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SHORT COMMUNICATION

THE EFFECT OF NORTRIPTYLINE AND ITS COMBINATION WITH MOMETASONE ON SECRETION OF IL-6 AND IL-8 BY STIMULATED BLOOD MONONUCLEAR CELLS *IN VITRO*

T.V. Mironova[1]*, A.D. Taganovich[1], V.V. Makarevich[1], T.S. Kolesnikova[2], O.V. Levandovskaya[3], I.P. Shilovsky[4], M.R. Khaitov[4], A.G. Kadushkin[1]

[1]Department of Biochemistry, Belarusian State Medical University,
83 Dzerzhinski ave., Minsk, 220083 Republic of Belarus; *e-mail: tomanis@mail.ru
[2]Research Institute of Experimental and Clinical Medicine, Belarusian State Medical University,
106-2 Lesnoy, Borovlyansky rural council, Minsk district, Minsk region, 223040 Republic of Belarus
[3]Minsk Scientific and Practical Center for Surgery, Transplantology and Hematology,
83 Semashko str., Minsk, 220045 Republic of Belarus
[4]Institute of Immunology, 24 Kashirskoe shosse, Moscow, 115522 Russia

Glucocorticosteroids (GCS) are often the medication of choice for chronic inflammation. Since not all patients are equally sensitive to GCS, certain efforts are undertaken to increase sensitivity and complement glucocorticosteroid therapy with other nonsteroidal medications that can enhance the anti-inflammatory effect of GCS. The tricyclic antidepressant nortriptyline has demonstrated anti-inflammatory properties in several experimental studies, as well as the ability to complement the action of GCS. The aim of this study was to investigate the effects of nortriptyline, as well as its combination with mometasone, on blood mononuclear cells (MNCs) under conditions of stimulated immune responses (IR) of types 1, 2, and 17. In isolated MNCs from six healthy donors, IR type I, type 2, or type 17 were stimulated in the presence of nortriptyline, mometasone, or their combination by adding recombinant activator proteins (IL-2, IL-25, IL-33, thymic stromal lymphopoietin (TSLP), IL-12, IL-1β, IL-23). After three days, the concentration of IL-6 and IL-8 was determined in the supernatants by enzyme-linked immunosorbent assay. In the presence of nortriptyline at a final concentration of 10^{-5} M, IR type 2 and type 17 were accompanied by a decrease in IL-6 concentration. Addition of a combination of mometasone and nortriptyline to the MNC culture medium under conditions of IR type II activation had a potentiating effect. This was evidenced by a decrease in IL-6 and IL-8 secretion compared to the use of mometasone alone. The study demonstrates the ability of nortriptyline to suppress the secretion of proinflammatory cytokines by blood cells, which is selective and dependent on the type of immune response.

Keywords: IL-6; IL-8; blood cells; immune response

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INTRODUCTION

The immune response (IR) is a complex, multicomponent process induced by the entry of a foreign molecule (antigen) into the body and aimed at its elimination.

The main function of the type 1 IR is to combat viruses, bacteria, and oncogenic cells. During the type 1 IR, Th1 cells (T helper 1 cells) are activated, releasing proinflammatory cytokines characteristic of these cells. Subsequently, Th1 cells activate cytotoxic T lymphocytes and natural killer (NK) cells, proliferation of T and B lymphocytes, and synthesis of IgM and IgG2 [1].

The development of the type 2 IR requires activation of Th2 cells, which are responsible for cooperation with B cells, activating the humoral immune response, and allergic inflammation. Th2 cells can also provide immunity against extracellular bacteria and their toxins by stimulating the production of IgG4 and IgA by plasma cells [1].

The Th17-type IR is aimed at maintaining inflammation through the production of IL-17 family cytokines, which act on a number of effector cells: T and B lymphocytes, neutrophils, eosinophils, fibroblasts, endothelial and epithelial cells, macrophages, etc. [2].

The development of the inflammatory reaction is often accompanied by a gradual involvement of components of these IRs [1]. The IRs of types 1, 2, and 17 function in an interconnected manner and Th cells of each type are capable of producing components of different IRs. Moreover, cytokines that are components of the type 1, 2, and 17 IRs can exhibit both pro-inflammatory and anti-inflammatory properties, thus implying the existence of complex mechanisms of interactions between Th populations [3].

