

## ИЗУЧЕНИЕ ВЛИЯНИЯ ПРОГЕСТЕРОНА НА АКТИВНОСТЬ ГЛИКОПРОТЕИНА-P *IN VITRO*

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**Актуальность.** Гликопротеин-P (Pgp, ABCB1) – белок-транспортер, участвующий в фармакокинетике лекарственных веществ, а также развитии резистентности опухолевых клеток к химиотерапии.

**Цель.** Изучить влияние прогестерона на активность Pgp *in vitro* на клеточной модели эпителия тонкого кишечника человека.

**Материалы и методы.** Исследования выполнены на линии клеток Caco-2. Активность Pgp оценивали по транспорту фексофенадина в специальной трансвелл-системе. Концентрацию фексофенадина анализировали методом ВЭЖХ. Количество Pgp определяли методом ИФА. Были выполнены четыре серии экспериментов: контроль – клетки, которые преинкубировали с чистой транспортной средой без добавления каких-либо веществ; влияние рифампицина на активность и синтез Pgp в концентрации 10 мкмоль/л при преинкубировании в течение 3 сут (контроль индукции); влияние прогестерона на активность Pgp в концентрациях 1, 10 и 100 мкмоль/л при преинкубировании в течение 30 мин; влияние прогестерона на активность и синтез Pgp в концентрациях 1, 10 и 100 мкмоль/л при преинкубировании в течение 3 сут.

**Результаты.** Прогестерон в концентрациях 1 и 10 мкМ при инкубации с клетками в течение 30 мин достоверно не влиял на активность Pgp, однако в концентрации 100 мкМ снижал активность белка-транспортера.

При инкубировании клеток линии Caco-2 с прогестероном в концентрациях 1, 10 и 100 мкМ в течение 3 сут активность Pgp не изменялась. Прогестерон в концентрации 100 мкМ при инкубировании в течение 3 сут значительно повышал синтез Pgp в энтероцитах на 114,3% по сравнению с показателями контроля, а в остальных используемых концентрациях (1 и 10 мкМ) достоверного эффекта не оказал.

**Заключение.** Прогестерон в эксперименте *in vitro* на клетках линии Caco-2 в концентрации 100 мкМ оказывает прямое ингибирующее действие на активность Pgp, однако при инкубации в течение 3 сут повышает синтез белка-транспортера, что нивелирует его ингибирующую активность.

**Ключевые слова:** гликопротеин-P; линия клеток Caco-2; прогестерон.

## A STUDY OF INFLUENCE OF PROGESTERONE ON ACTIVITY OF GLYCOPROTEIN-P *IN VITRO*

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**Background.** Glycoprotein-P (Pgp, ABCB1) is a transporter protein participating in pharmacokinetics of medical drugs, and also in development of resistance of tumor cells to chemotherapy.



**Aim.** To study the influence of progesterone on the activity of Pgp *in vitro* on a cell model of human small intestinal epithelium.

**Materials and Methods.** The work was conducted on Caco-2 cells. The activity of Pgp was evaluated by transport of fexofenadine in a special transwell-system. Concentration of fexofenadine was analyzed by HPLC method. The amount of Pgp was determined by EIA method. Four series of experiments were conducted: control – cells preincubated with clean transport medium without addition of any substances; influence of rifampicin on the activity and synthesis of Pgp in the concentration 10  $\mu\text{mol/l}$  in preincubation for 3 days (induction control); influence of progesterone on the activity of Pgp in concentrations 1, 10 and 100  $\mu\text{mol/l}$  in preincubation for 30 min; influence of progesterone on the activity and synthesis of Pgp in concentrations 1, 10 and 100  $\mu\text{mol/l}$  in preincubation for 3 days.

**Results.** Progesterone in the concentrations 1 and 10  $\mu\text{M}$  in incubation with cells within 30 minutes did not show any reliable influence on the activity of Pgp, however, in concentration 100  $\mu\text{M}$  it reduced the activity of the transporter protein.

