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ORIGINAL RESEARCH
ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Inflammatory response modulation by epinephrine and norepinephrine

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Abstract: *Relevance.* Inflammation is a defense response of an organism to a pathogen. It appears in order to maintain homeostasis and is regulated by the immune, nervous, and endocrine systems. The hormones epinephrine and norepinephrine are produced in the adrenal medulla and in the brain, and are universal messengers that trigger the transmission of nerve impulses at synapses, and also have a receptor-mediated effect on immunocompetent cells. *The aim* of this study was to investigate adrenergic pathway regulation of inflammation on the neutrophil granulocytes in the presence of activators of innate immunity receptors. *Materials and Methods.* Neutrophil granulocytes were obtained from peripheral blood of healthy volunteers in a density gradient of Histopaque 1077 and Histopaque 1119 (Sigma Aldrich, Steinheim, Germany), and cultured in the presence of LPS, GMDP, epinephrine and norepinephrine. The amount of human neutrophil peptides 1–3 (HNP1–3) was examined using an enzyme-linked immunosorbent assay; the gene expression of *TLR4, NOD2, ATF3* and *A20* was determined using RT-PCR. *Results and Discussion.* Norepinephrine (noradrenaline) was found to decrease the synthesis of human neutrophils peptides 1–3 (HNP 1–3 defensins, alone and in the combination with agonists of TLR4 and NOD2 receptors — LPS and GMDP respectively. It was found out that there was no a statistically significant effect of epinephrine (adrenaline) on the production of HNP 1–3, including when combined with LPS and GMDP. As a result of the study, an increase in the levels of expression of the genes *TLR4, NOD2* and regulator of inflammatory reactions *A20* both in LPS- and GMDP- induced neutrophil culture were uncovered, while *ATF3* was increased only in LPS-induced neutrophil culture. Epinephrine demonstrated the absence of a statistically significant effect on the expression of the studied genes. While norepinephrine significantly increased the expression of *A20* genes. *Conclusion.* The data obtained

shows that norepinephrine can reduce the synthesis of HNP 1–3, including the one induced by LPS and GMDP. Moreover, the ability of norepinephrine to induce the expression of *A20* may play a significant role in modulation of inflammation.

Key words: innate immunity, TLR4, NOD2, LPS, muramyl peptide, defensins, human neutrophil peptides 1–3, epinephrine, norepinephrine, catecholamine, inflammation regulation

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Conflicts of interest statement. The authors declare no conflict of interest.

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Introduction

Human immune homeostasis is maintained by adequate reactions of immunocompetent cells to external factors, including microorganisms inhabiting the skin and mucous membranes. The commensal microbiota can either directly affect pathogens, preventing their penetration and reproduction, or do it indirectly through the host's immune system. Pathogen-associated molecular pattern (PAMP) sensors are pattern recognition receptor (PRR) belonging to several families of innate immunity receptors: Toll-like receptors (TLRs), Nod-like receptors (NLRs), retinoic acid-induced gene I (RIG- I)-like receptors (RLRs), C-type lectin receptors (CLRs), and some others [1]. Orthologues of innate immunity receptors found in cnidarians indicate that they appeared in the first metazoans hundreds of millions of years ago and are an ancient and universal way of recognizing foreign organisms [2, 3]. The interaction of PRR with its ligands triggers cascades of intracellular processes, which result in the synthesis of cytokines and mediators, changes in the cell phenotype, additional recruitment of various cell populations to the pathogen penetration site, and elimination of the pathogen. Regulation of the intensity and type of the immune response depends on many factors, including readiness of the immune system to quickly and accurately recognize and respond to a pathogen. Active search is underway for compounds that prevent the development of inflammatory processes, including those from natural raw materials [4–9]. Commensal microorganisms help to keep the immune system in constant readiness for an adequate response. And from another side, commensal microorganisms take part in maintaining a tolerance to resident microflora keeping a balance of host proinflammatory and anti-inflammatory incentives.

During the course of life, microorganisms inhabiting the mucous membranes and skin not only produce a large amount of substances necessary for the existence of the host organism, they also, when disintegrated under the action of host enzymes, release pathogen-associated molecular patterns that constantly interact with innate immunity receptors. Interaction of the ligand with PRR induces production of pro-

inflammatory cytokines that activate anti-infective defenses and, later, anti-inflammatory factors that stop inflammation [10]. Individuals with genetic mutations in innate immunity receptors develop chronic, autoimmune, and oncological diseases [11–13]. When establishing the ligands' mechanisms of action, it is necessary to take into account numerous «classical» and «non-classical» pathways, the presence of positive and negative feedback, as well as the action of factors associated with various physiological conditions of the body.