In the treatment of chronic inflammation, glucocorticosteroids (GCS), which can effectively reduce the secretion of pro-inflammatory cytokines, are often the medication of choice [4]. Since not all patients are equally sensitive to GCS, certain efforts are undertaken to increase their responsiveness to glucocorticoid therapy [5].

The tricyclic antidepressant nortriptyline has been shown to enhance the effectiveness of glucocorticosteroid therapy by suppressing the production of IL-4, IL-8, TNF-α, and IFN-γ by natural killer (NK) cells in the blood of patients with chronic obstructive pulmonary disease (COPD) [6]. We previously conducted a study that demonstrated the ability of nortriptyline to reduce the secretion of TNF-α, IFN-γ, IL-6, and IL-8 by mononuclear cells (MNCs) from patients with allergic rhinitis *in vitro* under conditions of stimulated IRs types 1, 2, and 17 [7]. The aim of this study was to investigate the effect of nortriptyline, as well as its combination with mometasone, on blood MNCs under conditions of stimulated IRs types 1, 2, and 17.

MATERIALS AND METHODS

Six healthy subjects (5 women and 1 man, 18–19 years old) were included in this study. Cell cultures were obtained using the method described in our previous report [7]. Resuspended cells were placed in wells of a 96-well plate (at a density of 2×10^5 cells per well) and incubated in the presence of mometasone (final concentration 10^{-10} M) [8], nortriptyline (final concentration 10^{-5} M) [9], or a combination of both for 1 h in a CO_2 incubator at 37°C, 5% CO_2. After incubation, recombinant proteins were added to the cell culture to stimulate IRs types 1, 2, and 17 according to the scheme described in the previous study [7]. After 3 days of cell cultivation, the solution collected from the dishes was centrifuged (5 minutes, 400 *g*) and stored at -70°C. IL-6 and IL-8 concentrations were determined using ELISA reagent kits (Vector Best, Russia).

Statistical data processing was performed using MedCalc (MedCalc Software Ltd., Belgium). Results are presented as median (25%–75%, quartile) values. The Friedman test was used to assess the statistical significance of differences between groups. Differences were considered statistically significant at $p < 0.008$; values of $0.008 < p < 0.1$ were considered a statistical trend.

RESULTS

In the experiment with stimulated type 1 IR, mometasone addition to the cell culture medium was accompanied by a statistically significant decrease in the concentration of IL-6 (0.250 [0.025–0.300] ng/ml) and IL-8 (9.13 [3.89–14.50] ng/ml) compared to cell samples without added inhibitor (1.15 [0.90–1.80] ng/ml IL-6; 61.20 [31.80–84.80] ng/ml IL-8). In turn, after the addition of nortriptyline, only a tendency toward a decrease in the secretion of IL-6 and IL-8 was noted. A combination of inhibitors did not lead to a significant decrease in cytokine secretion compared to the effect exerted by mometasone only (Fig. 1).

Under conditions of type 2 IR stimulation, mometasone caused a statistically significant decrease in the IL-6 (0.73 [0.35–1.15] ng/ml) and IL-8 (12.68 [5.74–44.08] ng/ml) levels as compared to samples without mometasone (2.03 [1.70–3.40] ng/ml IL-6; 54.7 [42.3–72.5] ng/ml IL-8). Under the same conditions, the addition of nortriptyline significantly reduced the IL-6 level (1.58 [1.05–2.00] ng/ml) compared to the control. A combination of mometasone and nortriptyline led to a significant decrease in the secretion of both IL-6 (0.40 [0.18–0.63] ng/ml) and IL-8 (10.19 [4.55–30.78] ng/ml) compared to samples addition of mometasone only (see above) (Fig. 2).

