

THE INHIBITORY EFFECT OF MOMETASONE AND NORTRIPTYLINE ON THE PRODUCTION OF PROINFLAMMATORY CYTOKINES BY BLOOD MONONUCLEAR CELLS OF PATIENTS WITH ALLERGIC RHINITIS UNDER CONDITIONS OF STIMULATED IMMUNE RESPONSE

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Allergic rhinitis (AR) is a chronic inflammatory disease of the nasal mucosa; it develops when the immune system reacts to an allergen. Side effects of topical glucocorticosteroids (GCS) used for AR treatment, the development of steroid resistance in patients and the continuing increase in morbidity explain the clear need to search for new approaches for AR treatment. The tricyclic antidepressant nortriptyline has demonstrated anti-inflammatory properties in a number of experimental studies, as well as its ability to complement the action of corticosteroids. The aim of this study was to compare the effects of nortriptyline and the synthetic GCS mometasone on the culture of mononuclear cells (MNC) of AR patients. Blood MNCs from six AR patients were cultured in the presence of nortriptyline or mometasone, and then type 1, type 2, or type 17 immune response (IR) were stimulated by adding recombinant activator proteins (IL-2, IL-25, IL-33, TSLP, IL-12, IL-1 β , IL-23). After 3 days, concentrations of proinflammatory cytokines TNF- α , IFN- γ , IL-6, IL-8, and IL-4 were determined in cell supernatants by enzyme immunoassay. Mometasone final concentration 10⁻⁸ M effectively suppressed the secretion of proinflammatory cytokines TNF- α , IFN- γ , IL-6, and IL-8 under conditions of stimulation of IR of all types. A similar decrease in secretion, although less pronounced, occurred when stimulated cells were cultured in the presence of nortriptyline. The concentration of TNF- α in the culture medium decreased under these conditions both with stimulation of type 1, type 2, and type 17 IR. The level of IFN- γ secretion decreased only in the case of type 1 and type 17 IR as compared to MNCs with the stimulated IR, which were cultured without this inhibitor. The level of IL-6 secretion decreased only in the culture medium of cells with stimulated type 1 and type 2 IR and IL-8 secretion decreased only under conditions of stimulated type 1 IR. This study has shown that mometasone and nortriptyline are able to suppress the secretion of proinflammatory cytokines by blood cells; their effect is selective and depends on the IR type.

Keywords: cytokines; secretion; blood cells; allergic rhinitis (AR)

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INTRODUCTION

Allergic rhinitis (AR) is a chronic inflammatory disease of the nasal mucosa; AR develops when the immune system reacts to an allergen. The disease is mediated by immunoglobulin E (IgE) and is manifested by nasal congestion, rhinorrhea, sneezing, and other symptoms that significantly reduce the quality of life of patients. Common allergens associated with AR include house dust mites, plant pollen, animal dander and hair, mold, etc. [1].

According to the classical viewpoint, the leading role in the mechanism, responsible for the development of allergic inflammation, belongs to Th2 cells and their cytokines. Interleukin-4 (IL-4) is a key Th2 cytokine, involved in the regulation of antibody production during an expanded B-cell response. IL-6 is produced by monocytes, macrophages, fibroblasts, and endothelial cells and belongs to the Th2 profile [1, 2].

This concept is currently reconsidered, since in some cases, the action on the components

of the type 2 immune response (IR) does not eliminate allergic symptoms. At the same time, there is experimental evidence suggesting the involvement of Th1 and Th17 lymphocyte populations, producing cytokines participating in type 1 and type 17 IR, in the development of allergic diseases of the respiratory tract, such as bronchial asthma (BA) and AR [2].

Type 1 IR is characterized by the dominance of Th1 cells and their mediators: interferon γ (IFN- γ), tumor necrosis factor α (TNF- α), IL-2, etc. IFN- γ is involved in almost all IR stages and inflammation, in particular in the differentiation of Th1 and B cells, activation of cytotoxic CD8⁺ T cells, NK cells, macrophages, and neutrophils [2]. TNF- α is able to regulate many immune processes, mediate apoptosis, increase the production of other cytokines and chemokines [3].