It is known that stress and enhanced physical exercise lead to changes in the state of the immune system and the spectrum of cytokines [14,15], and additional exposure to bacterial ligands during stressful exposure can modulate negative effects. Lipopolysaccharides (LPS) and muramyl peptides (MPs) are the most studied fragments of bacterial walls due to their ubiquitous activity [16–18]. Lipopolysaccharides are components of the cell walls of Gram-negative bacteria and specific ligands of the innate immunity receptor TLR4 [17–20]. Muramyl peptides are included in the structure of the cell wall of all known bacteria and implement their biological activity through specific binding to NOD2 receptors of innate immunity related to NLR [21]. Muramyl peptides, acting on cells of the immune system and epitheliocytes, stimulates production of cytokines, immunoglobulins and defensins, changes the phenotype of immunocompetent cells [22–26].

Stress and exercise can have both positive and negative effects on immune function and disease susceptibility. Changes to stressful impact must occur very quickly following the principle of «fight-or-flight» to save the life of an organism in the event of a serious threat [27]. Rapid reactions are mediated primarily by catecholamines, epinephrine and norepinephrine, secreted by the adrenal medulla and brain [27]. Epinephrine (adrenaline) and norepinephrine (noradrenaline) interact with adrenergic receptors present on the cell membranes of all internal organs and smooth muscles, leading to activation of signaling pathways and subsequent changes in organ function, smooth muscle tone and blood pressure. Endogenous catecholamines such as epinephrine and norepinephrine can have a direct modulating effect on immune cell activity through interaction with adrenoreceptors (AR) on their cell membrane [28]. Adrenergic pathways represent the main communication channel between the nervous system and the immune system [29,30]. Adrenoreceptors α1 and β1 respond to norepinephrine activity. Adrenoreceptors α2 — respond to norepinephrine and epinephrine, and norepinephrine inhibits its own release, forming a negative feedback loop [31]. β2-ARs have a high affinity for epinephrine, and β2-AR-induced cAMP has an immunosuppressive effect [30]. It was shown that β2-adrenoreceptor agonists suppress the functions of Ca-dependent neutrophils, inhibit neutrophil extracellular traps in human polymorphonuclear leukocytes [32, 33], while α2-ARs are involved in the stimulation of neutrophil functions during exercise [32–34]. Antimicrobial components of granulocytes of neutrophilic granulocytes — alpha-defensins (Human neutrophil peptides 1–3, HNP1–3) — are constitutively produced by neutrophilic granulocytes and make up to 50 % of all proteins in neutrophils [35, 36]. HNP1, 2, and 3 have the same chemical structure, are differing in the N-terminal amino acid. HNPs are released upon activation of innate immune receptors and protect against pathogenic bacteria, fungi, and protozoa [37, 38].

It is known that fragments of bacterial cell walls activate signaling pathways, as a result of which the transcription factor NFkB induces synthesis of pro-inflammatory cytokines and the receptors of innate immunity, initiating positive feedback regulation [39, 40]. Negative feedback develops much later under certain conditions and contributes to the weakening of the inflammatory process [41]. The inflammatory response is downregulated by several pathways, in particular, by deubiquitinase A20 and the activating transcription factor ATF3. Thus, under the action of LPS and GMDP, the expression of the TLR4 and NOD2 genes indicates a positive regulation of the inflammatory response, while the expression of A20 and ATF3 contributes to the negative regulation of inflammation [42, 43].

The aim of this study was to uncover the effect of bioregulators of bacterial origin, when combined with catecholamines, on the production of alpha-defensins HNP 1–3 by human neutrophils, as well as their effect on the expression of genes for TLR4 and NOD2 receptors and regulators of inflammatory responses *ATF3* and *A20*.

Materials and Methods

Isolation of Human Neutrophils

Human neutrophils were isolated from peripheral blood from healthy volunteers on a gradient of Histopaque 1077 and of Histopaque 1119 (Sigma Aldrich), and centrifuged at 300g for 8 min. The granulocytes were washed in DPBS medium (Paneko, Russia), centrifuged at 800 g for 10 min, and resuspended in complete RPMI medium. Cell viability was 96 % determined by trypan blue staining [44].

In Vitro Studies

Primary human neutrophils were cultured (37 °C, 5 % CO_2) for 4 h in the presence of 10 ng/ml LPS (E. coli:055: B5, Merck), 5 μg/ml GMDP (JSC Peptek, Russia), 0.1 μM epinephrine and 0,1 μM norepinephrine (all from Sigma-Aldrich, Germany) and DPBS as control. Then the medium was removed and collected for ELISA, cell lysates were collected for analysis of gene expression.

