it was found by us that introduction of progesterone at the dose 2 mg/rabbit with ovariectomy led to increase

in the functional activity of Pgp in comparison with parameters of the animals subject to ovariectomy alone, however, activity of the transporter remained decreased in comparison with the data before the operation. Use of progesterone at the dose 15 mg/rabbit with ovariectomy increased functional activity of Pgp in comparison with castrated rabbits and recovered it to the level of intact animals [5]. Inducing influence of progesterone on the transporter protein in this experiment was due to its low concentrations in serum.

However, in the given research the level of progesterone in pregnant female rabbits considerably exceeded the parameters of animals with ovariectomy and with introduction of exogenous progesterone both at a low and high dose, that was probably the cause for inhibitory influence of steroid on Pgp. It should be noted that in animals with ovariectomy only the level of progesterone was replaced, and the level of estradiol remained low, while in pregnancy the transporter was influenced by both progesterone in high concentrations and by estradiol.

Functioning of Pgp may change both in result of direct influence on the transporter protein, and due to modification of expression of *MDR1* gene [3].

In this experiment, no study of expression of Pgp in organs and tissues of pregnant rabbits was conducted, so it is impossible to show what caused the change in the functioning the transporter protein (modulation of the expression of gene or its own activity). Besides, it is essential to identify the organ (intestine, kidneys, liver, hematoplacental barrier) in which a change in the activity of Pgp led to dynamics of pharmacokinetic parameters of fexofenadine.

Further studies of Pgp transporter protein in pregnancy will permit to identify organospecific molecular mechanisms of modulation of its functioning in different gestation periods.

Conclusion

Reduction in the functional activity of glycoprotein-P in rabbits of Soviet Chinchilla breed was found on the 14th and 21st day of

pregnancy determined by pharmacokinetics of its marker substrate fexofenadine, with the

underlying considerable increase in the level of progesterone.

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Дополнительная информация [Additional Info]

Источник финансирования. Работа поддержана грантом Российского фонда фундаментальных исследований № А 18-015-00259. [Financing of study. The work is supported by the grant of the Russian Foundation for Basic Research № А 18-015-00259.]

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, о которых необходимо сообщить в связи с публикацией данной статьи. [Conflict of interests. The author declares no actual and potential conflict of interests which should be stated in connection with publication of the article.]

Благодарности. Авторы выражают благодарность заведующему Центральной научно-исследовательской лабораторией ФГБОУ ВО РязГМУ Минздрава России Никифорову А.А. за помощь в выполнении радиоиммунных исследований. [Acknowledgments. The authors express their gratitude to Nikiforov A.A., the Head of the Central Research Laboratory of Ryazan State Medical University, for helping in performing radioimmune research.]

Участие авторов. Попова Н.М., Шулькин А.В. – концепция, обработка данных, написание текста, Черных И.В. – выполнение эксперимента, обработка данных, Есенина А.С., Градинарь М.М., Рябков А.Н. - выполнение эксперимента, Никифорова Л.В. – выполнение радиоиммунных исследований, Якушева Е.Н. – концепция, написание текста, редактирование. [Participation of authors. N.M. Popova, A.V. Shchulkin – concept, data processing, writing the text, I.V. Chernykh – execution of the experiment, data processing, A.S. Yesenina, M.M. Gradinar, A.N. Ryabkov – execution of the experiment, L.V. Nikiforova – execution of the radioimmune analysis, E.N. Yakusheva – concept, writing the text, editing.]

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Цитировать: Попова Н.М., Шулькин А.В., Черных И.В., Есенина А.С., Градинарь М.М., Никифорова Л.В., Рябков А.Н., Якушева Е.Н. Функциональная активность гликопротеина-P у кроликов породы «Советская шиншилла» при беременности // Российский медико-биологический вестник имени академика И.П. Павлова. 2018. Т. 26, №4. С. 466-473. doi:10.23888/PAVLOVJ2018264466-473

To cite this article: Popova NM, Shchulkin AV, Chernykh IV, Esenina AS, Gradinar MM, Nikiforova LV, Ryabkov AN, Yakusheva EN. P-glycoprotein functional activity in «Soviet chinchilla» rabbits during pregnancy. *I.P. Pavlov Russian Medical Biological Herald*. 2018;26(4):466-73. doi:10.23888/PAVLOVJ2018264466-473

Поступила/Received: 29.09.2018
Принята в печать/Accepted: 10.12.2018