In incubation of Caco-2 cells with progesterone in concentrations 1, 10 and 100  $\mu\text{M}$  within 3 days the activity of Pgp remained unchanged. Progesterone in concentration 100  $\mu\text{M}$  in incubation within 3 days significantly increased synthesis of Pgp in enterocytes by 114.3% as compared to control, and in other used concentrations (1 and 10  $\mu\text{M}$ ) it produced no reliable effect.

**Conclusion.** In *in vitro* experiments on Caco-2 cells progesterone in concentration 100  $\mu\text{M}$  produces a direct inhibiting effect on the activity of Pgp; however, in incubation within 3 days it increases synthesis of the transporter protein, which cancels out its inhibitory activity.

**Keywords:** glycoprotein-P; Caco-2 cells; progesterone.

Glycoprotein-P (Pgp, ABCB1) is a transporter protein expressed in the bilipid membrane of cells. Pgp protects organs and tissues against xenobiotics, which are its substrates, removing them from cells into the extracellular space and body fluids. For example, expressed in tumor cells, it forms their resistance to chemotherapy, in the intestinal enterocytes it prevents absorption of substances, in hepatocytes and epithelium of the renal tubules it excretes substances to the bile and urine, respectively, in the endothelial cells of the histohematic barriers prevents penetration of substances into the sequestered organs [1].

It was shown that some substances can influence functioning of Pgp. Inductors (rifampicin) increase the activity of the transporter protein, while inhibitors (verapamil, quinine) decrease it [2].

The regulatory effect of sex hormones on the functioning of Pgp has been found [3,4]. In studying the effect of progesterone on the activity and synthesis of Pgp, contradictory results were obtained.

On the human ovarian carcinoma cell line (NCI-ADR-RES) containing a significant amount of progesterone receptors, it was found that the expression of the *MDR1* gene increased after 8 hours of incubation with progesterone in concentration of  $10^{-7}$  M. The effect of progesterone on the human placental carcinoma cell line (JARs) with low level of progesterone receptors did not lead to increased expression of the *MDR1* gene. With this, the use of progesterone for 24 and 72 hours (in concentrations of more than  $10^{-8}$  M) increased the expression of Pgp protein in NCI-ADR-RES and JAR cells depending on the dose. An increase in transporter expression was accompanied by an increase in its activity, which was evaluated by accumulation of Pgp substrates – saquinavir and paclitaxel – by the cells [5].

On the L-MDR1 cell line formed by transfection of the pig kidney line LLC-PK1 with the human *MDR1* gene, and on the doxorubicin-resistant monocytic leukemia cell line of mice with increased expression of *mdr1a*

/1b (P388 / dx), it was found that progesterone reduced Pgp activity in concentration of  $13.3 \pm 3.2 \mu\text{M}$  on the L-MDR1 cell line and in concentration of  $30.2 \pm 9.8 \mu\text{M}$  on the P388/dx cell line [6].

Analysis of the literature showed that practically no studies were conducted on cell lines of the main organs responsible for the pharmacokinetics of drugs (intestinal and renal epithelium, hepatocytes, endothelium of histohematic barriers).

Earlier, it was shown by us in *in vivo* experiments on rabbits that progesterone increases the activity and synthesis of Pgp in intestinal enterocytes [4].

The aim of this work was to study the effect of progesterone on Pgp activity *in vitro* on a cell model of human small intestinal epithelium.

### Materials and Methods

Experiments were conducted *in vitro* on human Caco-2 cells received from Federal State Budgetary Institution of Science «Research and Scientific Center of the Russian Academy of Science» (FSBIS RSC RAS), Saint-Petersburg.

The Caco-2 cells were cultured at  $37^\circ\text{C}$  and 5%  $\text{CO}_2$  concentration in Dulbecco's modified essential medium (DMEM) containing glucose (4500 mg/l) (Sigma-Aldrich, Germany), L-glutamine (4mM) (Sigma-Aldrich, Germany), 15% bovine serum (Sigma-Aldrich, Germany), 100 Un/ml penicillin (Sigma-Aldrich, Germany) and 100  $\mu\text{g/ml}$  of streptomycin. Upon achievement of 70-90% confluence, the cells were removed from flask by addition of trypsin-EDTA solution (0.25% trypsin and 0.2% EDTA, Sigma-Aldrich, Germany) and were inoculated into Transwell system to evaluate the activity of Pgp, or into 6-well plates to determine the influence of progesterone on synthesis of the transporter protein. The cells were cultured for 21 days when they spontaneously differentiated into cells similar to the intestinal epithelium [7].

