

Covid and Oxytocin: Looking for Microbial Symbiosis

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ABSTRACT

Oxytocin is a hormone with broad implications for general health. This hormone has anti-inflammatory and antioxidant protective effects and has received particular attention due to the pandemic of COVID-19. This review examines materials on the role of microbial symbiosis in COVID-19 and the effect of microbiota on oxytocin. It opens new potential prospects for the use of microbiota and new “nature-like” technologies.

KEYWORDS

COVID-19; oxytocin; microbiota; symbiosis.

Declarations: Not applicable.

Funding: This work was supported by the Russian Ministry of Science and Higher Education.

Conflicts of interest/competing interests: All authors listed on the title page are aware of this submission and all contributions are attributed in the author list or acknowledgment section. The authors declare that they have no competing interests.

Ethics approval: The collection and investigation of the strains described in this work have the approval of the IRB of Institute of Cellular and Intracellular Symbiosis UB RAS.

Consent for publication: All authors read and approved the final manuscript.

Oxytocin is a nonapeptide hormone named by Lee (2009) “the Great Facilitator of Life”.¹ Recently, this hormone has received particular attention due to the COVID-19 pandemic and the difficulty in treating these patients. The key point is that the article will **not** summarize our vast knowledge of oxytocin, but it will try to ask questions for future researchers. The global medical community is seeking an effective drug treatment for COVID-19 and in this regard, the question was raised: “Is oxytocin the panacea for long-COVID?”.² What do we know today?

SOME OF OXYTOCIN’S EFFECTS

Oxytocin is a pleiotropic, peptide hormone with broad implications for general health. Its role is described in adaptation, development, reproduction, and social behavior.^{1, 3} Endogenous oxytocin promotes healing and functions as a stress-coping molecule. Oxytocin also has anti-inflammatory and antioxidant protective effects.³ Receptors of oxytocin are localized in areas of the nervous system that regulate social, emotional, and adaptive behaviors, including the amygdala, the hypothalamic-pituitary-adrenal (HPA) axis, and the autonomic nervous

system.⁴ External to the hypothalamus, oxytocin gene expression has been detected in a wide range of cells and tissues.⁵

As an hypothesis, it has been proposed to use oxytocin as a direct antiviral:⁶ “Even if oxytocin does not have direct antiviral effects it still has sufficient mechanisms that could make it effective against COVID-19 such as immunomodulatory, cardioprotective, anti-diabetic and anabolic functions as well as psycho-social functions”.^{7, 8}

A review by Buemann *et al.* in 2020⁹ summarized the data on oxytocin’s ability to mitigate tissue damage in sepsis, thermal trauma in rats, local gut injury (bacterial LPS-induced acute lung injury) and heat stroke elicited acute lung injury. The protective effects of oxytocin against damage caused by transient hypoxia have been confirmed in a number of ischaemia/reperfusion experiments in a variety of organs.¹⁰

Oxytocin has been demonstrated to possess potent cardioprotective properties in different models.¹¹ Oxytocin also plays a protective role by increased activation of anti-apoptotic and restorative pathways.^{12, 13} The tissue protective role of oxytocin may direct healing and regenerative effects on tissues. When oxytocin was included in the complex of therapeutic measures (the model of bone transplantation), an activated proliferation of genetically determined progenitor cells of connective and skeletal tissues was shown. Their further adequate cytodifferentiation and functional specialization led to the formation in the simulated cavity of not only tissue-specific regenerate consisting of coarse-fibrous (reticulofibrous) bone tissue, but also organ-specific bone structures (such as atypical osteons).¹⁴ The potential of oxytocin to promote the function of stem cells may be part of the regeneration.¹² An overall restorative potential of oxytocin is also demonstrated by experiments in rats showing increased rate of mitosis and an improved rate of wound healing following administration of oxytocin.¹⁵