HNP1–3 Quantification

For detection of quantity of HNP1–3 in supernatants commercial ELISA kits (Hycult Biotech) were used, according to the manufacturer's protocols. Samples were diluted in 5 times with PBS.

Quantitative RT-PCR

The study of gene expression was performed using real-time reverse transcription polymerase chain reaction (RT-PCR), described previously [45]. Primers used in RT PCR are represented in Table 1.

Statistical analysis

The results were processed in the Prism 8 program with two-way ANOVA followed by Bonferroni post-hoc tests to determine significance. Differences were considered statistically significant when reaching $p < 0.05$.

Results and discussion

At the first stage, the levels of HNP1–3 were determined after 1, 2, 4, 8, 12 and 24 hours of exposure to GMDP. It was found that the HNP1–3 synthesis significantly in-creased after 4 hours and remained at a high level for 24 hours (Figure 1). For further studies, an incubation time of 4 hours was chosen, due to the fact that after this exact time the level of defensin synthesis reaches a plateau.

Table 1

Primers used in RT PCR analysis

Genes	Forward primer	Reverse primer
A20	5'-GGACTTTGCGAAAGGATCG-3'	5'-TCACAGCTTTCCGCATATTG-3'
ATF3	5′-CATCTTTGCCTCAACTCCAG-3'	5′-GACACTGCTGCCTGAATCCT-3'
NOD2	5′-GCCACGGTGAAAGCGAAT-3′	5′- GGAAGCGAGACTGAGCAGACA-3′
TLR4	5′-TGGGCAACCTGCTCTACCTA-3'	5′-GCTGTAGCTCGTTGGCAGA-3'
GAPDH	5'-AGGTCGGAGTCAACGGATTTG-3'	5'-GTGATGGCATGGACTGTGGT-3'

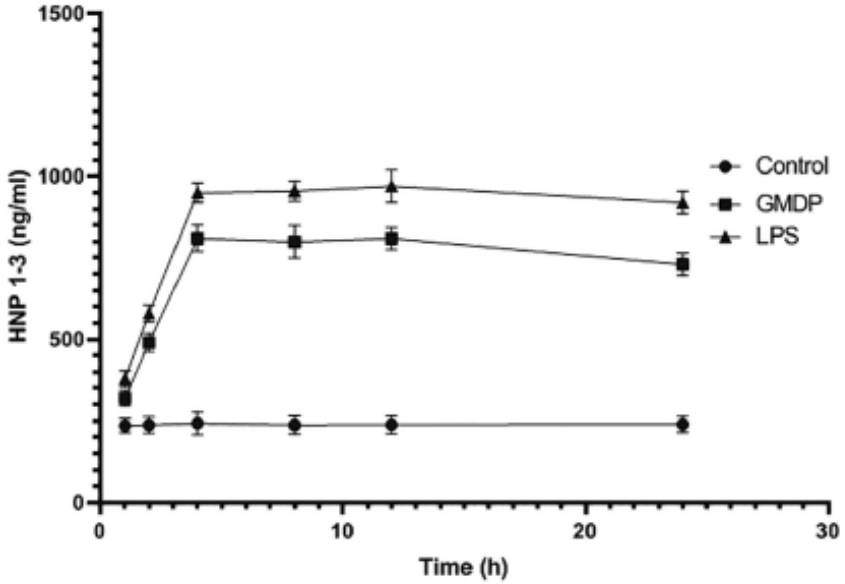

Fig. 1. Levels of HNP 1–3 in neutrophil samples in the presence of GMDP after 1, 2, 4, 8, 12 and 24 hours after GMDP or PBS (in control) exposure. Data for experiments are expressed as the mean ± SEM of the mean of three experiments; * p < 0.05

The investigation of the effect of LPS and GMDP in the presence of epinephrine and norepinephrine and on the production of alpha-defensins by neutrophils *in vitro* revealed that GMDP increased the synthesis of HNP1–3 by 3.2 times ($p < 0.05$) (Figure 2. and LPS increased the production of HNP1–3 by 5.8 times ($p < 0.05$) compared with unstimulated cells (Figure 3).

