Breast cancer development is associated with changes in expression of genes that involved in regulation of immune responses. Mucin 1 (MUC1) is aberrantly overexpressed in breast tumors. In cancer cells MUC1 gene expression changes, deviations from the normal protein glycosylation and intracellular localization changes is recorded. MUC1 properties changes lead to metabolic reprogramming, new functions appearance and play an important role in the development of tumors. NF-Kβ linking stimulates the release of inflammatory mediators, cytokines such as IL6. MUC1 is associated with the expression of FAS mRNA, which responsible for apoptosis. MUC1 plays an important regulatory role in the transcription of genes associated with tumor invasiveness, metastasis, angiogenesis, proliferation, apoptosis, drug resistant inflammation. The purpose of our study is investigation the relationship of gene expression.

We studied the expression of genes that may influence on inflammation - interleukin 32 (IL32), on cell metabolism - MUC1 and on Fas-dependent apoptosis (Fas).

Tumor samples were collected after surgery from 40 patients with breast cancer. Quantitative reverse transcription PCR (qRTPCR) was carried out to analyze mRNA levels of IL32, MUC1 and Fas. The B2M (Beta-2-microglobulin), UBC (Ubiquitin C), HPRT1 (Hypoxanthinephosphoribosyl transferase 1), YWHAZ (Tyrosine 3 monooxygenase activation protein, zeta polypeptide) house-keeping gene were used as endogenous controls. The levels of gene expressions were measured by comparative Ct-method (ΔΔCt). At first, we assessed stability of house-keeping gene expression in breast tumor samples. Analysis by the BestKeeper computer program shows that B2M is suitable for the normalization of mRNA expression in human breast tumors samples. MUC1 mRNA was detected in 32 (80%) tumor samples, mRNA IL32 – 26 (65%) tumor samples and Fas mRNA in 38 (95%) tumor samples. It has been noted that all MUC1 mRNA-negative samples were IL-32 mRNA-negative which may indicate common mechanisms of gene regulation. Comparison of mRNA levels of MUC1 and IL32 in the breast tumors showed no differences. Importantly, results of our investigation showed a correlation between increased levels of Fas mRNA and gene silencing IL-32 ($r = 0.47$, $p = 0.004$) and MUC1 ($r = 0.57$, $p = 0.002$) in breast tumors. This data show the correlation between gene expression mediating inflammation, metabolism and apoptosis in breast cancer tumors. We propose that common regulation mechanisms through NFk-B pathway may take part in the described processes.

Regulation Of Neuronal Chloride Homeostasis: A New Role For Extracellular Matrix

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Neuronal signaling relies on ion fluxes through membrane-bound channels. Such fluxes are allowed due to the transmembrane ionic gradients created and maintained by membrane transporters. The neuronal gradient for chloride, an anion mediating most of the inhibition in the mature CNS, is the result of activity of two chloride transporters working in opposite directions, NKCC1 moving chloride in and KCC2 moving chloride out of the cell. The KCC2 function may be both up- and down-regulated through a number of mechanisms which allow for the fine-tune adaptation to a varying transporting load which mostly depends on chloride influx through both synaptic and extrasynaptic inhibitory chloride-permeable ion channels such as GABAA- and glycine-receptors.

Besides intraneuronal factors affecting KCC2 function and, thus, the chloride gradient, there is a number of extra-neuronal factors suggested to have a great influence over the distribution of chloride across the neuronal membrane. The very recent experimental findings point to the extracellular matrix as an important player in regulation of intracellular chloride. It has been claimed that large anion groups located within the extracellular matrix set the chloride gradient due to the Gibbs-Donnan effect, thus, effectively sidelining KCC2 as a major contributor to the neuronal chloride homeostasis. However, our own experimental findings concerning chloride homeostasis in anterior hypothalamic neurons suggest quite a different mechanism of involvement of the extracellular matrix.