Type 17 IR involving Th17 is aimed at maintaining inflammation due to production of cytokines of the IL-17 family. Chemokines of the CXC family



are involved in the development of type 17 IR. CXCL8 (IL-8) is the main cytokine involved in attracting neutrophils to the lesion site or infection. IL-8 also stimulates phagocytosis and angiogenesis [3, 4].

Effective treatment of AR includes the use of pathogenetically targeted drug therapy. In particular, many years of clinical experience demonstrated high efficacy and safety of nasal glucocorticosteroids (GCS), such as mometasone, in the treatment of seasonal and perennial AR. Acting at the glucocorticosteroid receptor (GR), mometasone promotes the expression of a number of anti-inflammatory genes, suppressing the synthesis of inflammatory mediators. This leads to a decrease in the content of mast cells, basophils, and eosinophils in the area of allergic inflammation, as well as to the suppression of increased vascular permeability and mucus secretion [4]. However, topical administration of GCS can cause side effects such as irritation of the nasal mucosa, burning in the nose, nosebleeds, and mucosal candidiasis [5]. Some AR patients are poorly susceptible to this type of therapy due to the development of steroid resistance [6, 7].

The continuing increase in the incidence of AR stimulates the search for new approaches to the treatment of this disease and a more in-depth study of the mechanisms of the inflammatory process in AR. There is a clear need for agents that increase sensitivity to GCS, as well as those with antioxidant properties, since the formation of free radicals is one of the factors in the AR development [8].

Nortriptyline is a tricyclic antidepressant and the main active metabolite of another tricyclic antidepressant, amitriptyline, which belongs to the group of norepinephrine and serotonin reuptake inhibitors. This drug is used to treat depression, anxiety, and nicotine addiction [9, 10]. It has demonstrated anti-inflammatory properties, as well as the ability to complement the action of corticosteroids [11–13]. Nortriptyline suppressed production of IL-4, IL-8, TNF- α , and IFN- γ in blood cells belonging to natural killers (NK) in patients with chronic obstructive pulmonary disease (COPD) [14]. The effect of nortriptyline is associated with the increase in histone deacetylase 2 (HDA2) expression, which in turn leads to inhibition of transcription of genes encoding proinflammatory proteins [12]. The combined use of corticosteroids and nortriptyline decreases intracellular signaling via p38 MAPK and, as a result, suppresses the production of proinflammatory proteins [12]. However, p38 MAPK also impairs GR functioning due to Ser226 phosphorylation, which slows down GR binding to the hormone and subsequent translocation to the nucleus [14, 15]. As a result, GR loses its ability to inhibit transcription of genes encoding proinflammatory proteins.

We have not found studies involving the use of nortriptyline in AR patients. The aim of our study

was to compare the effects nortriptyline and mometasone on the culture of mononuclear cells (MNC) of AR patients.

MATERIALS AND METHODS

Six AR patients (2 men and 4 women, 19–22 years old) were included in the study. Cell cultures were prepared using venous blood (30 ml), which was collected from the patients from the cubital vein in the morning on an empty stomach. Blood samples were collected into test tubes containing 10 U/ml sodium heparin (Belmedpreparaty, Belarus) as an anticoagulant. MNC were isolated from the blood samples by centrifugation (30 min, 400 g) in a density gradient of 1.077 using Lymphosep solution (Biowest, France). Cells were resuspended at a concentration of 10^6 cells/ml in RPMI 1640 culture medium (Capricorn Scientific, Germany) with 10% (v/v) fetal bovine serum (Capricorn Scientific), 2 mM glutamine, 100 U/ml penicillin and 100 μ g/ml streptomycin (Capricorn Scientific).

