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Expression of adrenergic, acetylcholine and kappa opioid receptors on peripheral blood lymphocytes in patients with herpetic keratitis and those with idiopathic anterior and/or intermediate uveitis

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Purpose: *To assess the expression of adrenergic, acetylcholine (ACh) and opioid receptors on peripheral blood lymphocytes in patients with herpetic keratitis (HK) and those with idiopathic anterior and/or intermediate uveitis (IAIU).*

Methods: *Thirty one patients with HK (group 1; age, 40.7 ± 14.2 years), 36 patients with IAIU (group 2; age, 49.9 ± 12.5 years), and 12 healthy volunteers (controls; age, 43.5 ± 14.8 years) were included in the study and examined at Immunology laboratory, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine". Immunocytochemistry with monoclonal antibodies to receptors and fluorescein microscopy were used. IBM SPSS Statistics software and spreadsheets were used for the statistical analysis.*

Results: *Expression of β adrenergic receptors, Ach receptors and kappa opioid receptors (KOR) on lymphocytes was significantly increased in patients with HK and patients with IAIU compared to healthy controls. There was a significant difference in the ratio of expression of β adrenergic receptors to KOR on peripheral blood lymphocytes (expressed as percentage) between patients with HK and healthy controls and between patients with IAIU and healthy controls.*

Keywords:

uveitis, herpetic keratitis, opioid receptors, β2 adrenergic receptors, cornea

Introduction

It is an important task of current clinical ophthalmology to find biomarkers that would help predicting the nature of inflammatory process and assessing the probability of complications. The central nervous system (CNS) and immune system are the major adaptive systems of the body involved in a continuous functional interplay for maintaining homeostasis. Both innate and adaptive immune systems are controlled by the sympathetic nervous system (SNS) signaling through adrenergic receptors [1, 2]. Though all lymphocytes have adrenergic receptors, differential density and sensitivity of adrenergic receptors on lymphocytes may affect responsiveness to stress among cell subsets [3]. In addition, CD4 and CD8 T cells express various adrenergic receptors (α1, α2, β) [4].

Lymphocytes express most of the cholinergic components found in the nervous system, including acetylcholine (ACh), choline acetyltransferase (ChAT), muscarinic and nicotinic ACh receptors (mAChRs and nAChRs, respectively), and acetylcholinesterase. In the peripheral tissues, nicotinic ACh receptor α7nAChR is important for anti-inflammatory signaling in the efferent arm of the inflammatory reflex [5]. Although widely studied as a neurotransmitter, T cell-derived ACh has recently been reported to play an important role in regulating immunity and stimulate vasodilation. Under inflammatory conditions, lymphocytes have been shown to express choline acetyltransferase and produce Ach which stimulates vasodilation. Vasodilation is critical for immune responses and is one of the hallmarks of inflammation facilitating the entry of immune cells into infected tissues [6, 7]. Neurotransmitters and neuropeptides are important players in immune function and chronic inflammation due to their chemoattractive capacity. Studies have demonstrated a key role of the SNS and its neurotransmitters in the regulation of chronic inflammatory conditions [8].

Stress system is another complex regulatory system of the body which is involved in the coordination of homeostasis during body exposure to stressors of various origins and strength, which is followed by the hypothalamus-pituitary-adrenal axis and adrenergic activity. Stress system activity and reactivity are limited by mechanisms of self-regulation and outer regulation. The self-regulation of the stress-release system is built on the feedback principle, i.e., the production of stress hormones

is self-limiting. The external regulation mechanisms are implemented by the so-called stress-limiting systems that limit the activity of the stress system and excessive stress-reaction on the central and peripheral levels [9]. Gamma-aminobutyric acid (GABA)-ergic and opioid-ergic systems are major central self-limiting systems. Evidence has been accumulated that (1) the opioid and immune systems are closely interconnected and (2) endogenous opioid peptides are involved in immune modulation [10]. There are three major types of opioid receptors, delta (δ), mu (μ), and kappa (κ) [11, 12]. These receptors are activated by endogenous peptides (such as endomorphines, enkephalins, and dynorphines) and natural alkaloids and other synthetic and semisynthetic ligands of small molecules [13]. The presence of opioid receptors and intracellular signaling of these receptors associated with transcription factors allows to state that immune cells have a full-functional opoidergic regulation system [14, 15]. Therefore, it is important to investigate (1) the role of neural control in enabling fast, specific and selective immune response, and (2) the role of adrenergic and cholinergic regulation under inflammatory conditions in enabling the functions and cellular response to major neurotransmitters that can regulate migration, proliferation, differentiation and cooperation of immunocompetent cells.