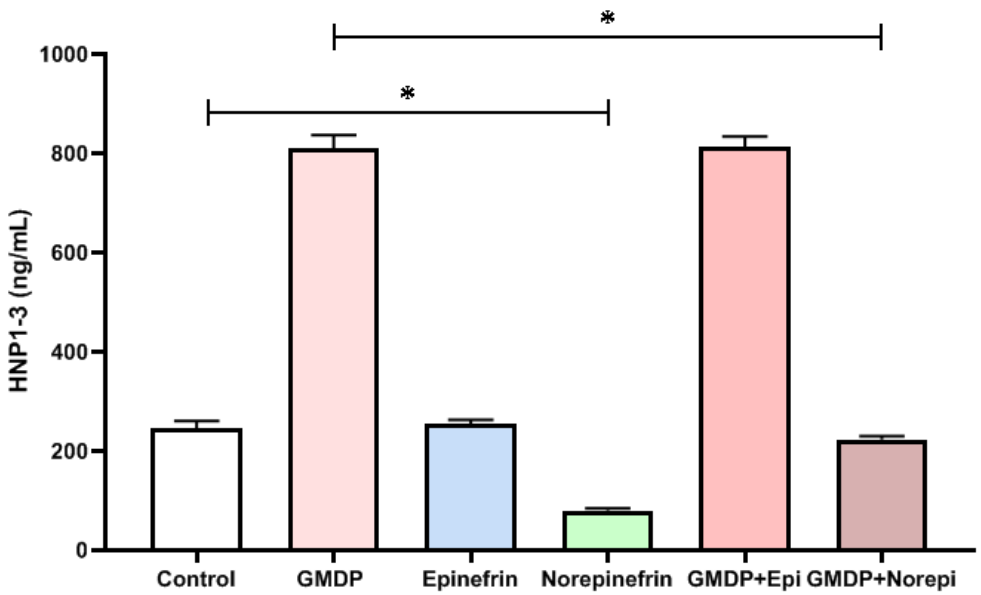

Fig. 2. Levels of HNP 1–3 in neutrophil samples in the presence of GMDP, epinephrine and norepinephrine. Data for experiments are expressed as the mean ± SEM of the mean of three experiments; * **p** < 0.05

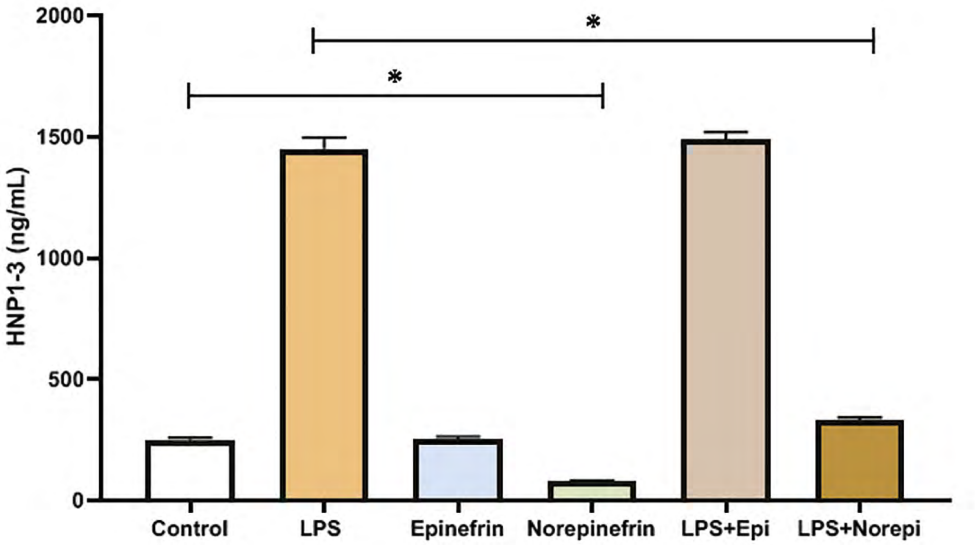

Fig.3. Levels of HNP 1–3 in neutrophil samples in the presence of LPS, epinephrine and norepinephrine. Data for experiments are expressed as the mean ± SEM of the mean of three experiments; * $p < 0.05$

Changes in the synthesis of HNP1–3 under epinephrine impact had no statistical significance. Norepinephrine (norepinephrine), when exposed to neutrophils, reduced the synthesis of defensins HNP 1–3 by 3 times ($p < 0.05$) in unstimulated cell culture.

Epinephrine activity did not abolish the stimulating effect of LPS, while norepinephrine significantly decreased the LPS-induced HNP1–3 synthesis by 4.4 times ($p < 0.05$). A similar effect of catecholamines was also observed in GMDP-induced neutrophil culture. Epinephrine did not abolish the stimulating effect of GMDP, and norepinephrine statistically significantly decreased the synthesis of HNP1–3 induced by GMDP by 3.6 times ($p < 0.05$) (Figures 2, 3).

