Oxytocin’s anti-inflammatory and proimmune functions in COVID-19: a transcriptomic signature-based approach

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19) respiratory disease, has triggered a worldwide pandemic infecting over 16 million people, killing over 600,000, and causing extensive economic and social disruption (6, 55a). COVID-19 is an infectious disease that is rapidly spreading and is associated with a significant mortality rate. While most cases show mild respiratory symptoms (fever, cough, shortness of breath, and fatigue), some progress to viral pneumonia, cardiovascular complications, and multiorgan failure, often associated with a “cytokine storm” (6, 18).

Cytokine storm is an escalating inflammatory response associated with COVID-19 disease severity and mortality (6, 18, 32, 50, 52). Cytokine storms are characterized by a severe inflammatory response triggering a series of immune responses that causes changes in lymphocytes, which can rapidly progress into acute respiratory distress syndrome (ARDS), damage to the alveolar lumen, often followed by multiorgan failure (6). Damage to T lymphocytes along with the cytokine storm are important factors that lead to exacerbations of patients’ cases. Severe cases are associated with decreased levels of total CD4+/CD8+ T lymphocytes compared with mild cases (52), while clinical improvement is associated with an increase in CD8+ T cells. Patients in the intensive care unit (ICU) display higher plasma concentrations of cytokines and chemokines [interleukin-6 (IL-6), IL-2, IL7, IL10 and TNF-α] compared with non-ICU patients (18). Today, there are no Food and Drug Administration (FDA)-approved drugs that are specifically targeting COVID-19 disease. Remdesivir and corticosteroids are showing promising results for severe cases, while no drugs have been suggested for hospitalized patients in early moderate phases. Repurposing existing drugs that can act on the adaptive immune response and prevent the cytokine storm in early phases of the disease is a priority.

In this report, we identify the neuropeptide oxytocin (OXT) as a potential candidate for an adjunct therapy to prevent or attenuate the cytokine storm associated with moderate COVID-19 cases. OXT is a highly conserved nonapeptide that is synthesized in the hypothalamus and is involved in reproduction and lactation. Intravenous OXT (i.e., Pitocin) has been used clinically for more than 50 yr to induce labor, and the safety and pharmacokinetic profile have been well established in the literature (34). Interestingly, OXT also has a regulatory role in immune and inflammatory responses. OXT has both 1) anti-inflammatory effects and 2) proimmune responses. Evidence from human studies shows that intravenous OXT administration reduces the proinflammatory cytokine response induced by bacterial endotoxin lipopolysaccharide (LPS), in-
including a reduction in TNF-α and IL-6 (7). Importantly, a recent study (2) found that OXT significantly reduced LPS-induced injury in the lungs as well as levels of interleukin (IL)-1β, IL-18, and IL-6. In vitro studies in human cells show that knockdown of the OXT receptor gene (OXTR) in cultured human skin cells exposed to UV irradiation led to increased oxidative stress and release of inflammatory cytokines (8). OXT has an immunosupportive and protective role in the heart and the lungs. The OXT receptor gene is expressed in the heart (13). It decreases mean arterial pressure (37, 39) and reduces the heart rate and the force of atrial contractions (11).

Here, we utilize a signature-based connectivity (25, 28, 35, 46) approach to provide supporting evidence for the hypothesis that OXT reduces inflammation and enhances adaptive immunity. We used “Omics” data sets available in the Library of Integrated Network-based Signatures (24, 25, 53) (LINCS) database to compare signatures from OXT-receptor agonist-treated cell lines versus gene knockdown signatures related to immune function inflammation, with the goal of identifying pharmacological interventions that may be repurposed for treating the COVID-19 cytokine storm.