Determining the expression of adrenergic, acetylcholine and opioid receptors on peripheral blood T cells in patients with herpetic keratitis (HK) and patients with idiopathic anterior and/or intermediate uveitis (IAIU) would be helpful in predicting an active inflammatory response. There are only isolated publications investigating these issues in ocular inflammatory diseases [16].

The purpose of the study was to assess the expression of adrenergic, acetylcholine and opioid receptors on peripheral blood T cells in patients with HK and patients with IAIU.

Methods

Thirty one patients with HK (group 1; age, 40.7 ± 14.2 years), 36 patients with IAIU (group 2; age, 49.9 ± 12.5 years), and 12 healthy volunteers (controls; age, 43.5 ± 14.8 years) were included in the study and examined at Immunology laboratory, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine".

The study followed the ethical standards stated in the Declaration of Helsinki, the European Convention on Human Rights and Biomedicine and relevant laws of Ukraine. Written informed consent was obtained from all participants. Fasting blood samples were collected. A 4-5-ml sample of heparinized blood was obtained from the cubital vein with a vacuum system, and twice diluted with 0.9% NaCl.

Immunocytochemistry with monoclonal antibodies to Kappa opioid receptors (McAbs to KOR; LifeSpan Biosciences via Biozol, Eching, Germany) and fluorescein microscopy were used to investigate KOR [17]. The high specificity of monoclonal antibodies minimizes background and eliminates cross-reactivity. Immuno Fluorescein Isothiocyanate (FITC; DAKO A/S, Glostrup, Denmark) dye was used for visualization. In brief, the method was as follows. Lymphocyte suspension was obtained by density gradient centrifugation in the presence of Ficoll (Simesta, Ukraine; density, 1.076 g/cm3). The suspension was washed twice by centrifugation. Smears were prepared and fixed in formalin vapor. Specific McAbs to KOR were applied to smears. Smears were incubated with FITC-conjugated anti-mouse antibodies for 3 hours. Slides were finally washed in phosphate buffer and examined by fluorescence microscopy (iSCOPE, Eupomax, Arnhem, The Netherlands).

To assess the specific sensitivity of lymphocytes to adrenaline and acetylcholine, we employed our complex methodology for assessing the individual's sensitivity to medications which has been developed at Immunology laboratory [18, 19]. A summary of the method procedure was as follows.

First, lymphocyte suspension was obtained by density gradient centrifugation in the presence of Ficoll (Simesta, Ukraine; density, 1.076 g/cm3) and washed twice by centrifugation. Second, (a) lymphocyte cell suspension (0.05 ml) was mixed with NaCl 0.9% (0.05 ml); (b) lymphocyte cell suspension (0.05 ml) was mixed with adrenaline 0.18% (0.05 ml; sterile solution, ready for use, manufactured by JSC Darnytsia, Kyiv, Ukraine); and (c) lymphocyte cell suspension (0.05 ml) was mixed with acetylcholine chloride 0.1% (0.05 ml; sterile solution, manufactured by Sinbias LLC, Kyiv) (dry substance with diluted with physiological saline); and these three mixture samples were incubated in parallel at 37oC for one hour.

Thereafter, T cells (CD 3) were determined immunohistochemically using a routine method with McAbs. CD3 counts were determined for study samples (with adrenaline and acetylcholine) and control samples (with physiological saline). CD3 assay was obtained from the Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, National Academy of Sciences of Ukraine. Microscopy was performed at an objective magnification of 80x and an ocular magnification of 15x. Staining was visualized with FITC (Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of National Academy of Science of Ukraine)-conjugated monoclonal CD3 antibodies using fluorescence microscopy (iSCOPE, Eupomax, Arnhem, The Netherlands). In order to examine changes in the regulation of immune response, we assessed the ratio of expression of β adrenergic receptors to KOR (expressed as percentage) on peripheral blood lymphocytes in patients with HK, patients with IAIU and healthy controls.