Cells (2×10^5) were placed in the wells of a 96-well plate and cultured in the presence of mometasone (10^{-8} M) or nortriptyline (5 μ M). Type 1, type 2, and type 17 IR were stimulated 1 h after administration of inhibitors by adding recombinant proteins to the culture medium (thymic stromal lymphopoietin (TSLP), IL-12, IL-23 produced by Prospec Bio (Israel); IL-1 β , IL-2, IL-25, IL-33 produced by Biolegend (USA); IL-12 (5 ng/ml) and IL-2 (20 U/ml) (for stimulation of type 1 IR), IL-25 (50 ng/ml), IL-33 (50 ng/ml), TSLP (50 ng/ml), and IL-2 (20 U/ml) (for stimulation of type 2 IR), IL-1 β (50 ng/ml) and IL-23 (50 ng/ml) (for stimulation of type 17 IR)). After 3 days of cell culturing, the supernatants were collected using an automatic dispenser, centrifuged (5 min, 400 g) and stored at -70°C until use. The concentrations of IL-4, IL-6, IL-8, TNF- α , and IFN- γ were determined by the enzyme immunoassay method using the Vector Best reagent kits (Russia).

Statistical data processing was performed in the MedCalc program (MedCalc Software Ltd, Belgium) using nonparametric statistical methods (Kruskal-Wallis test). Differences were considered statistically significant at $p < 0.05$.

RESULTS

In the experiment with MNCs, cultivated in the presence of mometasone, stimulation of type 1 IR was accompanied by a statistically significant decrease in the concentration of TNF- α , IFN- γ , IL-6, IL-8, in the culture medium. In the case of MNCs, cultivated in the presence of nortriptyline, stimulation of type 1 IR was also accompanied by a decrease in the concentration of TNF- α , IFN- γ , IL-6, and IL-8 in the culture medium.

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The most pronounced decrease was in the level of TNF- α (by 65.5%, median 10.2 pg/ml), and the least pronounced decrease was detected in the level of IFN- γ (by 43.0%, median 95.4 pg/ml) (Fig. 1). The concentration of IL-4 in the cell culture medium in both cases only tended to decrease.

Under conditions of type 2 IR stimulation mometasone caused statistically significant reduction in the levels of TNF- α , IFN- γ , IL-6, IL-8, and IL-4 in the MNC culture medium. The decrease

in the IL-4 level was less pronounced compared to other cytokines. Under the same conditions, nortriptyline significantly reduced the concentration of only TNF- α (by 35.0%, median 29.9 pg/ml) and IL-6 (by 45.0%, median 125.7 pg/ml) (Fig. 2).

Type 17 IR stimulation in MNCs treated with mometasone was accompanied by a significant decrease of TNF- α , IFN- γ , IL-6, and IL-8 concentrations in the cell culture medium. The decrease in the IL-6 level was most pronounced (by 93.9%, median 535.0 pg/ml),