METHODS

LINCS is a National Institute of Health initiative that aims to create a comprehensive network of molecular reactions in response to environmental and internal stressors (40). The LINCS project uses the L1000 assay, a gene expression array of 978 “hub” genes, to generate gene signatures. The L1000 genes are a reduced representation of the transcriptome, accounting for ~82% of the information content of the transcriptome (47). The LINCS database contains hundreds of thousands of gene signatures generated in human cell lines treated with chemical perturbagens (drugs) or following knockout or overexpression of individual genes. We accessed and analyzed LINCS gene signatures via the iLINCS portal (http://www.ilincs.org/ilincs/).

LINCS signatures were identified for the following drugs: carbococin, an OXT analog with purported anti-inflammatory and immune functions; desmopressin, an analog of neuropeptide vasopressin; lopinavir, a protease inhibitor used in the treatment of human immunodeficiency virus that may also have efficacy in the treatment of SARS-CoV-2; hydroxychloroquine, an immunosuppressant and anti-parasitic drug used to treat malaria and explored as a treatment for COVID-19; and bupropion, an antidepressant with no known antiviral properties used here as a negative control. Only genes with a log fold change (LFC) value of ≥ 0.85 or ≤ −0.85, indicating differential gene expression induced by the drug target compared with a corresponding control cell line, were included in a signature. To generate consensus gene signatures, L1000 genes with a minimum LFC ≤ −0.85 or ≥ 0.85 in expression were selected. Using LFC thresholds is an established method for selecting biologically relevant gene changes in transcriptomic data sets (5, 9, 14, 44). The LFC thresholds were selected to reduce excess noise or nonspecific gene data from the complete L1000 signature. The same thresholds were applied to generate all chemical perturbagen consensus gene signatures.

We downloaded signatures for each drug target with priority given to cell line signatures common to our drugs of interest. These drug signatures were searched against the LINCS consensus gene knockdown signatures (CGS) for the following immune cell markers: T cell markers CD40 and toll like receptor 9 (TLR9), T cell inhibitor CD46, macrophage marker ARG1, dendritic cell marker CD83, neutrophil activity marker carninoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), also known as CD66a, natural killer (NK) immune cells and other immune cell marker chemokine ligand 20 (CCL20), and transforming growth factor-β (TGF-β1), TGF-β receptor 1 (TGF-βR1), and TGF-βR2. CGS for inflammatory cytokines IL-6, IL-1β, and tumor necrosis factor (TNF) were also identified. We also included NF-κB, a transcription factor for a proinflammatory immune response. All immune cell markers and proinflammatory markers had minimum concordance scores ≥ 0.321 or discordance scores ≤ −0.321 with the drug target signatures (33, 40). The LINCS signature data were processed using a custom R Script (https://zenodo.org/record/3966718#.XyiZ2RNKhJs; supplemental material). Figure 1 summarizes our workflow.

Data and software availability. The scripts used to download and process data are available at https://github.com/AliSajid/OxyCovid-TNF.

RESULTS

In silico analysis of LINCS gene signatures showed that the OXT analog carbetocin induces similar patterns of gene expression as gene knockdown of inflammatory markers IL-6 (concordance score 0.74) and TNF (0.66) (Fig. 2, A and B). It had also positive concordance with gene knockdown of IL-1β

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and NFKB (0.64), suggesting that this drug may have potent anti-inflammatory effects (Fig. 2C). Lopinavir and carbetocin have comparable concordance scores to knockdown signatures for proinflammatory markers IL-1$\beta$ (0.50), IL-6 (0.67), TNF (0.73), and NFKB (0.48). This suggests that Lopinavir, a known antiviral explored as a treatment for COVID-19 (4), and carbetocin have similar anti-inflammatory effects. Hydroxychloroquine, which also has established anti-inflammatory properties (31, 41), induces discordant patterns of gene expression compared with IL-6 knockdown (0.35) and NFKB knockdown (−0.54), suggesting that this drug does not act on IL-6- and NFKB-related genes/pathways, although it may have a similar effect as knockdown of TNF (0.62) and IL-1$\beta$ (0.42) expression. Desmopressin has weak concordance patterns of gene expression compared with genes knockdown of IL-6 (0.39), IL1B (0.34), NFKB (0.40), and TNF (0.38).

