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β-ADRENERGIC RECEPTOR BLOCKERS AS A REGULATOR OF T CELL VIABILITY (IN THE MODEL SYSTEM OF THE JURKAT CELLS)

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β-ადრენერგული რეცეპტორების ბლოკატორები, როგორც T უჯრედების სიცოცხლისუნარიანობის რეგულატორები (Jurkat უჯრედების მოდელის სისტემაში)

საქართველოს დავით აღმაშენებლის სახელობის უნივერსიტეტი,
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რეზიუმე

ჩვენი კვლევა **მიზნად** ისახავდა დაედგინა სხვადასხვა β-ადრენერგული რეცეპტორების ბლოკატორების ეფექტურობა T უჯრედების პროლიფერაციის რეგულაციაში Jurkat უჯრედების მოდელურ სისტემაში.

მასალა და მეთოდები. კვლევა ჩატარდა ადამიანის ლეიკემიურ მომწიფებულ T უჯრედებზე (Jurkat უჯრედები) (DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen (გერმანია)), რომლებიც გააქტიურებულია ფიტოჰემაგლუტინინით (PHA). ნებილეტის, ეგილოკის, ბეტალოკ ზოკის და პროპრანოლოლის ზემოქმედებისას ვსწავლობდით ინტაქტური და PHA-სტიმულირებული Jurkat უჯრედების სიცოცხლისუნარიანობას და პროლიფერაციულ აქტივობას MTT ტესტის საშუალებით.

შედეგები. კვლევის შედეგებმა აჩვენეს, რომ β-ადრენერგული რეცეპტორების ბლოკატორები შერჩევით გავლენას ახდენენ როგორც ინტაქტური, ასევე მიტოგენით სტიმულირებულ Jurkat უჯრედების მიტოქონდრიული დეჰიდროგენაზების აქტივობაზე და, შესაბამისად, სიცოცხლისუნარიანობაზე. კერძოდ, Nebilet-მა, Betalok Zok-მა და Propranolol-მა გამოიწვია ინტაქტური Jurkat უჯრედების სიცოცხლისუნარიანობის სტატისტიკურად მნიშვნელოვანი შემცირება 63%, 20% და 32% შესაბამისად; ეგილოკი და Betalok Zok (25მგ) სტატისტიკურად მნიშვნელოვნად არ მოქმედებდა PHA-აქტივირებული Jurkat უჯრედების სიცოცხლისუნარიანობაზე. Nebilet, Betalok Zok (50მგ) და პროპრანოლოლმა შეამცირეს მიტოგენის (PHA) აქტივირებული Jurkat უჯრედების სიცოცხლისუნარიანობა (PHA დოზისთვის 20მკგ/მლ) და არ იმოქმედა Jurkat უჯრედების სიცოცხლისუნარიანობაზე (PHA დოზით 50მკგ/მლ).

დასკვნა. შეიძლება დავასკვნათ, რომ T უჯრედების სიცოცხლისუნარიანობა და, შესაბამისად, მათი ფუნქციური აქტივობა დიდწილად მგრძნობიარეა β-ბლოკატორების ეფექტების მიმართ. ეს მონაცემები და ასევე იმუნური სისტემის აქტივობის შესაძლო დარღვევები უნდა იქნას გათვალისწინებული კლინიკაში სხვადასხვა დაავადების სამკურნალოდ β-ბლოკატორების გამოყენებისას.

1.Introduction

A key component in the pathophysiology of hypertension is inflammation. It is determining not only hypertension development and/or progression but also leads to end-organ damage [1,2]. Metabolic/chemical, mechanical (wall stretch), or infectious endothelial aggressions trigger complex immune reactions, leading to a pro-inflammatory state [3]. Patients with essential hypertension have an altered profile of pro- and anti-inflammatory cytokines [4].