Changes In The Electrical Conductivity Of The Myocardium Of Isolated Rat Heart Under The Influence Of Verapamil

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Summary. The study was designed to investigate the effect of verapamil on the speed of propagation of electrical excitation in the myocardium. As a result, it was found that verapamil reduces heart rate, the speed of excitation in the

myocardium remains unchanged. The results obtained allow us to estimate the effect of verapamil on the condition of cardiac tissue, based on the change in its conductivity during treatment with the drug.
Key words. Langendorff method, verapamil, conduction velocity, multielectrode mapping

INTRODUCTION

Calcium antagonists are widely used in the treatment and prevention of heart diseases. Verapamil is a blocker of the slow L-type calcium channel. The action of verapamil in the heart accompanied by negative inotropic and chronotropic effects, since the restriction of entry of calcium ions leads to a quantifiable reduction in the formation of actin-myosin bonds in the working cardiomyocytes and to inhibition of spontaneous diastolic depolarization in the atypical cardiomyocytes of the conduction system [1]. The concentration of calcium ions also affect the speed of propagation of a wave of electrical excitation due to the regulation of connexons, which is placed in the intercalated discs of cardiomyocytes [2]. The aim of the study was to examine the effect of verapamil on the speed of propagation of the excitation wave in the ventricular myocardium of isolated rat heart.

MATERIALS AND METHODS

Isolated hearts of outbred white rats were perfused by the Langendorff method. After 10 minutes of perfusion with Krebs-Henseleit solution (NaCl 118, KCl 4,7, $CaCl_2$ 2, $MgSO_4$ 1,2, KH_2PO_4 1,2, $NaHCO_3$ 20, glucose 10 mkmol/L) in an experimental group perfusion was held with addition of verapamil with a concentration of 7 mol / L. For registration of the electrical activity of the myocardium multi-electrode mapping setting with flexible matrices was used. Heart rate measured by the number of heart beats per minute. The speed of propagation of the wave excitation of
the heart was calculated based on the difference between the values of time of occurrence of electrical potentials recorded by the electrodes of the matrix. Comparison of the average values of obtained parameters at different stages of the experiment, as well as a comparison of these values in the control and experimental groups, was performed by Student t-test for dependent samples. Differences were considered significant at a significance level of $p < 0.05$.

RESULTS

As a result of the study it was found that during the perfusion of the isolated rat heart with a solution containing verapamil, heart rate decreased to 1.52 times compare with the control group. The velocity of propagation of excitation between the detection electrode of the matrix was not changed (Fig.1).

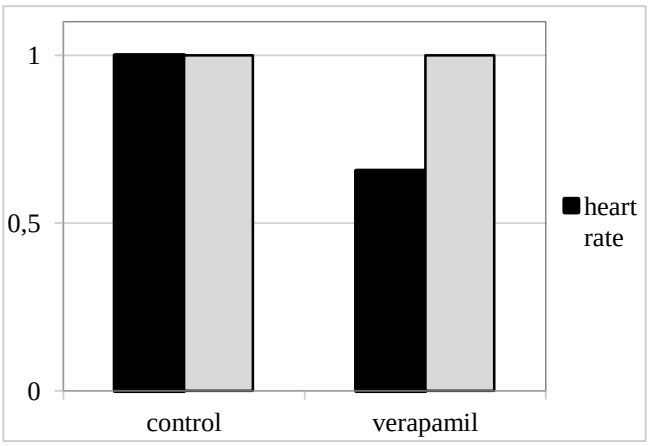

Fig. 1. Changes in heart rate and speed of propagation of the excitation wave in the isolated rat heart under the influence of verapamil

CONCLUSIONS

Perfusion with a solution containing verapamil influenced on the calcium dynamics in myocardium of the isolated rat hearts that was expressed in a negative chronotropic effect. But this influence did not cause changes in the speed of propagation of the wave of excitation along the surface of the myocardium, which indicates the existence of specific mechanisms to prevent a change in the conductivity of the myocardium, causing the termination of calcium channels of L-type. The work was supported by the Russian Science Foundation (Project No. 14-12-00811).

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