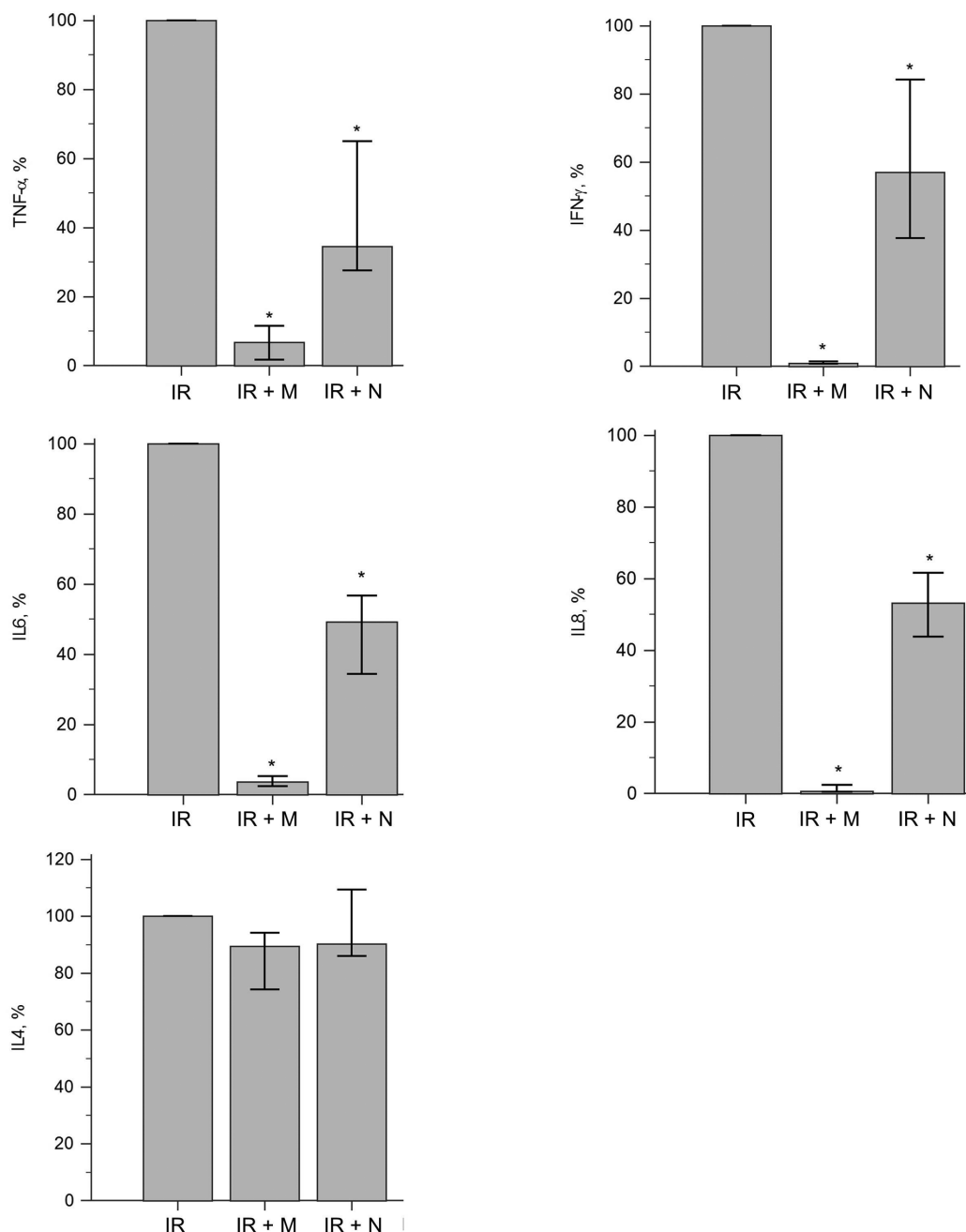


Figure 1. The effect of mometasone and nortriptyline on the secretion of TNF- α , IFN- γ , IL-6, IL-8, and IL-4 by peripheral blood MNCs under conditions of type 1 IR stimulation. Here, as well as in Figures 2 and 3, the results are expressed as % of the cytokine concentration in samples with stimulated IR without the addition of mometasone or nortriptyline and are presented as the median \pm interquartile range; IR – blood MNCs were stimulated with a complex (IL-25+, IL-33+, TSLP+), IR+M – stimulated MNCs were cultured in the presence of mometasone (10^{-8} M), IR+N – stimulated MNCs were cultured in the presence of nortriptyline (5 μ M); * – the difference is significant versus IR ($p < 0.05$).

while the IL-4 level showed only a slight tendency to decrease. The presence of nortriptyline in the culture medium was accompanied by a statistically significant decrease of TNF- α (by 27.2%, median 53.8 pg/ml) and IFN- γ (by 34.0%, median 65.7 pg/ml) concentrations in the culture medium (Fig. 3).

DISCUSSION

Mometasone is a GCS for inhalation and intranasal use. The mechanism of its antiallergic and anti-inflammatory action is associated with its ability

to inhibit the release of inflammatory mediators [16]. The results of our study showed that mometasone in the culture of blood mononuclear cells from AR patients actually reduced the concentration of secreted proinflammatory cytokines. Similar data were previously obtained by other authors on cultures of nasal epithelial cells [17].