Of great interest is the role of subtypes of T cells in hypertension and the mechanisms by which they contribute to this disease. There has been substantial interest in the role of subtypes of T cells in hypertension, and the mechanisms, by which they contribute to this disease. It was found that mice lacking CD8 + T cells were protected from hypertension, whereas mice lacking CD4+ T cells or MHC class II were not [5]. An interesting study by Youn et al. (2013) compared circulating T cell phenotypes in newly diagnosed hypertensive patients to age- and sex-matched controls and found that the number of

circulating “Immunosenescent” pro-inflammatory CD8+ T cells is increased in humans with hypertension [6]. These cells produce increased amounts of IFN-γ, TNF-α, and the cytotoxic molecules granzyme B and perforin compared with CD8+ T cells from normal subjects. There is also evidence that CD4+ T cells are activated in hypertension and likely play an important role. It was shown that IL-17A, produced in large part by CD4+ T cells plays a critical role in the regulation of blood pressure [7,8].

To regulate the functional activity of lymphocytes, the protective and damaging effect of T cell antibodies in the immune system, based on the interaction of immune cells with mediators of the nervous and endocrine systems, several autoregulatory mechanisms have been developed that ensure the maintenance of homeostasis of these systems and regulation of the immune response in various diseases [9,10]. This regulation is carried out by modulating the activity of receptors expressed on the surface of cells, in particular, β-adrenergic receptors. Early data of radioligand binding analysis confirmed the expression of the β-adrenergic receptor on both the human and the murine T cell populations, of which the β2 adrenergic receptor subtype is predominant; scarce evidence supports the expression of a high-affinity β1 adrenergic receptor on T cells [11,12]. It was shown that nonselective β-adrenergic blocker propranolol altered the mitogenic response of lymphocytes in essential hypertension, increased their proliferation and differentiation rate, and therefore changed the distribution of lymphocyte subclasses [13].

β-adrenoceptors under the influence of endogenous and exogenous stimuli initiate a cascade of biochemical reactions and intermolecular interactions and modulate cell activity. Their mechanism of action includes G-protein-mediated activation of adenylate cyclase, intracellular accumulation of cAMP, and activation of protein kinase A (PKA), which through phosphorylation regulates the activity of numerous targets (tyrosine and serine-threonine kinases) constitutionally associated with CRE (cAMP-responsible element) and transcription factors participating in the regulation of gene transcription [14].

Our research aimed to establish the effectiveness of various β-adrenergic receptor blockers in the regulation of T cell proliferation in the model system of the Jurkat cells.

Jurkat human CD4(+) T cell lymphoblast-like cell line was established from the propagation of peripheral blood cells of a 14-year-old boy with T cell leukaemia. Stimulation of these cells with phorbol esters, such as 12-O-tetradecanoylphorbol-13-acetate (TPA) and either lectin, such as phytohemagglutinin (PHA) or monoclonal antibodies leads to activation of T cell antigen receptors and induction of IL-2 expression. IL-2 is a key cytokine important for the proliferation and differentiation of T cells into effector T cells through interaction with the IL-2 receptor. Because these cells can produce IL-2 in response to stimulation, they are frequently used in research to study the T cell-mediated immunity and response, regulation of cytokine expression, proliferation, and differentiation of T cells.

2.Material and Methods

2.1 Cell culture. The research involved human leukemic mature T cells (Jurkat cells) (DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen (Germania)). Cells were proliferated in bioactive medium RPMI 1640 (GIBSO), inactivated embryonic bovine serum (Sigma), L-glutamine (4mM), penicillin (100un/ml), and streptomycin (100un/ml) containing suspension at 37^0C T, moist 5% CO_2 containing medium. Experiments will be carried out on cell concentrations 0,3 – 0,6 x 10^6 cells in 1ml of the medium. Stimulation of Jurkat cells (4 x 10^5 cells/ml) involved incubation with 20 μg/ml and 50 μg/ml PHA at 37^0 for 24 hours. PHA was then removed by brief centrifugation, cells were washed three times with RPMI-1640 and resuspended in a complete medium.

