
From the Researcher's Notebook

Natural Mechanisms that Underlie the Defense of Host Organisms against Infections

O. V. Bukharin[#]

*Orenburg Federal Research Center, Ural Branch, Russian Academy of Sciences,
Institute of Cellular and Intracellular Symbiosis, Orenburg, Russia*

e-mail: onckadri@mail.ru

Received December 27, 2018; revised December 27, 2018; accepted April 15, 2019

Abstract—The topic of human–microbe interactions is of unfading relevance. Which interactions take place? Are microbes of any use, or are they essentially harmful? As the years go by, new microbiological techniques emerge, new facts on the coexistence of microbes and humans are revealed, and a new understanding of the coexistence of humans and microbes emerges. Mechanisms that underlie the natural protection of the host organism from infections are addressed in this article. The three interconnected components of the defense system considered here are the hypothalamic-pituitary system, oxytocin, and the microbiota. At first glance, these structures appear independent: the human brain contains the central “control panel” that regulates behavior, decision-making, and health. It regulates the functions of the major vitally important organs through the production of the neurohormone oxytocin, and recent studies revealed the contribution of the gut microflora (microbiota) to this regulation. Thus, the circle is closed. One can then ask whether microbes really control us. Let us address this question.

Keywords: hypothalamic-pituitary neurosecretory system, oxytocin, microbiota, microsymbiogenesis, infection, homeostasis, persistence.

DOI: 10.1134/S1019331619040014

The hypothalamic-pituitary neurosecretory system of the host. The hypothalamus, a distinct structure of the human brain, plays a substantial role in the defense response of the organism to infection. The central “control unit” for defense against microorganisms—namely, the hypothalamic-pituitary neurosecretory system (HPNS)—emerged as a result of many centuries of cell and tissue evolution in the host organism.

The nonapeptide neurosecretory products of the hypothalamus are a key link of neuroendocrine regulation of visceral functions in eukaryotes [1]. In addition to the previously characterized viscerotropic effects of these hypothalamic neuropeptides that are exerted on the cell and tissue elements by the magnocellular (supraoptic and paraventricular) nuclei of the hypothalamus, a broader range of biological effects, including a role in the regulation of elemental processes of embryonic and reparative histogenesis, has been demonstrated for these humoral factors. The results of studies performed over many years [2, 3] enabled the formulation of a postulate concerning the positive (optimizing) role of the hypothalamic nonapeptides in the processes of proliferation, growth, and

cell differentiation in tissues of various origins. These effects were regarded as proof of the adaptogenic significance of hypothalamic nonapeptides, the most ancient humoral substrates in the regulation of cell and tissue homeostasis in extant organisms. Hypothalamic nonapeptides (oxytocin and vasopressin) can be evaluated according to their powerful effects on homeostatic processes in endocrine and nonendocrine epithelia and other tissues. These effects can be interpreted from the viewpoint of the formation of a regulatory center for homeostasis control (under the condition of cocultivation of various epithelia and other tissue structures with magnocellular nuclei of the hypothalamus, that is, conditions that imply a better preservation and mobilization of the cells' proliferative activity).

Neurohormones of the peptidergic neurosecretory centers of the hypothalamus, which are evolutionarily more ancient, can be regarded as epigenetic factors of cell and tissue development. They can probably act as signaling macromolecules that mediate the optimal regulation of DNA transcription and cell reproduction and sometimes evoke functional reprogramming of a eukaryotic cell's nuclear apparatus with subsequent modification of the functioning of the transcription and translation pathways and activation of membrane-bound receptors and intracellular messenger systems.

[#] Oleg Valer'evich Bukharin is an RAS Academician and Principal Research Fellow at the Institute of Cellular and Intracellular Symbiosis, Ural Branch, RAS.

Identification of oxytocin as one of the active “players” in the homeostasis of the host organism promoted research on the role of oxytocin in defense mechanisms activated by infection.