Previously revealed immunomodulatory and antimicrobial effects of oxytocin and its synergism with antibiotics was a reason for the use of an “oxytocin-antibiotic complex” in the treatment of different diseases.¹⁴ The use of oxytocin as a means of combined antibiotic therapy enhanced the effect of antibacterial drugs against bacteria (including persistence and antibiotic resistant strains) and obtained encouraging results in various clinical trials: post-injection abscesses; pyelonephritis; lactational mastitis; endometritis and salpingo-oopharitis; acute cholecystitis; diabetic foot; acute destructive pancreatitis; suppurative processes of the epithelial coccygeal passage; purulent sinusitis and acute purulent diseases of the lungs. For example, women with lactational mastitis who were treated with oxytocin and an antibiotic (in comparison with treatment with antibiotics alone) recovered faster and the length of hospital stay was reduced (9.6 ± 0.9 days versus 6.5 ± 0.2). In the treatment of post-injection abscesses,

patients' temperatures returned to normal earlier, the formation of exudate in the inflammation centre stopped, and the number of cases of an unfavorable course of the disease decreased. Optimistic results were also obtained in the treatment of patients with acute purulent diseases of the lungs and pleura and for the prevention of pleural empyema after pneumonectomy. Studies have shown that the antimicrobial effect of oxytocin can be associated with the effect on the cell wall of microorganisms. Under the action of oxytocin on bacteria, atomic force and electron microscopy revealed physical changes in the rigidity of the cytoplasmic membrane, disorganization of the cell surface, as well as loosening and vesiculation of the nucleoid components of prokaryotes. In vitro experiments have shown the effect of the "antibiotic-oxytocin" complex on decreasing of biofilm formation and bacterial resistance to antibiotics.^{16, 17}

COVID-19 – MICROBIOTA - OXYTOCIN

A number of publications have appeared indicating that the severity and consequences of COVID-19 are associated with gut microbiota.¹⁸⁻²¹ It was found that the viral RNA of SARS-CoV-2 was detected not only in respiratory secretions, but also in the faeces of patients for more than one month after the onset of the disease.²² In many patients with COVID-19, in addition to acute respiratory syndrome, extra pulmonary manifestations (nausea, vomiting, loss of appetite, diarrhea) were noted^{23, 24} as well as liver dysfunction and exacerbation of inflammatory bowel disease.^{25, 26} Moreover, in some cases, signs of intestinal upset appeared even before other signs.^{27, 28} All this confirms that the gastrointestinal tract can be the entrance gate of infection and indicates the involvement of the gut microbiota in the infectious process in COVID-19 and the formation of a "gut-lung" relationship.^{18, 29}

The relationship between the gastrointestinal tract and the respiratory tract has also been shown in works on the effect of respiratory viral infections and the composition of the gut microbiota with the subsequent development of dysbiosis.^{30, 31} Thus, patients with COVID-19 had significant dysbiosis of the gut compared to the control group, characterized by an increase in the proportion of opportunistic microorganisms against the background of a decrease in the level of normal microbiota. It is noted that the composition of the gut microbiome was significantly altered in patients with COVID-19 compared with patients without coronavirus infection, regardless of whether they were taking medications. Gut dysbiosis was present even after the elimination of SARS-CoV-2 and the disappearance of respiratory symptoms. Also, changes in the gut microbiome were found in patients with COVID-19 compared with the control group, characterized by an increase in the number of fungal pathogens of *Candida* and *Aspergillus*.^{32, 33}