Under conditions of type 17 IR stimulation, the presence of mometasone in the cell culture medium was accompanied by a significant decrease in the concentrations of IL-6 (6.4 [5.2–11.4] ng/ml) and IL-8 (60.9 [44.5–92.5] ng/ml) compared to samples without added inhibitors (20.0 [14.7–27.5] ng/ml IL-6; 136.9 [124.9–171.0] ng/ml IL-8). The introduction of nortriptyline was accompanied by a statistically significant decrease, but only in the level of IL-6 (18.60 [13.75–25.70] ng/ml) compared to samples without inhibitors. The use of a combination of mometasone and nortriptyline, as in the case of stimulated type 1 IR, did not result in a decrease in the secretion of the studied interleukins compared to cell samples treated with mometasone alone (Fig. 3).

DISCUSSION

The presence of nortriptyline in the culture medium of MNCs stimulated with type 2 or type 17 IRs was accompanied by a statistically significant decrease (by 22% and 7%, respectively) in the secretion of the cytokine IL-6 compared to cells cultured

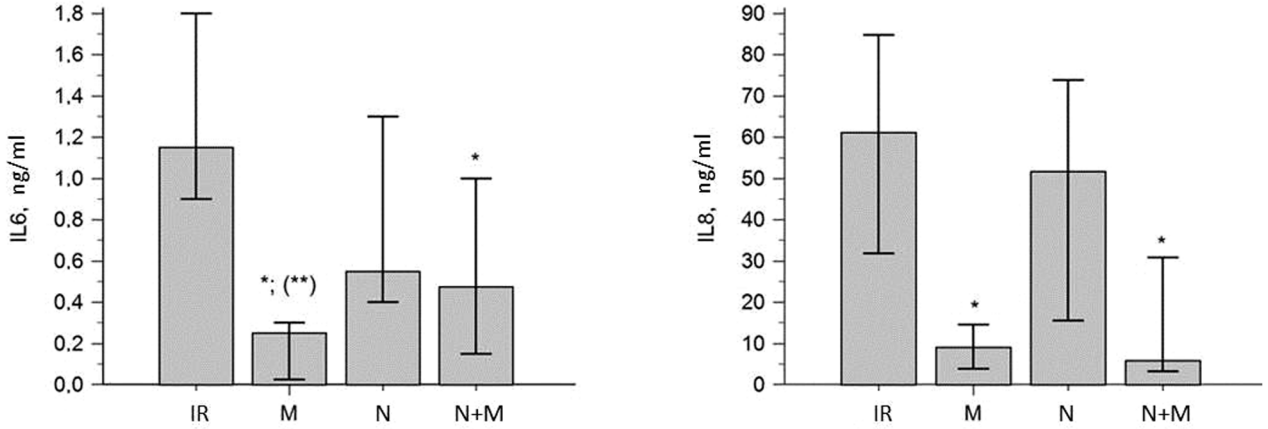

Figure 1. The effect of mometasone (M) and nortriptyline (N) on IL-6 and IL-8 secretion by peripheral blood MNCs under conditions of type 1 IR stimulation. IR: blood MNCs were stimulated with a complex (IL-2+, IL-12+), M: stimulated MNCs were cultured in the presence of mometasone (10^{-10} M), and N: stimulated MNCs were cultured in the presence of nortriptyline (10^{-5} M); * – statistically significant difference versus IR; (**) – statistically significant difference versus N.