Viability and proliferative activity of intact and PHA-stimulated Jurkat cells under the influence of Nebilet, Egilok Betalok Zok (25 mg. 50 mg), and Propranolol (0,2 mM) were studied.

2.2 Cell Viability Assay. For the analysis of cell proliferation, cell viability, and/or cytotoxicity, tetrazolium salts (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)) cleavage into a blue-coloured formazan product by mitochondrial dehydrogenases, are currently widely used.

PHA and β-blockers were added directly to the culture medium and incubated for 24 h. Cells were then washed twice with HEPES-buffered incubation medium (HBM; 140 mM NaCl, 5 mM KCl, 5 mM

$NaHCO_3$, 1.1 mM $MgCl_2$, 1.2 $CaCl_2$, 5.5 mM glucose, and 20 mM HEPES, pH 7.4) and incubated for 45 min at 37^0 C in HBM containing MTT (0.5 mg/ml). After this period, the HBM was removed carefully and the blue formazan product was dissolved in 300 µl of 100% dimethylsulfoxide (DMSO). The spectrophotometric absorbance *(A)* was read at 570 nm.

We calculated the coefficient of viability through the formula below:

$$K = A_{trial}/A_{control}$$

2.3 Statistical Analysis Statistical processing of the obtained results was conducted according to SPSS 11.0 program. The Student's t-test was used for the analysis of differences between means and a change with a p-value < 0.05 was considered statistically significant.

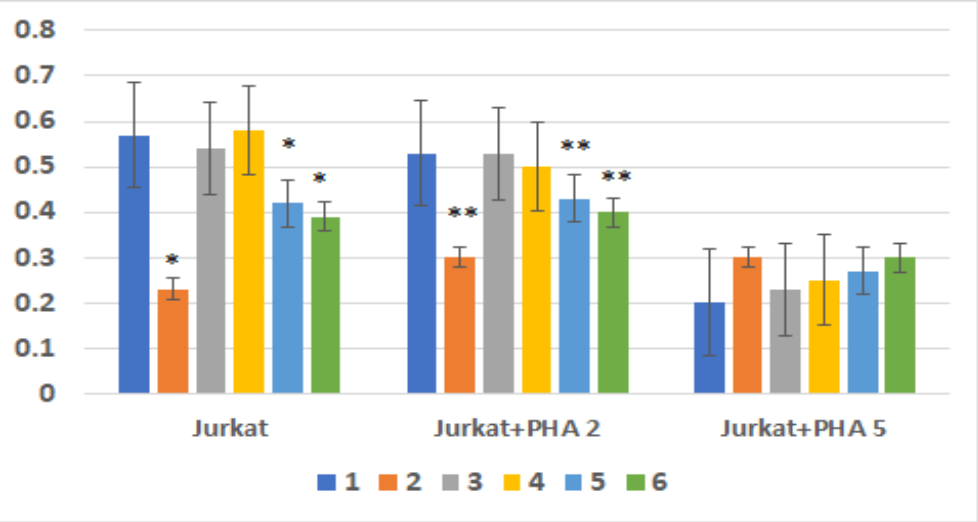
3. Results

We investigated the viability of intact and PHA-stimulated Jurkat cells under exposure to β-adrenergic receptor blockers (Nebilet, Egilok, Betalok Zok, and Propranolol) (Figure 1).

The results of the study show that PHA at a dose of 20µg/ml does not significantly affect the viability of intact cells, whereas a dose of 50µg/ml exhibits revealed cytotoxicity, which is consistent with the literature data [15].