In order to identify a possible correlation between changes in the synthesis of HNP1–3 and changes in the expression levels of receptors responsible for the binding of LPS and GMDP, we studied the effect of catecholamines and bacterial cell wall fragments on the genes expression levels of their receptors, *TLR4* and *NOD2*, respectively. The innate immunity receptors *TLR4* and *NOD2*, when interacting with their ligands, not only trigger a cascade of downstream pathways to stimulate pro-inflammatory responses, but also increase the expression of their own receptors, demonstrating positive feedback. The study of the expression levels of the TLR4 and NOD2 receptor genes revealed the stimulating effect of bacterial cell wall fragments, which is consistent with the previously obtained data [45, 46]. Moreover, bacterial fragments of LPS and GMDP increased the expression of not only the genes of their own receptors, their cross-effect was also observed. In particular, LPS increased the expression of its own TLR4 receptor genes by 9 times ($p < 0.05$) and the expression of the NOD2 receptor gene by 3 times ($p < 0.05$). GMDP increased the expression of its own NOD2 receptor gene by 5.8 times ($p < 0.05$), and also increased by 4.4 times ($p < 0.05$) the gene expression of TLR4, which is responsible for binding to LPS (Figure 4).

The catecholamines epinephrine and norepinephrine did not affect the expression levels of the TLR and NOD2 genes and did not abolish the stimulating effect of LPS and GMDP on the expression of innate immunity receptor genes. Epinephrine did not affect the expression of the *A20* and *ATF3* genes too. The increase in expression of *A20* gene in the presence of norepinephrine in unstimulated cell culture and in combination with stimulated LPS and GMDP cell culture by 110 %, 169 % and 141 %, respectively, was statistically significant. Thus, the study of genes expression levels of A20 inflammation regulator showed a statistically significant effect of norepinephrine on its expression.