Conversely, carbetocin also induces highly discordant patterns of gene expression compared with knockdown of immune cell response markers including T cell and macrophage cell markers CD40 (concordance score −0.5322) and ARG1 (−0.62) (Fig. 3, A and B), as well as markers TLR9 (−0.59) CEACAM (−0.54), CD83 (−0.58), CCL20 (−0.53), TGF-β1 (−0.55), and TGF-βR2 (−0.71) (Fig. 3C). These results support the hypothesis that carbetocin induces immune cell responsiveness. Carbetocin’s gene signature is also similar to the gene knockdown signature of CD46 (0.55), a T cell inhibitor, suggesting that carbetocin induces similar patterns of gene expression as knockdown of a T cell inhibitor. The hydroxychloroquine gene signature is only discordant to TLR9 (−0.50), ARG1 (−0.56), and TGF-β1 (−0.49), while Lopinavir’s gene signature is discordant to TLR9 (−0.60), CCL20 (−0.56), and TGF-β1 (−0.53). This suggests that carbetocin is more effective at inducing immune cell response than lopinavir or hydroxychloroquine, both of which have been explored for the treatment of COVID-19. As expected, bupropion and desmopressin gene signatures do not appear to have proimmune properties.

**DISCUSSION**

The COVID-19 crisis is an escalating public health concern, and despite several months of social distancing and lockdown, we are now witnessing another surge of positive cases and deaths. Therapeutics and drug repurposing are currently a high priority. OXT and OXT analogs provide an interesting angle to pursue as an adjunctive COVID-19 therapy.

In our study, we show that the OXT analog, carbetocin, has a signature similar to the knockdown signatures of IL-6, IL-1B, NF-κB, and TNF. These inflammatory markers and proteins

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**Fig. 2.** In silico analysis of transcriptional profiles of inflammation-related gene knockout (KO) cell lines in comparison with drug-treated cell line signatures. Maximum concordance scores are shown. A: the IL6 KO signature compared across different drug-treated signatures. B: the TNF KO signature compared across different drug-treated signatures. C: heatmap summarizing the concordance scores of TNF, IL6, IL1B, and NFKB KO cell lines with drug-treated cell lines.
are key factors that can trigger a COVID-19-associated cytokine storm. In vivo this can translate into a mechanism that can oppose the cytokine storm and the associated mortality. Carbetocin’s signature was similar to the one of Lopinavir, which is an antiretroviral being investigated in COVID-19 disease.

In addition, we found that the carbetocin gene signature is discordant to the knockdown signature of CD40, ARG1, CD83, CCL20, TGF-β1, and TGF-β2. While CEACAM (16) and CCL20 (29) are involved in chemotaxis, CD40, CD83, TGF-β2, and TLR9 are at least partially involved in T and B cell development, differentiation, and activation (17, 43, 51).

Interestingly, TLR9 recognizes viral double-stranded DNA (56, 57), while COVID-19 is a positive single-stranded RNA virus. However, TLR9 has also been reported to interact with Dengue virus (27), which is also a positive single-stranded RNA virus. Therefore, these further indicate that OXT may play a role in activating and modulating adaptive immunity. In addition, we found the carbetocin signature is similar to the knockdown signature of CD46.

CD46 is a complement regulatory product but also plays a role in T cell regulation. It induces the proliferation and differentiation of T regulatory 1 cells, which produce large amount of IL10 and inhibit T cell activation. Therefore, reducing CD46 expression may increase T cell activation (3, 30, 54, 55). Interestingly, while carbetocin’s signature profile was in support of a T cell activation hypothesis, Lopinavir and hydroxychloroquine were not. Given that severe cases of COVID-19 are characterized by a profile of increased plasma cytokine levels and decreased levels of lymphocytes, it is very promising that OXT, with the appropriate dosage, may reverse these pathways.