Transwell system contains the apical (a) and bilateral (b) compartments. The bottom

of the apical compartment is a semipermeable membrane on which cells were inoculated with  $10^5/\text{cm}^2$  density (33 000 cells/well). In the study, a 12-well plate was used with a semipermeable membrane (12 mm Transwell® with 0.4  $\mu\text{m}$  Pore Polycarbonate Membrane Insert, Sterile, Corning, USA). Upon achievement of transepithelial resistance more than  $500 \text{ mOhm} \cdot \text{cm}^2$ , transport experiments were conducted. The interval between transport experiments in Transwell system was not less than 7 days.

Functioning of Pgp was evaluated by transport of its marker substrate – fexofenadine (Sigma-Aldrich, Германия) in the Transwell system. For this, nutritive medium was replaced with transport medium – Hanks' solution (Sigma-Aldrich, Германия) buffered with 25 mM Hepes at pH 7.4 (Sigma-Aldrich, Германия) with 1% dimethylsulfoxide (Pan-Eco, Russia). After that fexofenadine in the final concentration  $150 \mu\text{M}$  was added to the apical compartment [7], and in 1, 2, and 3 hours samples of transport medium (50  $\mu\text{l}$ ) were taken from the basolateral compartment to determine the concentration of marker substrate (*a-b* transport by passive diffusion opposite to functioning of Pgp).

Then in other Transwell systems transport of fexofenadine was evaluated from the basolateral to apical compartment (*b-a* transport by passive diffusion and transporter protein). For this, fexofenadine in the concentration  $150 \mu\text{M}$  was added to the basolateral compartment, and in 1, 2, and 3 hours samples of transport medium (50  $\mu\text{l}$ ) were taken from the apical compartment to determine concentration of the marker substrate.

Transport of fexofenadine from compartment *a* to compartment *b* and back was evaluated by the formula [8]:

$$P_{\text{app}} = \frac{dQ}{dt} \times \frac{1}{(A \times C_0)}$$

where  $P_{\text{app}}$  – apparent permeability coefficient,  $dQ/dt$  – change in the concentration of the substrate in the receiver compartment during incubation time,  $A$  – surface area of semipermeable membrane of a well of

Transwell system on which cells were cultured,  $C_0$  – initial concentration of the substrate in the donor compartment.

After that the ratio of apparent permeability coefficients was determined: *ba* to *ab*.

This parameter being an integral one, shows the total contribution of Pgp transporter protein to transfer of the marker substrate fexofenadine across the bilipid membrane.

The content of fexofenadine in the transport medium was determined by the method of high performance liquid chromatography with UV detection on Stayer chromatograph (Russia) using the method developed by us [2]. The obtained sample of transport medium (50  $\mu$ l) containing fexofenadine, was diluted in 150  $\mu$ l of mobile phase, and 100  $\mu$ l of the resultant solution was introduced to the chromatograph.

To evaluate the influence of progesterone on the activity of Pgp *in vitro*, it was added to both compartments (apical and basolateral) irrespective of the direction of transport of fexofenadine.

To study the influence of progesterone on the synthesis of Pgp, cells were removed from the wells of 6-well plate by adding trypsin-EDTA solution (0.25% of trypsin and 0.2% of EDTA, Sigma-Aldrich, Germany). The obtained cells were lysed by three frost-defrost cycles. In the obtained lysate, the content of Pgp was determined by IEA method using Human Permeability glycoprotein ELISA kit (Blue gene, China). The amount of protein in the samples was determined using Pierce Coomassie Plus (Bradford) Assay Kit, (ThermoFisher, USA).