IBM SPSS Statistics software version 26 (IBM Corp., Armonk, NY) was used for the statistical analysis. The data obtained were entered into a spreadsheet database. Shapiro-Wilk test was performed to determine normality of data. Mean and standard deviation (SD) values were

calculated. The Student t test was used to compare mean values of normally distributed numerical variables. P values ≤ 0.05 were considered significant.

Results

Expression of KOR on peripheral blood lymphocytes in patients with HK and patients with IAIU was 16.2 ± 2.9% (Fig. 1) and 15.7 ± 2.8%, respectively, with a significant difference from healthy controls (9.4 ± 1.6%; $p < 0.01$).

Expression of β-adrenergic receptors on peripheral blood lymphocytes in patients with HK was 12.9 ± 0.5% (Fig. 2), which was lower than in patients with IAIU (13.9 ± 0.8%) and 1.7-1.9 times higher than in controls (9.4 ± 1.6%), and these differences were significant ($p < 0.05$).

Expression of ACh receptors on peripheral blood lymphocytes in patients with HK was 13.1 ± 2.1% (Fig. 3), which was 1.6-1.8 times higher than in controls (7.8 ± 1.5%), and this difference was significant ($p < 0.05$). Compared to controls, the percentage expression of ACh receptors on peripheral blood lymphocytes in patients with IAIU was 1.8-2.0 times higher (14.3 ± 2.4%), and this difference was significant ($p < 0.05$).

Our previous studies have shown a clear tendency toward higher expression of β-adrenergic receptors and ACh receptors on peripheral blood lymphocytes in the period of active inflammation, and toward lower expression of these receptors in the period of remission [20, 21]. Of note that the expression of β-adrenergic receptors and ACh receptors on peripheral blood lymphocytes was higher, whereas the expression of KOR on peripheral blood lymphocytes was lower in patients with IAIU than in patients with HK.

Because lymphocytes express β adrenergic receptors and KOR, the ratio of expression of these receptors may have an impact on the nature of immune response. Since changes in immune response regulation may, in turn, result in the development of immunopathological responses, we assessed the ratio of expression of β adrenergic receptors and KOR. We found that the ratio of expression of β adrenergic receptors and KOR was 0.93 ± 0.03% for patients with HK (Fig. 4), 0.97 ± 0.04% for patients with IAIU (Fig. 4), and 0.7 ± 0.04% for controls, with a significant difference between the any pair of groups ($p < 0.05$).

Discussion

Major advances in twentieth-century neuroscience and immunology revealed that neuronal circuits maintain homeostasis during immune responses. Homeostatic control of immune responses by neural reflex circuits occurs in a time frame that operates extremely fast relative to humoral and cell-trafficking mechanisms. The role of neural control and neurotransmitters in the development of immune

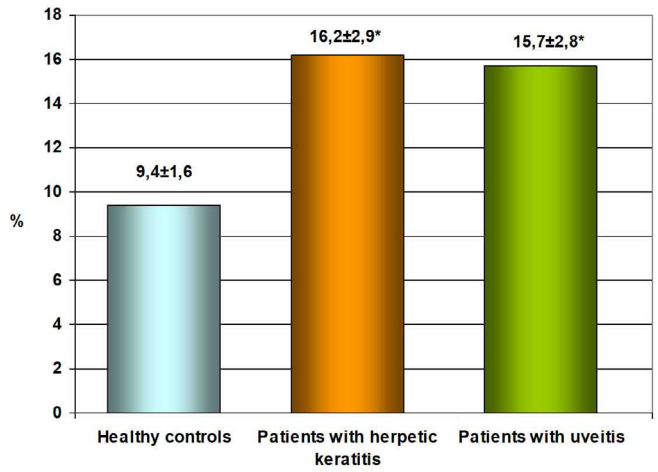

Fig. 1. Expression of kappa opioid receptors on peripheral blood T cells in healthy controls, patients with herpetic keratitis and patients with idiopathic anterior and/or intermediate uveitis (IAIU), expressed in percentages, mean ± standard deviation