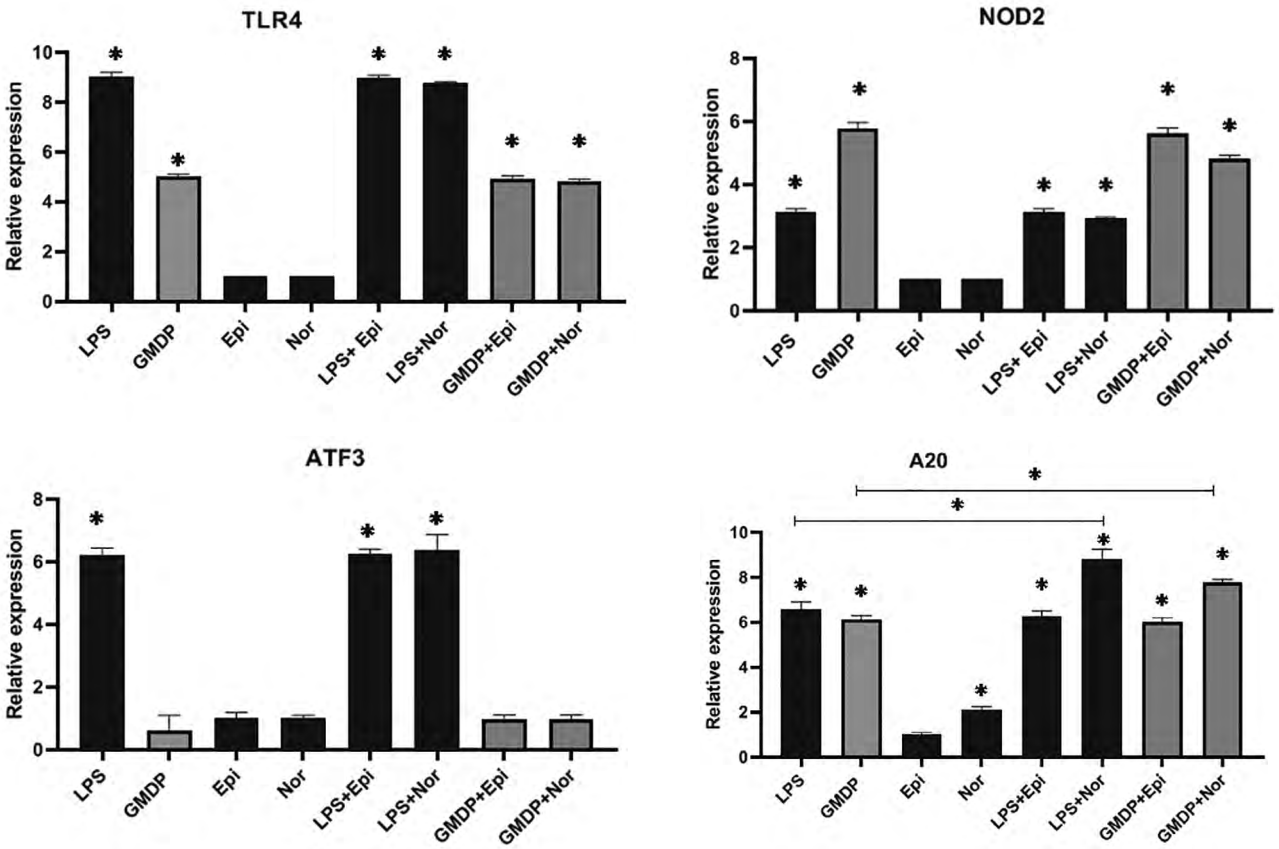

Fig.4. Relative expression (RT-qPCR) of *TLR4, NOD2, ATF3* and *A20* genes in human neutrophils. Relative expression was normalized to GAPDH. Data are represented as an average of three independent samples and error bars represent standard deviation; Nor – norepinephrine; Epi – epinephrine; * $p < 0.05$

Neutrophil granulocytes are important participants in inflammatory processes of bacterial and viral etiology, as well as inflammatory processes in allergic pathology. They are the first to go to the site of pathogen entry, activating pro-inflammatory reactions and use 3 strategies to destroy the pathogen: using the contents of their granules, throwing out extracellular traps or phagocytosis. Neutrophils play an important role in chronic diseases such as atherosclerosis, diabetes mellitus, non-alcoholic fatty liver disease and autoimmune diseases, their role in these diseases is not yet well understood [47]. Neutrophils, along with a protective function, can aggravate the disease with tumor growth and ischemia-reperfusion damage of the heart and brain [48].

Effector functions of neutrophils are implemented by releasing content of their granules, which not only destroys microorganisms, but also protects cells from death, for example, when combined with LL-37 [49]. Dysregulation of neutrophil functions can provoke a respiratory burst, as well as death of neutrophils, including necrosis, apoptosis, necroptosis, pyroptosis, netosis, and autophagy observed during the progression of sepsis [50, 51]. At the same time, high levels of human neutrophil peptides 1–3 can be markers of serious pathologies, such as myocardial infarction, lupus nephritis, and colorectal cancer [52–54]. In the study of HNP1–3 in the development of colorectal cancer, it turned out that HNP1–3 is expressed by tumor cells and significantly contributes to tumor

development [54]. The negative effect of HNP1–3 is also associated with their ability to enhance the development of viral and bacterial infections in certain biological conditions [55].

Our study demonstrates an increase in HNP1–3 levels under the impact of fragments of bacterial cell walls, which is consistent with the results of other researchers on a several-fold increase in the concentration of HNPs in the blood serum during inflammation [56]. Our data is consistent with the previously established dependence of HNP-1 secretion on NOD2 and absence of HNP1–3 secretion in the case of the NOD2 3020insC mutant variant associated with increased susceptibility to Crohn's disease [57].

For the first time this study shows the absence of effects of epinephrine to reduce levels of HNP 1–3 in both unstimulated culture and if induced by LPS and GMDP. The decrease in HNP1–3 synthesis in 3 times ($p < 0.05$) under the impact of norepinephrine alone was statistically significant. Norepinephrine significantly reduced the level of HNP 1–3 by 4.4 times ($p < 0.05$) in stimulated by LPS culture, and by 3.6 times ($p < 0.05$) in GMDP- induced cell culture. This observation is important because HNPs, along with their antimicrobial properties, can also have a negative effect under certain conditions, acting as a «double-edged sword» in host immunity, in infectious, oncological and cardiovascular diseases [52, 54–57]. On the other hand, it is important to distinguish between the effects of epinephrine and norepinephrine on the synthesis of HNPs with subsequent extrapolation of the obtained data on the state of immunity under various types of stress. In this regard, it is interesting to observe the immune system in a state of clinical depression and acute stress [58]. After analyzing levels of pro-inflammatory cytokines in a stressful situation, the authors of this study suggested that the state of depression is associated with greater resistance to molecules that normally stop the inflammatory cascade [58].

When examining the plasma level of endogenous epinephrine in children, it was found that in exercise-induced asthma, bronchoconstriction was accompanied by an increase in the level of norepinephrine. This increase in norepinephrine was much more pronounced than in the control group of children with allergen-induced asthma [59].