In experiments on cells with type 2 IR stimulation the effect of mometasone was more pronounced than in experiments with type 1 and type 17 IR stimulation. The weakest effect of mometasone on cytokine secretion was observed under conditions of type 17 IR

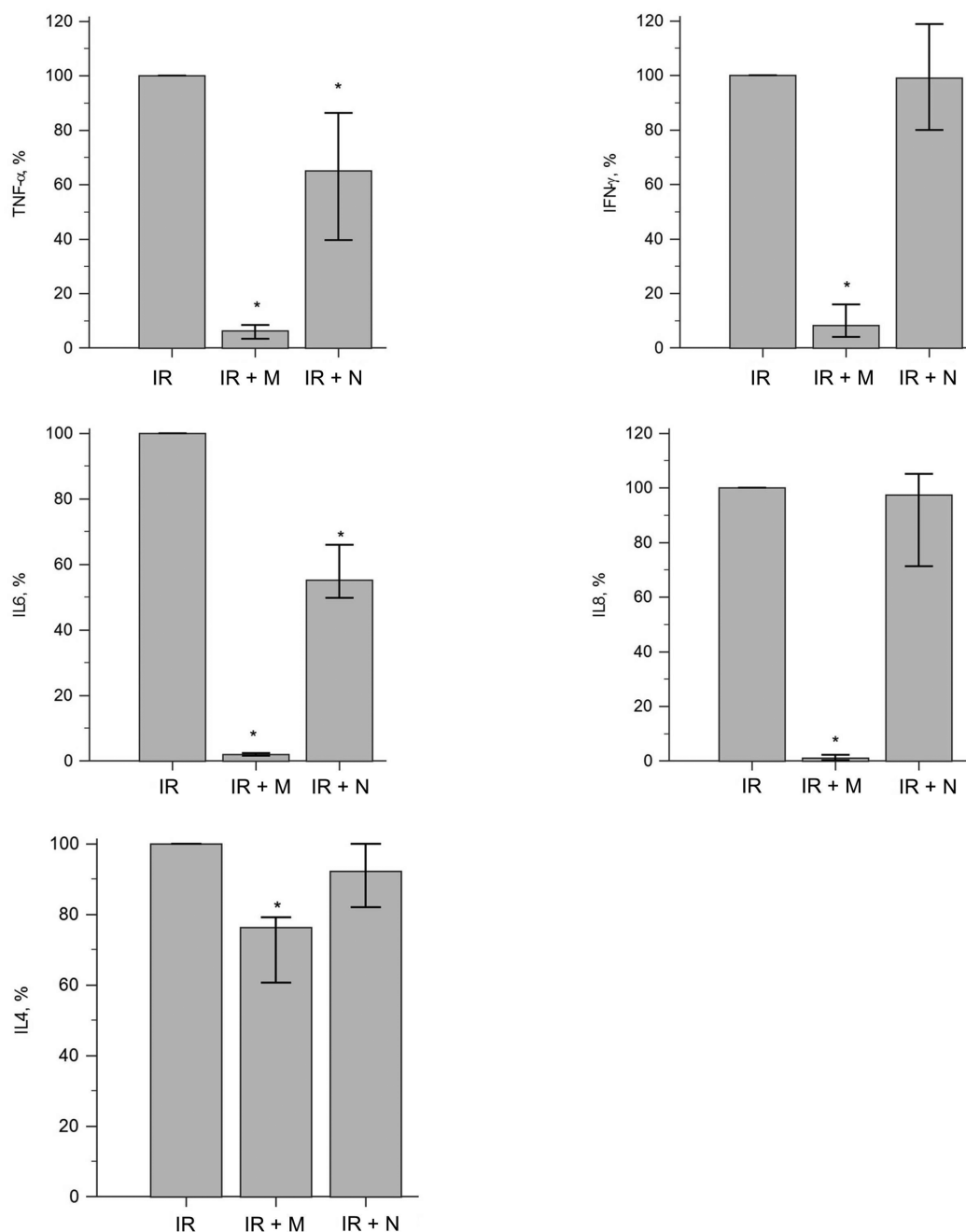


Figure 2. The effect of mometasone and nortriptyline on the secretion of TNF- α , IFN- γ , IL-6, IL-8, and IL-4 by peripheral blood MNCs under conditions of type 2 IR stimulation. IR – blood MNCs were stimulated with a complex (IL-2+, IL-12+), IR+M – stimulated MNCs were cultured in the presence of mometasone, IR+N – stimulated MNCs were cultured in the presence of nortriptyline; * – the difference is statistically significant versus IR ($p < 0.05$).