In the course of study, the following series of experiments were conducted;

1) Control – cells preincubated with pure transport medium without addition of any substances;

2) Influence of rifampicin on the activity and synthesis of Pgp in the concentration 10  $\mu$ mol/l with preincubation within 3 days – control of induction;

3) Influence of progesterone on the activity of Pgp in the concentrations 1, 10 and 100  $\mu$ mol/l with preincubation within 30 min;

4) Influence of progesterone on the activity and synthesis of Pgp in the concentrations 1, 10 and 100  $\mu$ mol/l with preincubation within 3 days.

The obtained results were processed using Stat Soft Statistica 13.0 (USA, license JPZ811I521319AR25ACD-W) and Microsoft Excel for MAC ver. 16.24 (ID02984-001-000001). Statistical significance of differences was evaluated by dispersion analysis (ANOVA), pair-wise comparisons were performed using Newman-Keuls test. Statistically significant were differences at  $p < 0.05$ .

### Results and Discussion

Results of the experiment are presented in Table 1 and Figure 1.

Culturing of Caco-2 line cells with 10  $\mu$ M of rifampicin within 3 days led to increase in the activity of Pgp manifested by reduction of Papp *ab* by 31.7% ( $p < 0.05$ ) and increase in the ratio of Papp *ba* to Papp *ab* by 93.2% ( $p < 0.05$ ).

Progesterone in the concentrations 1 and 10  $\mu$ M in incubation with Caco-2 cells within 30 minutes did not show any reliable influence on the activity of Pgp. At the same time, in the concentration 100  $\mu$ M it decreased the ratio of Papp *ba* to Papp *ab* by 26.2% ( $p < 0.05$ ), which evidences reduction of the activity of the transporter protein.

In incubation of Caco-2 line cells with progesterone for 3 days in the concentration 1, 10 and 100  $\mu$ M the studied parameters Papp *ba*, Papp *ab* and their ratio did not show any reliable changes in comparison with the control values.

In the next series of experiments, influence of progesterone and rifampicin on the synthesis of transporter protein Pgp in Caco-2 line cells was studied.

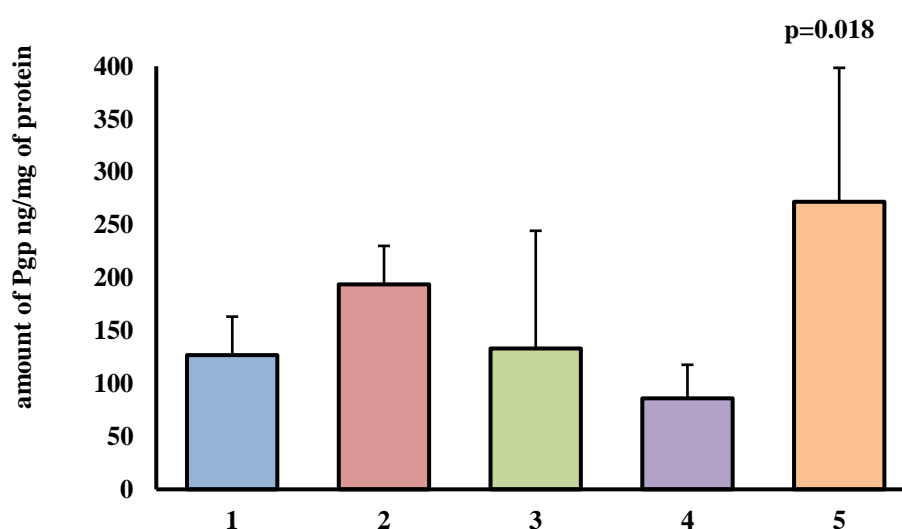
Rifampicin in concentration 10  $\mu$ M in incubation for 3 days caused an increase in the amount of Pgp in enterocytes by 52.7%

Table 1

***Influence of Progesterone on Transport of Fexofenadine across Bilipid Membrane of Caco-2 Cells ( $M \pm SD$ ,  $\times 10^{-6}$  cm/sec)***