Oxytocin and microorganisms. As shown already by the first studies in this research area, oxytocin efficiently modified the persistent (adaptive) potential of microbial cells, even though it did not exert a substantial antimicrobial effect. A pronounced inhibitory action of the preparation towards anti-lysozyme activity, the most universal sign of bacterial persistence, was demonstrated by *in vitro* studies [4, 5]. The anti-lysozyme activity (ALA) is a factor that protects bacterial cells from the ubiquitous lysozyme (muramidase) found in virtually all biotopes of the human and animal organism. Indeed, lysozyme distribution could not have been different, because all living organisms require protection. This is a law of Nature. The microbes that attack the human organisms do it for the “ecological” purpose of finding suitable “accommodation.” As the microbes create a niche in the host organism, they neutralize the host lysozyme by means of anti-lysozyme activity and the pathogens can even use lysozyme as a food source. The invaders settle in the host organism. Bacteria carriers, which provide an excellent model for research on bacterial persistence, emerge. The selection of therapeutics that would suppress the “appetite” of pathogenic microorganisms is an important direction of medical research. The current situation requires novel approaches to the selection of preparations that suppress the persistence potential of microorganisms, especially *Staphylococcus aureus*, the most common culprit in the emergence of purulent inflammatory processes.

The action of a range of therapeutics at subinhibitory concentrations was studied *in vitro* by O.L. Chernova (1989). This work could have contributed to the selection of preparations that suppressed the persistent properties of microorganisms and could thus be applied for rehabilitation of bacteria carriers [5]. Experiments showed that oxytocin was the most efficient regulator of the persistence potential (as revealed by *Staphylococcus* ALA analysis). Oxytocin, vitamin A (a solution in oil), and interferon were the three most efficient preparations that suppressed the persistence of *S. aureus*. Rosehip oil and iodinol exerted a similar effect (on *S. aureus*). Lysozyme did not suppress *Staphylococcus* ALA at the doses tested. It is necessary to note that oxytocin itself did not possess an antimicrobial effect but suppressed the persistence potential of microorganisms, as demonstrated by clinical studies.

Let us mention several results of clinical use of oxytocin [6]. Antibiotic therapy (that did not include oxytocin) was substantially less efficient than multicomponent therapy (that included oxytocin) for treatment of lactation mastitis in women. These differences are apparent if treatment times (in bed-days) are com-

pared: the value for the control group was 9.6 ± 0.9 , that for multicomponent treatment (antibiotic + oxytocin) was 6.5 ± 0.2 , the value for women that received antibiotic, oxytocin, and helium–neon laser (HNL) treatment was also 6.5 ± 0.7 , whereas the addition of ultra-high frequency treatment to the therapeutic regimen resulted in a slight decrease in the treatment time (6.0 ± 0.3).

A similar trend of the enhancement of the antimicrobial effects of antibiotics by oxytocin was also observed in the treatment of postinjection abscesses. Earlier normalization of body temperature, more frequent cessation of exudate formation in the inflammation focus, a decrease in the cases with an unfavorable course of the disease, and earlier convalescence were observed in the patients that received oxytocin and antibacterial therapy. The studies also showed that patients (150 individuals) with other purulent diseases of the soft tissues recovered after 4–7 days (that is, 1.8–4.4 times faster than provisioned by the medical and economic standards for these nosological forms) if oxytocin was administered in combination with antibiotics, and the time spent in the hospital was 2–3 times shorter than that for the patients given the traditional treatment.

The data collected by O.M. Abramzon is of no less interest [7]: he used the persistence potential of pathogens as a biological target during the development of a topical closed treatment technique for patients with acute purulent diseases of the lungs and pleura. The authors reported encouraging data on the use of oxytocin combined with other drugs for topical treatment of patients with acute purulent diseases of the lungs and pleura [8]. The studies showed that the dynamic pattern of the biological properties of the isolated microflora was similar for aerobic and anaerobic isolates regardless of whether the course of the disease was normal or protracted and enabled the selection of the most informative parameters (anti-lysozyme, anti-complement (ACA), and hemolytic (HA) activity of microorganisms) for the prognosis of the course of the disease at an early stage of the disease. The results of the experiments were corroborated by documented clinical application of topical “antibiotic + oxytocin” treatment in patients with acute pulmonary–pleural purulent processes and in the prevention of pleural empyema after pneumonectomy (Table 1).