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stimulation. Cytokines involved in type 17 IR are associated with the development of steroid resistance in BA [18]. It has been shown that the use of corticosteroids is not effective enough in cases where inflammation is maintained by activating type 17 IR components, which activate neutrophils [19].

Neutrophils produce biologically active compounds that mediate airway inflammation. These include matrix metalloproteinase-9 (MMP-9), neutrophil elastase, α -defensin, transforming growth factor β 1 (TGF- β 1), and reactive oxygen species (ROS).

They support eosinophil migration and participate in the first contact of antigen-specific T cell precursors with an antigen (T cell priming) [20]. Long-term release of neutrophil elastase and free radicals damages the epithelium and is most likely responsible for the vasomotor symptoms characteristic of AR. In addition, changes in ROS generation by blood neutrophils can induce an imbalance of oxidants and antioxidants, which also leads to tissue damage [21].

The presence of nortriptyline in the culture medium of stimulated MNCs was also accompanied by a decrease in the secretion of TNF- α , IFN- γ , IL-6,

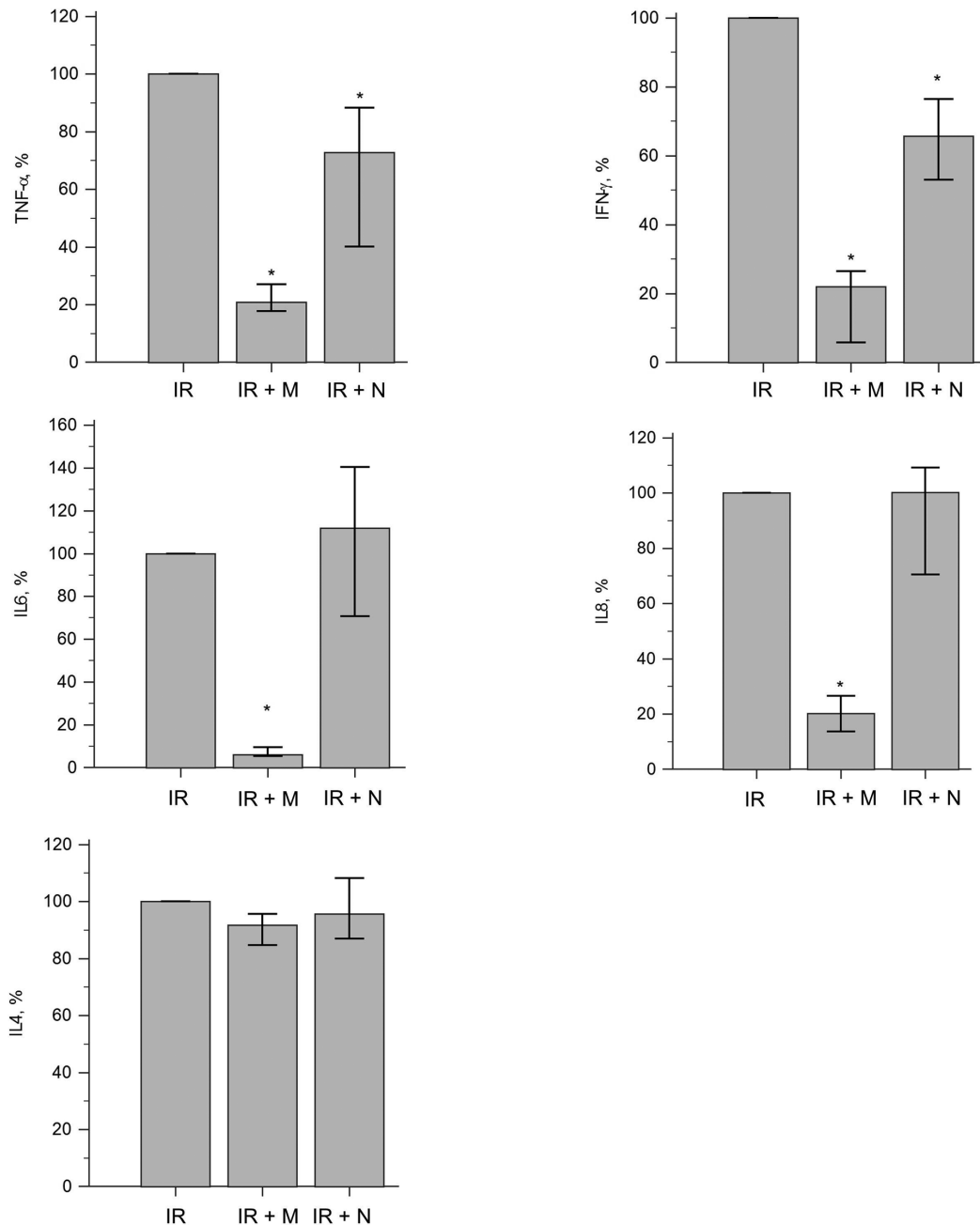


Figure 3. The effect of mometasone and nortriptyline on the secretion of TNF- α , IFN- γ , IL-6, IL-8, and IL-4 by peripheral blood MNCs under conditions of type 17 IR stimulation. IR – blood MNCs were stimulated with a complex (IL-1 β +, IL-23+), IR+M – stimulated MNCs were cultured in the presence of mometasone, IR+N – stimulated MNCs were cultured in the presence of nortriptyline; * – the difference is statistically significant versus IR ($p < 0.05$).

and IL-8 cytokines as compared to cells cultured without nortriptyline. This phenomenon was observed under conditions of type 1, type 2, and type 17 IR. The decrease in the level of secreted TNF- α , IFN- γ , IL-6, and IL-8 was the most pronounced in the case of type 1 IR stimulation.

Proinflammatory cytokines IFN- γ and TNF- α are known to contribute to the exacerbation of allergic diseases due to stimulation of the production of CXC family chemokines and other proinflammatory cytokines. They, in turn, activate neutrophils and eosinophils [22]. Similar results were obtained during examination of COPD. The addition of nortriptyline to the culture medium of MNCs isolated from the peripheral blood of such patients led to a decrease in the components of the type 1 IR [15].