	<b>Papp<sub>ba</sub></b>	<b>Papp<sub>ab</sub></b>	<b>Papp<sub>ba</sub>/ Papp<sub>ab</sub></b>
Control, n=5	2.32 $\pm$ 0.66	0.82 $\pm$ 0.15	2.79 $\pm$ 0.36
Rifampicin 10 $\mu$ M 3 days, n=3	2.9 $\pm$ 0.31	0.56 $\pm$ 0.09*	5.39 $\pm$ 1.24*
Progesterone 1 $\mu$ M 30 мин, n=3	1.96 $\pm$ 0.18	0.72 $\pm$ 0.17	2.83 $\pm$ 0.76
Progesterone 10 $\mu$ M 30 мин, n=3	2.4 $\pm$ 0.24	0.89 $\pm$ 0.25	2.93 $\pm$ 1.23
Progesterone 100 $\mu$ M 30 min, n=3	2.03 $\pm$ 0.42	0.99 $\pm$ 0.19	2.06 $\pm$ 0.17*
Progesterone 1 $\mu$ M 3 days n=3	1.95 $\pm$ 0.46	0.63 $\pm$ 0.31	3.36 $\pm$ 0.83
Progesterone 10 $\mu$ M 3 days, n=3	2.13 $\pm$ 0.18	0.71 $\pm$ 0.15	3.1 $\pm$ 0.71
Progesterone 100 $\mu$ M 3 days, n=3	2.32 $\pm$ 0.42	0.76 $\pm$ 0.66	3.1 $\pm$ 0.84

Note: \*  $p < 0.05$  – statistically significant differences in comparison with control parameters



Note: 1 – control (n=7), 2 – rifampicin 10  $\mu$ M, 3 days (n=4), 3 – progesterone 1  $\mu$ M, 3 days (n=3), 4 – progesterone 10  $\mu$ M, 3 days (n=3), 5 – progesterone 100  $\mu$ M, 3 days (n=3)

Fig. 1. The amount of Pgp in Caco-2 line cells on exposure to progesterone ( $M \pm SD$ , ng/mg of protein)

( $p < 0.05$ ), which confirms the correctness of the experiment, because rifampicin is a classic inducer of the transporter protein, increasing its activity due to increased synthesis [2].

Progesterone in concentration 100  $\mu$ M in incubation for 3 days increased the synthesis of Pgp in enterocytes by 114.3% ( $p = 0.018$ ) compared with the control parameters, but did

not show a reliable effect in other concentrations (1 and 10  $\mu$ M) (Figure 1).

The results show that progesterone is a direct inhibitor of Pgp, that is, it can suppress its activity by direct interaction with its molecule, which was found in experiments with incubation of the hormone in concentration of 100  $\mu$ M with Caco-2 cells within 30 minutes.



At the same time, in prolonged incubation (3 days) progesterone increases synthesis of the transporter protein in cell culture. Here, the activity of Pgp does not reliably differ from the control parameters, which is probably due to direct inhibition of Pgp molecule by the hormone, with probable compensatory activation of the synthesis of the transporter.

The direct inhibitory effect of progesterone on the activity of Pgp and at the same time its ability to increase the synthesis of the transporter protein probably underlie the contradictory results described in the literature.

The mechanisms for increasing Pgp synthesis under the influence of progesterone can be associated with the influence on the expression of *MDR1* gene encoding the transporter protein, in the interaction with specific progesterone receptors, or with transcription factors,

for example, pregnan-X receptor (PXR) or constitutive androstane receptor (CAR) [5,9].

Progesterone receptors in the Caco-2 cells have not been described, although their expression has been found in the human intestine [10].

Thus, the mechanism of activation of Pgp synthesis under the influence of progesterone requires further study and clarification.

### Conclusion

Progesterone in *in vitro* experiment on Caco-2 cells in concentration of 100  $\mu$ M produces a direct inhibitory effect on Pgp activity, however, when incubated for 3 days, it increases the synthesis of the transporter protein, which neutralizes its inhibitory activity. The direct inhibitory effect of progesterone on Pgp activity in enterocytes is probably accompanied by compensatory activation of its synthesis.

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