To date, it is assumed that the disruption of the gut microbiota contributes to disease progression in patients with COVID-19 due to the bidirectional connection of the intestinal microbiota with the immune and respiratory systems.^{34, 35} Firstly, the formation of microbial disorders leads to an increase in the permeability of the gut, and, as a result, is one of the factors in the development of bacterial

translocation, sepsis, systemic inflammation and multiple organ failure.³³ Previously, bacterial translocation from the gut to the lungs has been identified in sepsis and acute respiratory distress syndrome. Secondly, there is an effect on homeostasis through immunological coordination (cytokines, immune cells). Thirdly, gut dysbiosis has also been found to be associated with various chronic diseases (asthma, arthritis, obesity and diabetes type 2 etc.).¹⁸ All these are additional risk factors complicating COVID-19 in the presence of pre-existing dysbiosis in patients. In addition, the altered microbiota serves as an additional reservoir for antibiotic-resistant bacterial strains (the so called resistome),^{36, 37} which can complicate therapy for patients with COVID-19 and delay recovery.³⁸

Currently, it is assumed that probiotic bacteria can be used for prophylactic or therapeutic purposes to induce hormonal and immune changes. It has been discovered that the presence of *L. reuteri* leads to higher levels of oxytocin in mice.^{39, 40} In C57BL/6 mice it was shown that *L. reuteri* ATCC PTA 6475 in drinking water enhanced skin wound-healing which occurred in half the time required for matched control animals via up-regulation of oxytocin.⁴⁰ In the research by Varian in 2017⁴¹ it was concluded that non-viable *L. reuteri* are sufficient to elevate blood levels of oxytocin and increase the number of oxytocin-positive cells in the PVN of mice. Microbe-triggered (in mice consuming *L. reuteri*) increases in blood and brain oxytocin were associated with improved wound healing capacity, lowered blood levels of stress hormone (corticosterone), a larger thymus gland and fewer pro-inflammatory blood neutrophils. Sterile preparations of *L. reuteri* lysate were sufficient for achieving health benefits in mice. These findings are a continuation of a recent study using a different *L. reuteri* isolated from dogs.⁴² In that research, an extract of *L. reuteri* strain 2546 counteracted obesity and decreased blood neutrophils, recapitulating earlier findings for viable *L. reuteri* ATCC PTA 6475.^{40, 41}

In our research (unpublished data), we also confirmed an increase in oxytocin in mice. The introduction of bifidobacteria strains (cells and cell-free supernatants) to laboratory animals led to increased oxytocin in serum (up 2-4 rates via control). There are currently insufficient observations that provide similar results from volunteers, but the search for bacterial strains that increase oxytocin may open new prospects for recovery of patients.

OTHER SUSPECTED MICROBIOTA-RELATED TARGETS

One of the pathogenic mechanisms of COVID-19 is the appearance of a "cytokine storm", which is the cause of high mortality. By preventing this response to pathogenic infections such as COVID-19, a healthy gut microbiome can be critical to maintaining optimal immune function. The physiological role of the gut microbiota (particularly bifidobacteria and lactobacilli) is linked with the ability of prokaryotes to regulate the function of the innate and adaptive human immune system.^{43, 44} Gut immune homeostasis is maintained by a balance of pro-inflammatory factors such as Th17 versus regulatory T cells (Tregs), which are ultimately controlled by the representation of

normal human microbiota through a system of receptors (TLRs, NODs) and cytokines (bifidobacteria and lactobacilli).^{44, 45} The production of cytokines in response to microbiota involves not only indirect (through the regulation of immunity), but also direct contact of bacteria with these “signaling” molecules. Gut microbiota affect the secretion of antimicrobial peptides, anti-inflammatory cytokines, and compete for nutrients and habitats, thereby contributing to the maintenance of homeostasis.⁴⁶ Some pathogenic and opportunistic bacteria secrete enzymes that allow microorganisms to break down the main types of macromolecules. It is known that “signaling” molecules of the intestinal microbiota (short-chain fatty acids such as butyrate, acetate, propionate, and secondary bile acids) are able to regulate systemic anti-inflammatory responses.⁴³ Inactivation of cytokines (secretory inhibitor of cytokine (SIC), anti-peptide activity),⁴⁷ which are the product of activated T-lymphocytes, macrophages, dendritic cells, can also lead to a “shift” in local immune homeostasis.