Like mometasone, nortriptyline was less effective in suppressing the secretion of cytokines under conditions of type 17 IR stimulation, although the concentrations of TNF- α and IFN- γ were significantly lower than in experiments where the cells were cultured without nortriptyline. IL-17 family of cytokines, secreted by Th17, activate a wide range of effector cells involved in maintaining inflammation. For example, IL-17A and IL-17F stimulate synthesis of proinflammatory cytokines (TNF- α , IL-1 β , IL-6) and chemokines (CXCL1, IL-8) in airway epithelial cells, which recruit and activate neutrophils [22]. Similar mechanisms are likely to determine the involvement of type 17 IR components in the development of allergic airway inflammation.

CONCLUSIONS

Thus, mometasone and nortriptyline exhibit a pronounced ability to reduce the level of allergic inflammation participants secreted by stimulated MNCs. Mometasone has a much more pronounced ability for such inhibition compared to nortriptyline. The achieved effect of the mometasone in suppressing all types of IR does not raise doubts about the selected concentration. However, the difference obtained with nortriptyline suggests that the addition of mometasone to the culture medium may not adequately reflect its concentration in the body.

In order to bring the conditions of the *in vitro* experimental study in cell culture closer to the *in vivo* state, the dose-dependent effects of mometasone *in vitro* have been studied in a wide range of concentrations from 10^{-11} M to 10^{-5} M [17, 23]. In this work, we used the final mometasone concentration of 10^{-8} M. Since mometasone is a topical GCS and is used for local application in the nasal cavity, its concentration in blood plasma is 20–50 pg/ml (corresponding to 10^{-10} M) [16]. This is two orders of magnitude less than the concentration of the glucocorticoid used in our study. In the future, we plan to compare the effect of mometasone on a culture with a lower

concentration, thus expecting a less pronounced effect on the concentration of secreted cytokines in order to bring it closer to the real values in the body of AR patients.