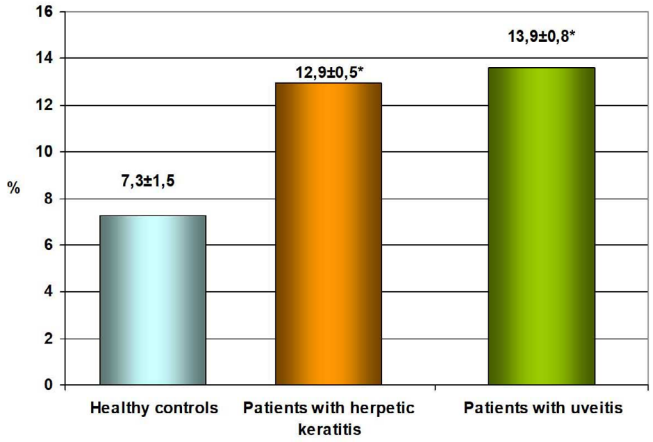

Fig. 2. Expression of adrenergic receptors on peripheral blood T cells in healthy controls, patients with herpetic keratitis and patients with idiopathic anterior and/or intermediate uveitis (IAIU), expressed in percentages, mean ± standard deviation

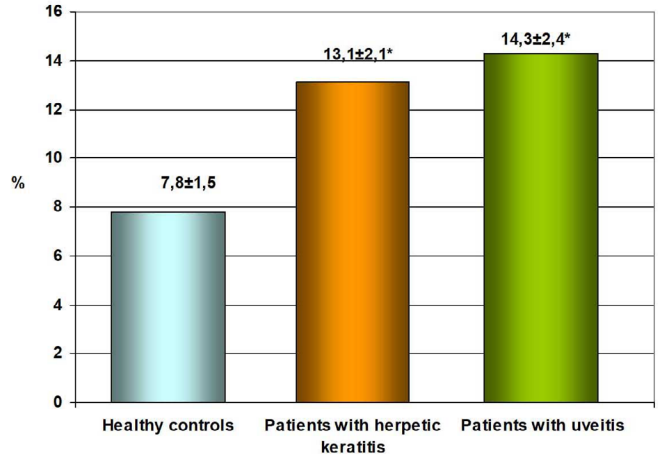

Fig. 3. Expression of acetylcholine receptors on peripheral blood T cells in healthy controls, patients with herpetic keratitis and patients with idiopathic anterior and/or intermediate uveitis (IAIU), expressed in percentages, mean ± standard deviation

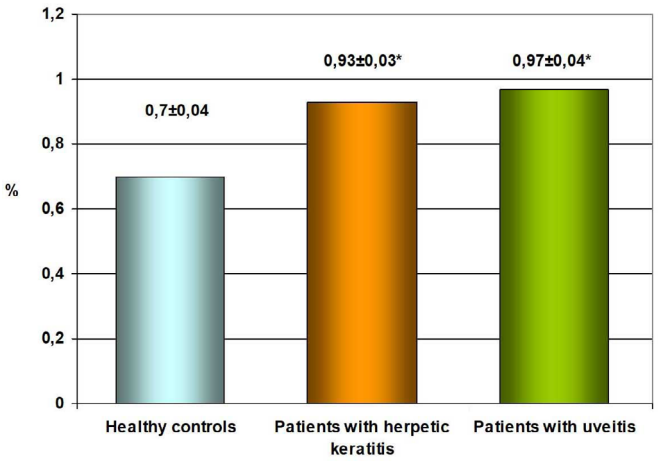

Fig. 4. Ratio of expression of adrenergic receptors to opioid receptors on peripheral blood T cells in healthy controls, patients with herpetic keratitis and patients with idiopathic anterior and/or intermediate uveitis (IAIU), expressed in percentages, mean ± standard deviation

response in eye disease has been poorly studied. Interactions between the immune system and the nervous system are vital for controlling inflammation. The inflammatory reflex is a centrally integrated physiological mechanism in which afferent vagus nerve signalling, activated by cytokines or pathogen-derived products, is functionally associated with efferent vagus nerve-mediated output to regulate proinflammatory cytokine production and inflammation. Efferent vagus nerve endings might directly regulate the immune function by releasing acetylcholine, without the requirement for either signalling along the splenic nerve or T cells. The absence of this inflammatory reflex—resulting from neural lesions or genetic ablation of essential components—results in excessive innate immune responses and cytokine toxicity [22].

Primary and secondary lymphoid organs are innervated by adrenergic sympathetic endings of the autonomic nervous system; however, cholinergic parasympathetic innervation of primary and secondary lymphoid organs remains controversial. During active inflammation, pro-inflammatory cytokines increase SNS activity [1]. We have previously found an association between the type of recurrence of herpetic keratitis and an increased tone of the sympathetic nervous system in inflammation [20].