These findings corroborate our hypothesis that OXT is a potential anti-inflammatory and proimmune candidate for COVID-19 infectious disease. Oxytocin abolishes the sep sis-induced increase in TNF-α and protects against multiple organ damage (10, 20, 38). In humans, OXT treatment resulted in a reduction of endotoxin-induced increases in plasma cortisol, TNF- α, and IL-6, decreasing the cytokine activation caused by bacterial endotoxin (7). One mechanism by which OXT exerts its anti-inflammatory functions is through weakening the transition of macrophages, by acting on its receptors, into a proinflammatory mode, which results in an inhibition of NF-κB signaling (48). NF-κB, a
transcription factor for a proinflammatory immune response, is inhibited by OXT treatment, which leads to a decreased release of TNF-α (12).

OXT plays a role in inflammation and may have antimicrobial effects. OXT protects against organ damage during sepsis and aseptic global trauma in rats. Priming mesenchymal stem cells with OXT enhanced the cardiac repair in ischemia injury. It can help the body fight pathogens and increase the efficacy of antibiotics, for instance during the treatment of septic wounds (45). Also, microbiome-driven effects on accelerating wound healing in animals was shown to be mediated by an upregulation of OXT (42). Studies show that OXT treatment reduces cardiac apoptosis, fibrosis, and hypertrophy (21). The OXT system is downregulated in mouse models of diabetes, and OXT infusion can stimulate glucose uptake in cardiac stem cells and increase cell resistance to diabetic conditions (21). OXT has also been shown to stimulate cell proliferation in nontumor vascular cell lines and increases vascular thickness (23) and has been reported to reduce postmenopausal vaginal atrophy (22).

In addition, OXT has a protective role in the heart and in the lungs. At high concentrations, OXT leads to the stimulation of the atrial natriuretic peptide release (15). It has been proposed that OXT and vasopressin act in concert to control the body fluid and cardiovascular homeostasis (15). OXT seems to bind also to its vascular endothelial receptor of pulmonary artery and stimulate the release of calcium, which activates nitrergic oxide synthase and nitric oxide (NO) production and protein kinase C-dependent cellular proliferation response, leading to vascular dilatatory effects (49). Previous studies have reported that NO compounds inhibit SARS-coronavirus infection in vitro and that NO inhibits viral replication in severe acute respiratory syndrome coronavirus (1, 26).

Thus, OXT could be potentially an interesting target to investigate in translational and clinical settings in the domain of infectious disease. It is a safe drug that has been used extensively in hospitals in its intravenous form (Pitocin). In contrast to glucocorticoids, it promotes adaptive immune responses and has protective properties for the heart and the lung. Pitocin is an FDA-approved drug that can be repurposed for use as an adjunctive therapy for infectious diseases. Conducting translational and clinical studies on the role of OXT in reducing inflammation and symptom severity in infectious diseases is needed. Understanding the mechanisms by which OXT or the OXT system can be a new immune target is crucial. During clinical trials, safety profiles need to be also assessed; that includes heart rate monitoring (given the potential side effects on heart rhythm) and hyponatremia. Safety and efficacy of intravenous oxytocin in hospitalized patients with COVID-19 remain to be assessed.

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AUTHOR CONTRIBUTIONS

E.A. conceived and designed research; S.M.O., C.B.M., K.U.-M., and R.E.M. participated in the design of the research/analysis; A.S.I. and H.E. analyzed data; E.A. and A.S.I. interpreted results of experiments; A.S.I. and J.F.C. prepared figures; E.A. and S.M.O. drafted manuscript; X.W., K.U.-M., and R.E.M. edited and revised manuscript; A.S.I., S.M.O., J.F.C., X.W., H.E., C.B.M., K.U.-M., R.E.M., and E.A. approved final version of manuscript.

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DISCLOSURES

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405 OXYTOCIN AND COVID-19
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