Based on the obtained results, the following conclusions can be drawn:

1. Mometasone at a final concentration of 10^{-8} M effectively suppresses the secretion of proinflammatory cytokines TNF- α , IFN- γ , IL-6, and IL-8 caused by stimulation of type 1, type 2, and type 17 IR.
2. The presence of nortriptyline in the MNC culture medium under conditions of type 1, type 2, and type 17 IR activation reduced TNF- α secretion, in the case of type 1 and type 2 IR nortriptyline reduced IL-6 secretion. Type 1 and type 17 IR stimulation in MNCs treated nortriptyline was accompanied by a decrease in IFN- γ , and in the nortriptyline-treated cells with type 1 IR stimulation the IL-8 secretion decreased.
3. The inhibitory effect 10^{-8} M mometasone on secretion of proinflammatory cytokines was significantly higher than the inhibitory effect of nortriptyline.

FUNDING

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COMPLIANCE WITH ETHICAL STANDARDS

The study was approved by the Biomedical Ethics Committee of the Belarusian State Medical University (Protocol No. 1 dated 31 August 2023). All subjects signed informed consent to participate in the study and the use of their biomaterial.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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**ИНГИБИРУЮЩЕЕ ВЛИЯНИЕ МОМЕТАЗОНА И НОРТРИПТИЛИНА НА ПРОДУКЦИЮ
ПРОВОСПАЛИТЕЛЬНЫХ ЦИТОКИНОВ МОНОНУКЛЕАРНЫМИ КЛЕТКАМИ КРОВИ
ПАЦИЕНТОВ С АЛЛЕРГИЧЕСКИМ РИНИТОМ В УСЛОВИЯХ
СТИМУЛИРОВАННОГО ИММУННОГО ОТВЕТА**

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Аллергический ринит (АР) — это хроническое воспалительное заболевание слизистой оболочки носа, возникающее как иммунный ответ при контакте с аллергеном. Побочные эффекты топических глюкокортикостероидов (ГКС), применяемых при лечении АР, развитие стероидорезистентности у пациентов и продолжающийся рост заболеваемости обосновывают необходимость поиска новых подходов к лечению АР. Трициклический антидепрессант нортриптилин продемонстрировал в ряде экспериментальных исследований противовоспалительные свойства, а также способность дополнять действие кортикостероидов. Целью данной работы было изучить влияние синтетического ГКС мометазона на культуру мононуклеарных клеток (МНК) пациентов с АР, сопоставив эффект с влиянием нортриптилина. МНК крови шести пациентов с АР культивировали в присутствии нортриптилина или мометазона, после чего в них стимулировали иммунный ответ (ИО) по первому, второму или семнадцатому типу путём внесения рекомбинантных белков-активаторов (IL-2, IL-25, IL-33, TSLP, IL-12, IL-1 β , IL-23). По истечении 3 дней в супернатантах методом иммуноферментного анализа определяли концентрацию провоспалительных цитокинов TNF- α , IFN- γ , IL-6, IL-8 и IL-4. Мометазон в конечной концентрации 10⁻⁸ М эффективно подавлял секрецию провоспалительных цитокинов TNF- α , IFN- γ , IL-6 и IL-8 в условиях стимуляции ИО всех типов. Аналогичное снижение секреции, хотя и менее выраженное, имело место, когда стимулированные клетки культивировались в присутствии нортриптилина. Концентрация TNF- α в среде культивирования снижалась в этих условиях как при стимуляции ИО первого, так и второго, семнадцатого типов. Уровень секреции IFN- γ уменьшался только при ИО первого и семнадцатого типов по сравнению с МНК со стимулированным ИО, которые культивировали без этого ингибитора. Уровень секреции IL-6 уменьшался только в среде культивирования клеток со стимулированным ИО первого и второго типов, а IL-8 — только в условиях стимулированного ИО первого типа. Проведённое исследование демонстрирует выраженную способность мометазона и нортриптилина подавлять секрецию провоспалительных цитокинов клетками крови, которая носит избирательный характер и зависит от типа иммунного ответа.

Полный текст статьи на русском языке доступен на сайте журнала (<http://pbmc.ibmc.msk.ru>).

Ключевые слова: цитокины; секреция; клетки крови; аллергический ринит (АР)

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