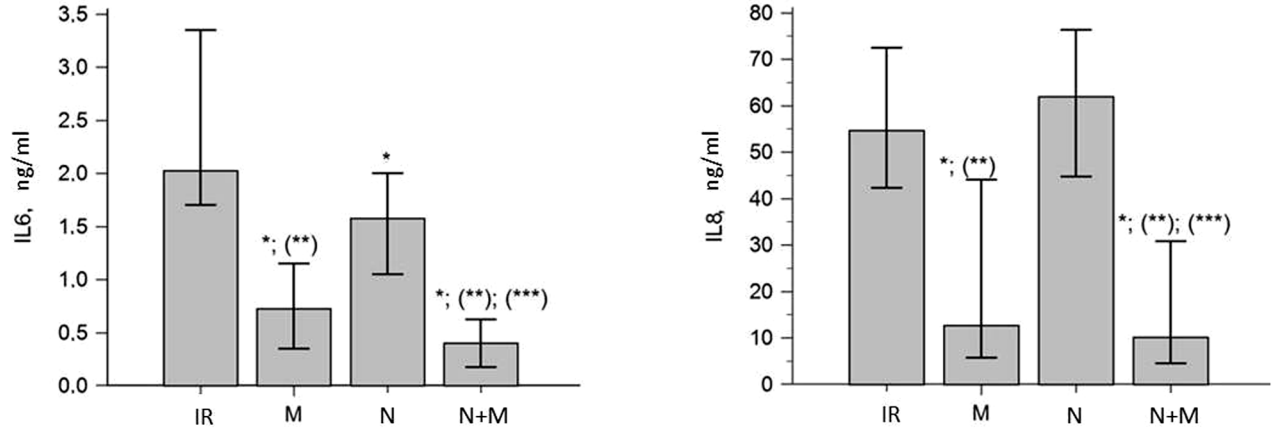

Figure 2. The effect of mometasone (M) and nortriptyline (N) on IL-6 and IL-8 secretion by peripheral blood MNCs under conditions of type 2 IR stimulation. IR: blood MNCs were stimulated with a complex (IL-25+, IL-33+, TSLP+), M: stimulated MNCs were cultured in the presence of mometasone (10^{-10} M), and N: stimulated MNCs were cultured in the presence of nortriptyline (10^{-5} M); * – statistically significant difference versus IR, (**) – statistically significant difference versus N, (***) – statistically significant difference versus M.

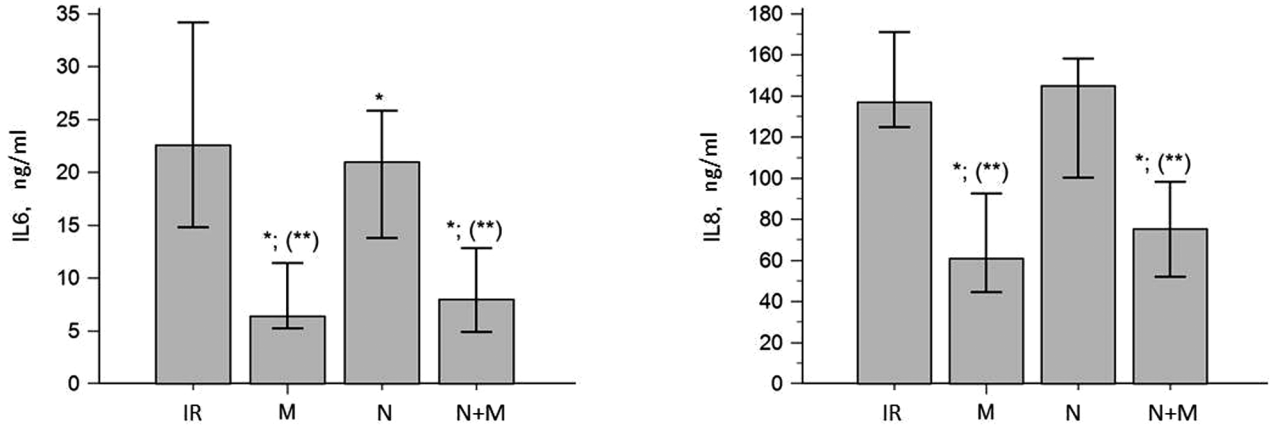

Figure 3. The effect of mometasone (M) and nortriptyline (N) on IL-6 and IL-8 secretion by peripheral blood MNCs under conditions of type 17 IR stimulation. IR: blood MNCs were stimulated with a complex (IL-1β+, IL-23+), M: stimulated MNCs were cultured in the presence of mometasone (10^{-10} M), and N: stimulated MNCs were cultured in the presence of nortriptyline (10^{-5} M); * – statistically significant difference versus IR, (**) – statistically significant difference versus N.

without nortriptyline. Under conditions of type 1 IR stimulation, the effect of nortriptyline was manifested only as a tendency when compared with the positive control. A similar effect was noted by other researchers and was associated, in their opinion, with the suppression of nuclear factor κB (NF-κB) activation induced by nortriptyline and similar drugs, which also decreased secretion of proinflammatory proteins, including IL-6 and IL-8 [10, 11]. However, in our study, IL-8 levels did not change significantly in any of the studied IR types as a result of adding nortriptyline to the cell culture medium; in the case of type 1 IR there was a statistical tendency for a decrease in the cytokine concentration.