A study by Yu.I. Skorobogatykh [9] showed that simultaneous addition of ciprofloxacin and oxytocin to the culture medium caused a reduction in the minimal suppressive concentration (MSC) of the antimicrobial drug as compared to the control sample: a 4- to 8-fold reduction was observed for both S- and R-strains. Elimination of ciprofloxacin resistance from all the microorganism R-strains analyzed was observed. The MSC of ciprofloxacin towards obligate anaerobes decreased 4–6 times, on average, if the antibiotic was used together with oxytocin, whereas

Table 1. Comparative assessment of treatment results in patients with acute pleural empyema and pneumothorax

Parameter	Main group	Control group
Number of patients	67	28
Time of body temperature normalization, days	13.8 ± 1.2*	25.8 ± 2.1
Time of peripheral blood parameter normalization, days	12.9 ± 0.8*	26.2 ± 2.9
Time of X-ray result normalization, days	15.0 ± 1.0*	32.2 ± 3.3
Treatment time, days	26.0 ± 1.2*	42.3 ± 3.0
Operative activity, %	4.5*	28.6
Mortality, %	4.5	10.7
Transition to chronic disease, %	8.1*	36.4

* $p < 0.01$ for the patient groups compared.

the MSC towards facultative anaerobes decreased 6–8 times. Thus, sensitivity to ciprofloxacin is widespread among the pathogen strains that cause purulent inflammatory diseases (PIDs) of soft tissue. However, resistance of the microorganisms to the drug was observed in 17–50% of all cases. The introduction of ciprofloxacin combined with oxytocin into the culture medium promoted both an increase in the antibiotic sensitivity in the S-strains and the emergence of sensitivity in the R-strains, and this may provide a method for reduction of antibiotic resistance in hospital microflora. A connection between this phenomenon and the action of the preparation on the persistence potential of the pathogen cannot be ruled out. Moreover, the preparation is known to contain a cyclopropyl moiety essential for blockading the pathogen's persistence potential, as demonstrated in the study by D.A. Kirillov [10]. This statement was confirmed by experiments in which population analysis was applied to other microbial cultures (Fig. 1). The MSC towards the microorganism species studied was reduced relative to the value for single drug treatment if ciprofloxacin was used in combination with oxytocin: this was accompanied by an increase of the sensitivity to ciprofloxacin in antibiotic-sensitive cultures and the emergence of strains sensitive to the drug among antibiotic-resistant bacteria. The combination of ciprofloxacin and oxytocin turned out to be more efficient than an individual preparation, as it suppressed both ALA and pathogen biofilm formation.

Experimental data were used to develop experimental cream specimens for the treatment of purulent wounds during phase I of the wound process (ciproxin cream I): the cream contained ciprofloxacin and oxytocin dispersed in a polyethylene oxide base [11]. The use of a “ciprofloxacin + oxytocin” combination dispersed in a silicone–glycerol hydrogel base enabled the production of a cream (ciproxin cream II) applicable for the treatment of phase II and III purulent wounds [12].

Experiments showed that local application of ciproxin cream I and II provided for a faster elimination of microflora from the inflammation foci, cessation of

purulent exudate secretion, and stimulation of repair processes in the wound. As a result, wound healing was accelerated. These studies demonstrate that the use of ciprofloxacin combined with oxytocin and a polyethylene oxide mix for purulent wound treatment during wound process phase I is justified, whereas the treatment of phase II and III wounds calls for the use of ciprofloxacin combined with oxytocin and a silicone–glycerol hydrogel, and thus the range of efficient preparations for treatment of surgical infections of soft tissues is expanded.

The range of the effects of hypothalamic nonapeptides (vasopressin and oxytocin) is reportedly broad: these peptides are among the most important regulatory molecules produced by the host and involved in the maintenance of the organism's homeostasis [13]. The adaptogenic function of the nonapeptides stimu-