Study results show that β-adrenergic receptors blockers selectively influence the activity of mitochondrial dehydrogenases, and therefore viability in both intact and mitogen-stimulated Jurkat cells. In particular, Nebilet, Betalok Zok (50mg), and Propranolol induced a statistically significant decrease of intact Jurkat cells viability by 63%, 20%, and 32%, respectively; Egilok and Betalok Zok (25mg) didn't statistically significantly affected the Jurkat cells PHA) activated Jurkat cells viability. Nebilet, Betalok Zok (50mg), and Propranolol decreased viability on the mitogen (PHA) activated Jurkat cells (for PHA dose 20µg/ml) and didn't affect at a PHA dose of 50µg/ml.

Figure 1. Viability of Jurkat Cell under the Influence of β-adrenergic receptors blockers



1 - intact Jurkat; 2 - Jurkat + Propranolol; 3 - Jurkat + Egilok; 4 - Jurkat + Betalok Zok 25 mg; 5 - Jurkat + Betalok Zok 50 mg; 6 - Jurkat + Nebilet

4. Discussion

Despite the extensive use of β-blocker for the treatment of hypertension and many cardiovascular problems, the mechanisms responsible for their important clinical effects are not well elucidated. β-blockers can be classified into three groups: first-generation non-selective β-blockers, second-generation beta-selective β-blockers, and additional third-generation β-blockers with addition to previous actions, have vasodilatory effects by different mechanisms: concomitant α-1 adrenergic receptor blockade, increased synthesis and release of nitric oxide in the vascular endothelium [16]. Our research used first-

generation non-selective β-blocker Propranolol, second-generation beta-selective β-blockers Egilok and Betalok Zok, and third-generation β-blocker with blocker addition to previous actions, ability to increase synthesis and release of nitric oxide (NO).

The main component of selective β-blockers Egilok and Betalok Zok is Metoprolol (Egilok - Metoprolol tartrate, Betalok Zok - Metoprolol succinate) - a cardioselective beta-adrenoceptor antagonist (it has a higher affinity for β1 - receptors than for the β-2 receptor subtype - β1/β2 selectivity = 74 [17]. Receptor-subtype selectivity is diminished at higher doses. Egilok contains Metoprolol tartrate, characterized by immediate release, it exhibits a weak effect, in contrast to the long effect of Betalok Zok, containing metoprolol succinate, characterized by an extended-slowly release. This circumstance allows us to explain the relatively strong inhibiting effect of high doses of Betaloc Hawk on intact and PHA-stimulated Jurkat cells in comparison to Egilok (Fig.1).

Nebivolol β1/β2 selectivity = 321 [17] allows us to assume its inhibitory effect on intact and PHA-stimulated cell proliferation (where β2-adrenoreceptors are highly prevalent) is related to the NO-dependent mechanisms.

For propranolol β1 / β2 selectivity = 1 [17].

The antagonist of β-adrenergic receptors, propranolol contributed to a significant decrease in the activity of mitochondrial dehydrogenases, and hence the viability of both intact and mitogen-stimulated Jurkat cells. The cytotoxic activity of β-blockers has also been identified in other studies on various cell types [18,19]. It is known that activation of mitochondrial dehydrogenases requires an increase in the content of Ca^{2+} ions [8]. Takemura H. et al showed that β-adrenergic receptor-dependent calcium mobilization in Jurkat cells occurs via cAMP and IP3 activation [20]. Thus, the cytotoxic activity of β-blockers should be due to the blocking of cAMP-dependent Ca2+ mobilization in mitochondria with a subsequent decrease in the activity of their dehydrogenases, and hence the viability of Jurkat cells. The beta-blocker effect on T helper type 1 cytokine profile in human leukemic T cells has been assessed in vitro [4,21,22,23].

5. Conclusion

Thus, it can be concluded that the viability of T cells, and hence their functional activity, is largely sensitive to the effects of β-blockers. These data and possible disturbances in the immune system's activity must be considered when using β-blockers for the treatment of various diseases in the clinic.