Our study revealed an interesting, previously unknown phenomenon. Co-administration of mometasone and nortriptyline to the MNC incubation medium resulted in a significant reduction in the secretion of IL-6 (by 45%) and IL-8 (by 20%) under conditions of stimulated type 2 IR, compared to cell samples treated with mometasone. The potentiating effect of the nortriptyline/mometasone combination in reducing proinflammatory cytokine concentrations allows to recommend it for further study for use in the treatment of diseases associated with type 2 IR activation, such as allergic rhinitis.

CONCLUSIONS

1. The presence of nortriptyline at a final concentration of 10^{-5} M in the MNC culture medium reduced IL-6 secretion under conditions of activation of type 2 and type IRs.

2. The combination of mometasone and nortriptyline had a potentiating effect on the reduction of IL-6 and IL-8 secretion under conditions of type 2 IR activation.

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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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ВЛИЯНИЕ НОРТРИПТИЛИНА И ЕГО КОМБИНАЦИИ С МОМЕТАЗОНОМ НА СЕКРЕЦИЮ IL-6 И IL-8 СТИМУЛИРОВАННЫМИ МОНОНУКЛЕАРНЫМИ КЛЕТКАМИ КРОВИ *IN VITRO*

Т.В. Миронова[1]*, А.Д. Таганович[1], В.В. Макаревич[1], Т.С. Колесникова[2], О.В. Левандовская[3], И.П. Шиловский[4], М.Р. Хаитов[4], А.Г. Кадушкин[1]

[1]Кафедра биологической химии, Белорусский государственный медицинский университет, Республика Беларусь, 220083, Минск, пр-т Дзержинского, 83; *эл. почта: tomanis@mail.ru
[2]Научно-исследовательский институт экспериментальной и клинической медицины, Белорусский государственный медицинский университет, Республика Беларусь, 223040, Минская обл., Минский р-н, Боровлянский с/с, а.г. Лесной, 106-2
[3]Минский научно-практический центр хирургии, трансплантологии и гематологии, Республика Беларусь, 220045, Минск, ул. Семашко, 83
[4]Институт иммунологии, 115522, Москва, Каширское шоссе, 24

При лечении хронического воспалительного процесса нередко средством выбора оказываются глюкокортикостероиды (ГКС). Поскольку не все пациенты одинаково чувствительны к ГКС, в настоящее время ведётся поиск путей повышения чувствительности и дополнения глюкокортикостероидной терапии другими лекарственными препаратами нестероидной природы, способными усилить противовоспалительное действие ГКС. Трициклический антидепрессант нортриптилин продемонстрировал в ряде экспериментальных исследований противовоспалительные свойства, а также способность дополнять действие ГКС. Целью данной работы было изучение влияния нортриптилина, а также его комбинации с мометазоном на мононуклеарные клетки (МНК) крови в условиях стимулированных иммунных ответов (ИО) первого, второго и семнадцатого типа. В изолированных МНК крови шести здоровых доноров в присутствии нортриптилина, мометазона или их комбинации стимулировали ИО по первому, второму или семнадцатому типу путём внесения рекомбинантных белков-активаторов (IL-2, IL-25, IL-33, тимический стромальный лимфопоэтин (TSLP), IL-12, IL-1β, IL-23). По истечении трёх дней в супернатантах методом иммуноферментного анализа определяли концентрацию IL-6 и IL-8. В присутствии нортриптилина в конечной концентрации 10^{-5} М ИО второго и семнадцатого типов сопровождался снижением концентрации IL-6. Внесение в среду культивирования МНК комбинации мометазона и нортриптилина в условиях активации ИО второго типа оказывало потенцирующий эффект. Об этом свидетельствовало снижение секреции IL-6 и IL-8 по сравнению с использованием только мометазона. Проведённое исследование демонстрирует способность 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: IL-6; IL-8; клетки крови; иммунный ответ

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