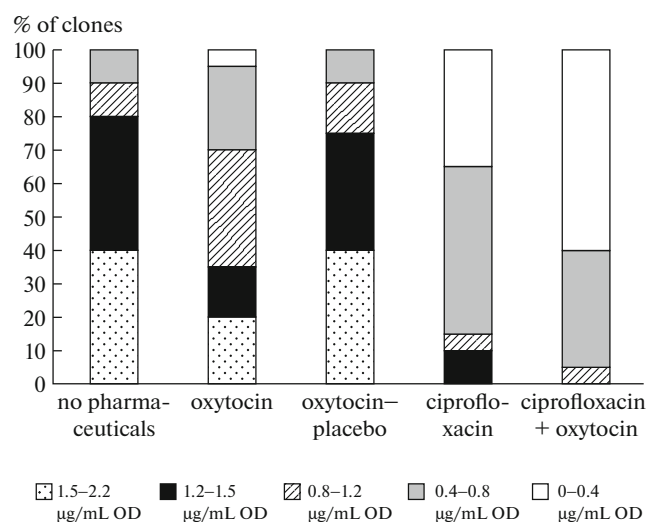


Fig. 1. ALA in a *Klebsiella pneumoniae* no. 278 population and ALA changes in populations exposed to oxytocin, ciprofloxacin, and combinations thereof (5%). The average ALA level in *Klebsiella pneumoniae* no. 278 was 1.27 ± 0.03 µg/mL OD.

lated during the infection process caused by persistent pathogens has been characterized [14].

Analysis of the mechanisms that underlie the protective effect of oxytocin in infectious diseases revealed that the hormone's effect on microorganisms was mediated by immunomodulation, including the enhancement of blastic transformation of lymphocytes and the phagocytic reaction of macrophages [15], and the direct effect of the peptide on prokaryotic cells manifested as suppression of the persistence potential [8], including biofilm formation [9]. The slight antimicrobial effect of nonapeptides is, presumably, largely related to the effect of the molecules on the cell walls of microorganisms, since atomic force microscopy and electron microscopy revealed physical changes in the cytoplasmic membrane rigidity, cell surface disorganization, and expansion and vesiculation of the nucleotide components of the bacteria exposed to oxytocin [14].

The insulinlike effect of oxytocin has been observed in vitro and in animal experiments: the peptide promoted glycogen synthesis from glucose, suppressed lipolysis, and enhanced intracellular H_2O_2 formation [16]. The capacity of oxytocin to simulate endogenous insulin secretion has been described in a number of studies [17, 18]. Moreover, the results of oxytocin use in the treatment of purulent diseases of soft tissues and purulent necrotic foot disease in diabetes mellitus patients have been positive. An original treatment procedure for purulent necrotic foot disease in diabetes patients, which involves the use of oxytocin during complex treatment, has been developed [19]. The authors analyzed biopsy material from the areas affected by disease and revealed a decrease in necrobiotic and necrotic modifications of skin tissue, the hypoderm, and the skeletal muscle, and enhanced DNA synthesis in adventitial cells, fibroblasts, and endothelial cells. The cell proliferation impaired in diabetes mellitus was normalized to some extent if oxytocin was used in multicomponent therapy. Oxytocin exerted a substantial stimulatory effect on the reparative regeneration of tissue in the wounds of diabetes mellitus patients, so that efficient cleaning of the wound and the formation of fully functional granulation tissue, which provided a suitable environment for wound surface repair, were ensured.

Integrative microbiota–host interactions. How do these interactions arise? Has considerable progress occurred in our understanding of this issue? Gram-negative bacteria are known to interact with signaling molecules of the human immune system, including the signaling polypeptides called cytokines. The balance of these regulatory molecules is important for human homeostasis, because cytokines participate in the regulation of the immune response to infection [20]. Cytokine production in the presence of microorganisms implies the direct contact of bacteria with these signaling molecules, in addition to the indirect

stimulation mediated by regulation of the immune system. Therefore, the effects of cytokines on the physiological properties (growth/reproduction) of bacteria in vitro were studied [21]. The studies showed that the interleukins IL-1, IL-2, and IL-6, interferon (INF) γ [22], and tumor necrosis factor (TNF) α [23] promoted bacterial growth, whereas the IL-4 interleukin did not [24]. The presence of a microbial receptor, the Caf1A (capsule assembly antigen F1) protein located in the external membrane and capable of binding to IL-1 β , was demonstrated in a model culture of the plague bacillus (*Yersinia pestis*) [25]. The external membrane of *Pseudomonas aeruginosa* bacteria contained a protein capable of specific binding to INF- γ ; the binding was followed by induction of synthesis of the *Pseudomonas* siderophore pyocyanin and quorum mechanism activation [26].

As currently admitted, the microbiota, in turn, can affect the production of specific cytokine types as growth factors and the stimulation/suppression of cytokine synthesis [27]. Some pathogenic and opportunistic bacteria produce enzymes that enable the degradation of the major classes of organic macromolecules by microorganisms. Inactivation of cytokines produced by activated T-lymphocytes, macrophages, and dendritic cells can evoke considerable disturbances in innate and adaptive immunity mechanisms.