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ТАМАР ШАРАШЕНИДЗЕ, МАЙЯ ЭНУКИДЗЕ, МАРИНЕ МАЧАВАРИАНИ, НИНО ОТАРИШВИЛИ,
ТЕА ГАБУНИЯ, ТАМАР САНИКИДЗЕ

БЛОКАТОРЫ β-АДРЕНОРЕЦЕПТОРОВ КАК РЕГУЛЯТОРЫ ЖИЗНЕСПОСОБНОСТИ Т-КЛЕТОК (В МОДЕЛЬНОЙ СИСТЕМЕ КЛЕТОК JURKAT)

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РЕЗЮМЕ

Целью наших исследований было установление эффективности различных блокаторов β-адренорецепторов в регуляции пролиферации Т-клеток в модельной системе клеток Jurkat.

Материал и методы. Исследования проводились на зрелых лимфоидных Т-клетках человека (клетки Jurkat) (DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen (Германия)), активированных фитогемагглютинином (ФГА). С помощью МТТ-теста определяли жизнеспособность и пролиферативную активность интактных и ФГА-стимулированных клеток Jurkat под влиянием препаратов Небилет, Эгилок, Беталок Зок и Пропранолол.

Результаты. Результаты исследования показывают, что блокаторы β-адренорецепторов избирательно влияют на активность митохондриальных дегидрогеназ и, следовательно, на жизнеспособность как интактных, так и стимулированных митогеном клеток Jurkat. В частности, Небилет, Беталок Зок и Пропранолол вызывали статистически значимое снижение жизнеспособности интактных клеток Jurkat на 63%, 20% и 32% соответственно; Эгилок; и Беталок Зок (25 мг) не оказывали статистически значимого влияния на жизнеспособность ФГА-активированных клеток Jurkat. Небилет, Беталок Зок (50 мг) и пропранолол снижали жизнеспособность активированных митогеном (ФГА) клеток Jurkat (для дозы ФГА 20 мкг/мл) и не влияли при дозе ФГА 50 мкг/мл.

Вывод. Можно сделать вывод, что жизнеспособность Т-клеток, а значит, и их функциональная активность в значительной степени чувствительны к действию β-адреноблокаторов. Эти данные, а также возможные нарушения деятельности иммунной системы необходимо учитывать при применении β-адреноблокаторов для лечения различных заболеваний в клинике.

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β-ADRENERGIC RECEPTOR BLOCKERS AS A REGULATOR OF T CELL VIABILITY (IN THE MODEL SYSTEM OF THE JURKAT CELLS)

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SUMMARY

Our research **aimed** to establish the effectiveness of various β-adrenergic receptor blockers in the regulation of T cell proliferation in the model system of the Jurkat cells.

Material and Methods. The research was conducted on the human leukemic mature T cells (Jurkat cells) (DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen (Germany)) activated by phytohemagglutinin (PHA). Viability and proliferative activity of intact and PHA-stimulated Jurkat cells under the influence of Nebilet, Egilok, Betalok Zok, and Propranolol were studied with the MTT test.

Results. Study results show that β-adrenergic receptors blockers selectively influence the activity of mitochondrial dehydrogenases, and therefore viability in both intact and mitogen-stimulated Jurkat cells. In particular, Nebilet, Betalok Zok, and Propranolol induced a statistically significant decrease of intact Jurkat cells viability by 63%, 20%, and 32%, respectively; Egilok and Betalok Zok (25mg) didn't statistically significantly affect the PHA- activated Jurkat cells viability. Nebilet, Betalok Zok (50 mg), and

Propranolol decreased the viability of the mitogen (PHA) activated Jurkat cells (for PHA dose 20μg/ml) and didn't affect at a PHA dose of 50μg/ml.

Conclusion. It can be concluded that the viability of T cells, and hence their functional activity, is largely sensitive to the effects of β-blockers. These data and also possible disturbances in the activity of the immune system must be considered when using β-blockers for the treatment of various diseases in the clinic.

Keywords: β-blockers, T cells viability, adrenoreceptors