The process of induction of inflammatory reactions is studied quite widely, at the same time; reactions aimed at stopping inflammation require close study. The limitation of inflammation by LPS and GMDP on the cellular level was demonstrated in a mouse model of asthma [60]. In this experiments if LPS and GMDP were administered before the allergen, the level of eosinophilia and IgE in bronchoalveolar lavage decreased. Joint introduction of the allergen and LPS or GMDP, resulted in increasing of eosinophils, neutrophils, and Ig E. Other studies have also observed with a time delay the anti-inflammatory effect of LPS in mouse macrophages. Time delay was associated with the need for autocrine activity of type I interferons (IFN) and the subsequent formation of IL10 [61–63]. It was also found that cAMP transiently regulates IL-10 transcription in LPS-stimulated macrophages by synergism with LPS only in the early but not in the late phase. This has been demonstrated at the level of the IL-10 reporter promoter, mRNA expression and protein secretion. In addition, this finding has been replicated in primary macrophages as well as in vivo in an LPS 3-induced mouse model of septic shock [64–66].

Intracellular regulators of biological processes also contribute to limiting inflammation. It is known that transcription factors, such as activating transcription factor 3 (ATF3) and deubiquitinase, in particular A20, can act as negative regulators of inflammatory processes [67, 68]. ATF3 is produced during physiological stress and, depending on the context, can be an activator or suppressor of transcription [69, 70]. Deubiquitinase A20 removes ubiquitin from ubiquitinated substrates, thus inhibiting signal transduction in downstream pathways, stopping the inflammatory cascade. A20 is required for normal NF-κB signaling and suppression of inflammation [68]. At the same time, both TLR4 and NOD2, when activated, trigger the translocation of NF-κB to the nucleus, and, as a result, the synthesis of pro-inflammatory cytokines.

Experimental material was accumulated confirming the possibility of regulation of both pro-inflammatory and anti-inflammatory reactions by bacterial fragments [71]. In the present work, one of the possible explanations for the negative regulation

of inflammation is proposed — through the activation of ATF3 and A20. The effect of norepinephrine significantly increasing the expression of A20 genes requires further study. It is a first study of the influence epinephrine and norepinephrine on the neutrophils from healthy donors. Investigation of the detailed mechanism of anti-inflammatory properties of pathogen associated molecular patterns requires a wide range of experiments.

The data obtained confirms the critical role of adrenergic mechanisms in the regulation of innate immunity [72]. Regulation of the innate immune system via sympathoadrenergic pathways may represent novel anti-inflammatory and immunomodulatory targets with significant therapeutic potential.

Conclusion

Through research, analysis and experiments we meticulously studied the influence of bioregulators of bacterial origin LPS and GMDP, when combined with catecholamines, on the production of alpha-defensins HNP 1–3 by neutrophils, as well as their influence on the expression of genes of *TLR4* and *NOD2* receptors and regulators of inflammatory reactions *ATF3* and *A20*.

As a result of this work, we uncovered that there was no effect of epinephrine on the production of HNP 1–3 when combined with LPS and GMDP, and the ability of norepinephrine to reduce the level of HNPs induced by LPS and GMDP.

Next, there was an increase in the expression levels of the *TLR*, *NOD2* genes and *A20* regulator of inflammatory responses in LPS- and GMDP- induced neutrophil culture and there was an absence of a statistically significant effect of epinephrine upon co-administration.

Besides, when using norepinephrine, its ability to reduce the level of HNPs alone and in cell culture with LPS or GMDP should be taken into account.

Thus, the ability of norepinephrine to reduce the level of alpha-defensins, thereby reducing nonspecific resistance, must be taken into account during exercise in order to maintain immune homeostasis.

Therefore, it is crucial to highlight that the fragments of bacterial cell walls and norepinephrine are involved in the regulation of inflammatory processes, demonstrating the relationship between the immune and nervous systems (Figure 5).