The study by A.S. Petrovskii (2012) provided additional proof of host–microbiota integration mediated by the signaling molecules of microorganisms acting as modulators of human immunity. The author demonstrated a change in the functional activity and substrate specificity of lysozyme exposed to alkoxybenzene (AOB) homologues. Lysozyme modified by C7-AOB showed activity against both chitin (and therefore, fungi) and intact *Saccharomyces cerevisiae* yeast cells. The maximal yield of reducing sugars was observed at a C7-AOB concentration of 2 mg/mL in both cases [28].

Analysis of the data presented here demonstrates that the integration of the molecular systems of the microsymbionts and the macropartner (host) is probably mediated by signaling molecules: the signaling molecules produced by the microbiota include low molecular weight metabolites, quorum mediators, and others, whereas those produced by the host include mediators of the hormone and immune systems. The formation of a unified regulatory environment, which determines the diversity of these connections, under the conditions of symbiosis cannot be ruled out. An example can be found in the gut–brain axis (a bidirectional communication system, which mediates the modulation of the function of the gastrointestinal tract by the brain, and vice versa), which has stimulated considerable interest among researchers [29]. The study by G. Camara (2009) contained a description of a bidirectional connection between the gastrointestinal tract and the brain; this connection is of great

importance for the homeostasis of the human organism mediated by hormonal, immunological, and neuronal regulation. Regulation of homeostasis of the host gut microbiota is apparently mediated by specialized (dendritic) cells involved in signaling communication with other microbial cells, and finally the signals arrive to the hypothalamic-pituitary system (HPNS), and the brain can decide whether host defense is required or not. Therefore, the communication of microbes with each other and with the host is rightfully considered an extremely important component of decision-making, and therefore the communication of microorganisms can be regarded as a highly significant component of signaling [29, 30].

It is necessary to admit that the connection between the gut microbiota and the behavioral reactions of the host is also of interest for theoreticians, rather than for clinicians only [31]. The term “microbiota–gut–brain axis” (the MGB axis) is in use. The discovery of the correlation between the patients’ state (encephalopathy, depression, unrest, and the like) and changes in the gut microbiota was corroborated by in vitro studies that revealed an elevated anxiety level in experimental animals infected with pathogenic bacteria that caused intestinal inflammation and regulated the adrenocorticotrophic hormone (ACTH) level in mice [32], whereas the administration of probiotics (*Bifidobacterium longum* and *Lactobacillus helveticus*) promoted a decrease in anxiety.

It is hard to overestimate the role of the microbial factor, and the microbiome in particular, and since it has been created by Nature and has coexisted with the host over many centuries, one only has to understand the physiological purpose of this factor. It is easy to notice that the microbiome cannot remain “idle” in the presence of HPNS, the universal and powerful center of health control in the mammalian organism, which produces the nonapeptide neurosecretory hypothalamic hormones (oxytocin and vasopressin). The intestinal microflora have turned out to stimulate the host’s immune defense and protect the organism in a rather curious way, that is, by promoting the translocation of the host’s beneficial microflora and its metabolites [33]. This is by far not the only beneficial function of the hypothalamic hormone oxytocin. This hormone is known to make diverse contributions to the host defense: it contributes to the control of reproductive function and development of obesity, affects social behavior, improves mood and general condition, and, finally, maintains a high quality of life and health [34].

Microbial regulation of the production of the neuropeptide hormone oxytocin in experiments was enabled when probiotic model microorganisms were administered to the host, and this opens up new opportunities for harnessing new biological effects of the microbiota. The connection of oxytocin to the processes of obesity development, reproductive

health, and innate immunity, along with the materials presented above, provides a foundation for the recognition of this neurohormone as a universal and global hormonal regulator that opens new opportunities for the improvement of humans’ physical, intellectual, and social status (health). The above-described beneficial effects of oxytocin in the regulation of host homeostasis might still be incompletely characterized, but only time and intellectual fearlessness are required to solve this problem. Interest in this problem is growing steadily nowadays, and this guarantees new discoveries and solutions in the three-component HPNS–oxytocin–microbiota system described here. Thus, new light can be discerned “at the end of the tunnel.”

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Translated by S. Semenova