In the current study, the expression of KOR on peripheral blood lymphocytes was higher in patients with HK than in patients with IAIU. In addition, the expression of β-adrenergic receptors and ACh receptors on peripheral blood lymphocytes was higher in patients with IAIU than in patients with HK. We have previously investigated the expression of adrenergic receptors and ACh receptors on peripheral blood lymphocytes in patients with anterior uveitis complicated by macular edema. We found that, in the period of recurrence, the expression of adrenergic receptors and ACh receptors on peripheral blood lymphocytes in the above patients was 32.7% and 25.2%, higher than in patients with uncomplicated uveitis [16].

Other researchers demonstrated that the opioidergic system of immunocytes is largely inducible, and its activity increases under conditions of inflammation. Activation of the transcription factor Nuclear Factor kappa B (NF-κB) induces the expression of opioid receptors, whereas the stimulation of immune cells of various types by proinflammatory cytokines (interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6 and interferon (IFN)-γ) induces not only the expression of opioid receptors in immunocytes, but also the secretion of opioid peptides by immunocytes. Consequently, it may be stated that the opioidergic system of immunocytes is activated in inflammation [23, 24]. Given the key role of the canonical pathway of NF-κB activation in cytokine expression realized when activating a variety of receptors, suppression of this pathway using opioid peptides provides a new pharmacological approach to solving the "cytokine storm" problem [25, 26]. Activation of opioid receptors by an exogenous agonist (opioid preconditioning) has been shown to elicit a protective effect during situations of stress produced by hypoxia, ischemia, cold; it was demonstrated that opioid receptors play a key role in the mechanisms of this protection [27].

We believe that, given the functional role of the opioidergic system of immunocytes in the modulation of immune response, this system may become a promising pharmacological target in a wide range of chronic inflammatory ocular diseases mediated by the activation of the NF-κB pathway [15]. Opioid receptors exert a regulatory function in inflammatory processes. Studies assessing the ratio of expression of β-adrenergic receptors to KAR are believed to be important because the development of an imbalance between expressions of these two types of receptors results in impaired immune regulation, potentially leading to complicated inflammatory process. We found that the ratio of expression of β-adrenergic receptors to KAR was significantly higher both in patients with HK and patients with IAIU compared to healthy donors.

Studies by Husain and colleagues [28, 29] provided evidence for the presence of opioid receptors in the retina, optic nerve, and optic nerve head astrocytes. These receptors were measured by more than one technique including Western blotting, immunohistochemistry, and functional assays such as scotopic electroretinogram (ERG) and Pattern ERG. Husain and colleagues [28] also have provided evidence that opioid receptors, more specifically δ-opioid receptors, play crucial roles in retina neuroprotection against ischemic and glaucomatous injuries. Immunohistochemical and Western blot data demonstrated that the δ-, κ-, and μ-opioid receptor subtypes are expressed in the retina [29]. Husain and colleagues [29] demonstrated that opioid receptors activated by endogenous or exogenous

agonists can ameliorate ischemic retinal injury; this study was particularly important for ophthalmology. Their data provided evidence that activation of one (or more) opioid receptor(s) facilitates the development of ischemic preconditioning within the retina and can reduce ischemic retina injury [29].

In our study on assessing the expression of β adrenergic receptors, Ach receptors and KOR on lymphocytes, there was evidence of marked activation of these receptors, which indicated their involvement in inflammation during HK or IAIU. Our findings are in agreement with those by others emphasizing the important role played by these receptors in regulating the immune response in inflammation. Therefore, further research is warranted on the contribution of KOR to the mechanisms of immunoregulation of inflammatory processes.

Conclusion

First, expression of β adrenergic receptors, Ach receptors and KOR on lymphocytes was significantly increased in patients with HK and patients with IAIU compared to healthy controls. Second, there was a significant difference in the ratio of expression of β adrenergic receptors to KOR between patients with HK and healthy controls and between patients with IAIU and healthy controls.

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Disclosures

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Data Availability Statement: *All the data obtained or analyzed during this study are reported in the article.*

Abbreviations: *CNS, central nervous system; GABA, gamma-aminobutyric acid; HK, herpetic keratitis; IFN, interferon; IL, interleukin; KOR, kappa opioid receptors; McAbs, monoclonal antibodies; OR, opioid receptors; SNS, sympathetic nervous system; TNF, tumor necrosis factor.*