The use of bifidobacteria and lactobacilli can help normalize immune responses and could be one method of treatment, as well as reducing the risk of SARS-CoV-2. The administration of probiotic strains (*B. lactis*) to healthy elderly volunteers led to a significant increase in mononuclear leukocytes and activity of NK cells.⁴⁸ It is known that the composition of the intestinal microbiota, primarily the normobiota (bifidobacteria and lactobacilli), has a great influence on the effectiveness of lung immunity.⁴⁹ Experiments on animals have shown that in mice lacking gut microbiota, the ability to eliminate pathogens in the lungs was impaired.⁵⁰ Disruption of the gut microbiota (dysbiosis) with widespread use of antibiotics can also have an effect similar to that observed in population studies showing that increased use of penicillins, cephalosporins, macrolides and quinolones correlates with an increased risk of lung cancer.³²

The use of probiotics based on cultured *Lactobacillus* and *Bifidobacterium* has shown positive results as a result of anti-inflammatory and immunoregulatory reactions.⁵¹ It has been established that the introduction of probiotic bacteria (*L. rhamnosus*, *B. lactis*, *B. breve*) to experimental animals promotes the proliferation of Treg lymphocytes, suppressing inflammatory and allergic reactions.⁵²

Of particular interest for the treatment and prevention of COVID-19 is nitric oxide (NO), which is a key signaling molecule that acts as a modulator of the host's response to viral infections. Activation of the oxytocin receptor, which is expressed by endothelial cells of the pulmonary artery, has a vasolidating effect by stimulating the nitric oxide pathway.⁵³ Studies were performed on (CBAXC57B16)F1/c line mice using the bacterial cell-free supernatant of *B. bifidum* strain ICIS-202. The macrophages, obtained from the peritoneal cavity of the mice, were individually cultivated with the *B. bifidum* strain ICIS-202's culture medium cell-free supernatant for evaluation of its effect on nitric oxide production in the macrophages. The bifidobacteria's cell-free supernatant displayed a stimulating effect on NO/NO₂ produced by macrophages in vitro.⁵⁴ Tiso and Schechter⁵⁵ investigated nitric oxide (NO) and ammonia formation in cultures of *Escherichia coli*, *Lactobacillus* and *Bifidobacterium* strains grown at different sodium nitrate concentrations

and oxygen levels. As a result of the research, the authors suggested that the bacterial nitrate reduction to ammonia, as well as the related NO formation in the gut, could be an important aspect of the overall mammalian nitrate/nitrite/NO metabolism and is yet another way in which the microbiome links diet and health.⁵⁵

CONCLUSION

We now see a variety of COVID and long-COVID manifestations. Could this be related to innate individual oxytocin levels? And if so, can we correct oxytocin levels to prevent infection and its consequences?

It is clear that further research on oxytocin is needed. First of all, maybe in three main directions: 1) in clinical trials on the effect of oxytocin on immunity regeneration; 2) to investigate the effect of oxytocin with antibiotics, as this can help overcome the resistance of microbes to antibiotics and affect microbial biofilms; 3) search for strains of non-pathogenic bacteria that can increase the levels of oxytocin. This symbiotic relationship between the microbiota and the host through the “gut-brain axis” (via oxytocin) may hold further promise for COVID and long-COVID manifestations. The microbial regulation of the production of oxytocin in the experiment became possible with the introduction of a host of probiotic model microorganisms. It opens new potential prospects for microbiota. The connection of oxytocin with obesity, reproductive health, and innate immunity with the already cited materials gives reason to believe this neurohormone is a “universal global regulator” that determines new prospects for improving physical, intellectual and social health. The beneficial effects of oxytocin in regulating host homeostasis have not yet been fully elucidated, but this is a very interesting and promising topic for identifying new “nature-like” technologies.

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The care of patients with eye problems is being vastly enhanced by a £90,000 investment in new diagnostic equipment at University Hospitals of Morecambe Bay