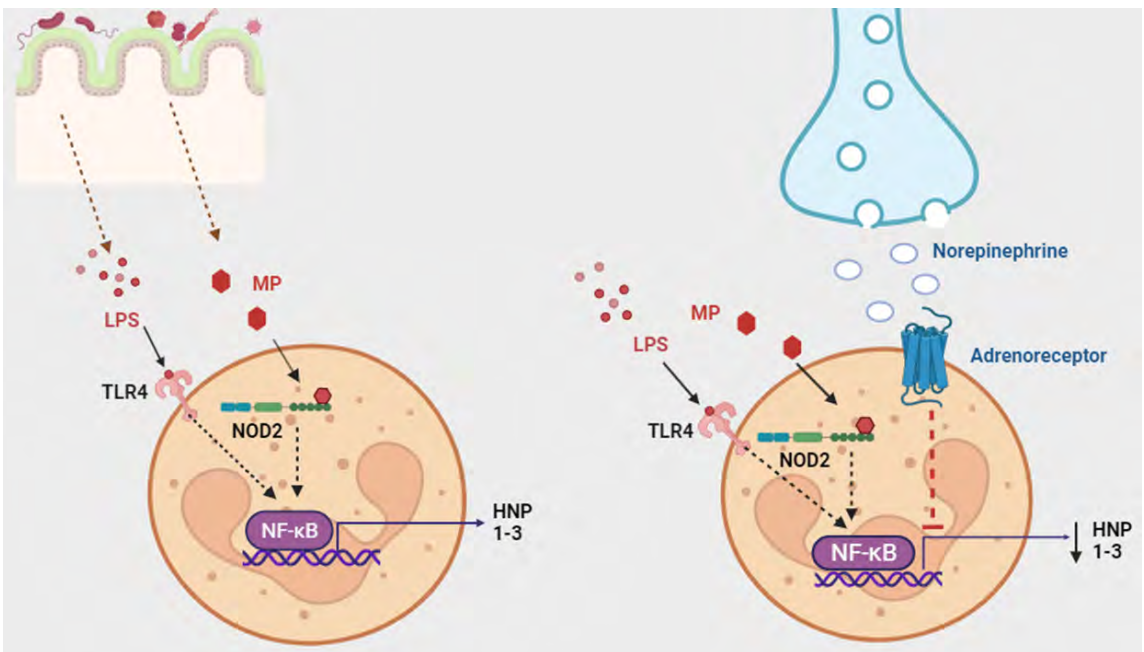

Fig. 5. Norepinephrine reduces production of human neutrophil peptides 1–3

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Модуляция воспалительного ответа адреналином и норадреналином

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Аннотация. *Актуальность.* Воспаление является защитной реакцией организма на патоген с целью поддержания гомеостаза и регулируется иммунной, нервной и эндокринной системами. Гормоны адреналин и норадреналин вырабатываются в мозговом веществе надпочечников и в головном мозге и являются универсальными мессенджерами, запускающими передачу нервного импульса в синапсах, а также оказывают рецептор-опосредованное действие на иммунокомпетентные клетки. Цель настоящего исследования — изучение адренергического пути регуляции воспаления нейтрофильных гранулоцитов в присутствии активаторов рецепторов врожденного иммунитета. *Материалы и методы.* Нейтрофильные гранулоциты получали из периферической крови здоровых добровольцев в градиенте плотности

Histopaque 1077 и Histopaque 1119 (Sigma Aldrich, Штайнхайм, Германия) и культивировали в присутствии липополисахарида (ЛПС), глюкозаминилмурамилдипептида (ГМДП), адреналина и норадреналина. Количество нейтрофильных пептидов человека 1–3 (HNP1–3) исследовали с помощью иммуноферментного анализа; экспрессию генов *TLR4*, *NOD2*, *ATF3* и *A20* определяли с помощью RT-PCR. *Результаты и обсуждение*. Установлено, что норадреналин снижает синтез дефензинов HNP 1–3 как отдельно, так и в сочетании с агонистами рецепторов TLR4 и NOD2 — ЛПС и ГМДП соответственно. Установлено отсутствие статистически значимого влияния адреналина на продукцию HNP 1–3, в том числе при сочетании с ЛПС и ГМДП. В результате исследования выявлено повышение уровня экспрессии генов *TLR4*, *NOD2* и регулятора воспалительных реакций *A20* как в ЛПС-, так и в ГМДП-индуцированной культуре нейтрофилов, тогда как уровень *ATF3* повышался только в ЛПС-индуцированной культуре нейтрофилов. Адреналин продемонстрировал отсутствие статистически значимого влияния на экспрессию исследуемых генов, тогда как норадреналин значительно повышал экспрессию *A20*. *Выводы*. Полученные данные показывают, что норадреналин способен снижать синтез HNP 1–3, в том числе индуцируемый ЛПС и ГМДП. Более того, способность норадреналина индуцировать экспрессию *A20* может играть значительную роль в модуляции воспаления.

Ключевые слова: врожденный иммунитет, TLR4, NOD2, ЛПС, мурамилпептид, дефензины, пептиды нейтрофилов человека 1–3, адреналин, норадреналин, катехоламины, регуляция воспаления

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