Review Article

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Oxytocin, the panacea for long-COVID? a review

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Abstract

Objectives: In this hypothesis paper we explore the underlying mechanisms for long-COVID and how the oxytocinergic neurones could be infected by SARS-CoV-2 leading to a reduction in plasma oxytocin (OXT). Furthermore, we aim to review the relevance of OXT and hypothalamic function in recovery from long-COVID symptoms and pathology, through exploring the pro-health effects of the OXT neuropeptide.
Methods: A review of published literature was surveyed using Google Scholar and PubMed.
Results: Numerous experimental data can be shown to correlate with OXT and long-COVID symptoms and conditions, thus providing strong circumstantial evidence to support our hypothesis. It is postulated that the reduction in plasma OXT due to acute and post-viral damage to the hypothalamus and oxytocinergic neurones contributes to the variable multi-system, remitting and relapsing nature of long-COVID. The intranasal route of OXT application was determined to be most appropriate and clinically relevant for the restoration of oxytocinergic function post COVID-19 infection.
Conclusions: We believe it is imperative to further investigate whether OXT alleviates the prolonged suffering of patients with long-COVID. Succinctly, OXT may be the much-needed post-pandemic panacea.

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Introduction

The post-infection long term effects of COVID-19, "long-COVID" for short, is emerging as a post-viral, multi-system, remitting and relapsing illness similar in some respects to Chronic Fatigue Syndrome (CFS) and its variants. The global medical community is seeking effective drug treatments for both acute COVID-19 and for long-COVID. Principally FDA-approved drugs ivermectin, hydroxychloroquine and azithromycin –separately or in combinations- significantly improved COVID-19 outcomes via inhibiting the replication of SARS-CoV-2 [1a-h]. Moreover vitamin D [2], melatonin [3], and oxytocin (OXT) [4a–b] are proposed for acute COVID-19 therapy as the focus of this paper. Markedly proimmune and anti-inflammatory IV oxytocin infusion could counteract hyperinflammation in COVID-19 infected patients. Relatively recent data demonstrate the anabolic effect of oxytocin on bone micro-architecture. Conversely common side effects of oxytocin administration may include erythema at the site of injection, intensified contractions, more frequent contractions, nausea, vomiting, stomach pain, and loss of appetite. Serious adverse effects that require monitoring after oxytocin administration include cardiac arrhythmias, seizures, anaphylaxis, confusion, hallucinations, extreme increase in blood pressure, and blurred vision [4c,d].

The current pandemic of severe acute respiratory distress syndrome is attributed to the virus SARS-CoV-2; previous viral causes of severe acute respiratory distress syndrome include SARS-CoV and MERS-CoV [5]. The exact mechanism, by which SARS-CoV-2 putatively causes COVID-19, and all its multiple-system pathologies, is the source of unprecedented interest and research. The aetiopathogenic link between the virus SARS-CoV-2 and the disease COVID-19 has not been fully elucidated; there is much we do not know and therefore much we need to learn. It would be wise to move forward with humble scientific rigor and not presume what we cannot predict. Indeed, it is possible that COVID-19 may be an endpoint of a complex combination of genetic and epigenetic vulnerabilities [6] as well as physiological and environmentally induced

vulnerabilities [7]. For example, some of the pathology and severity associated with COVID-19 and/or long-COVID may be due to reactivation of latent viruses such as Epstein–Barr virus [8] and cytomegalovirus (CMV) [9].

Hopefully hidden factors can be brought to light via an appropriate scientific method that incorporates sufficient data and unbiased critical analysis from multiple points of view [10]. What will truly be identified as a cause and what will be identified as merely an association needs to be made clear. We await the clarifying light of time. Meanwhile the COVID-19 pandemic has accelerated research and understanding of coronaviruses, and this may be one positive result that we can take from our time under its shadow. Whilst we analyze the present data and await future answers, we can explore the published scientific literature of the past for strong clues to help with this pandemic puzzle.

Viruses such as SARS-CoV [11], CMV [12] and the Human Immunodeficiency Virus (HIV) [13] are known to infect the hypothalamus. Also, viral infection can also down-regulate OXT receptor expression, thus providing key viral pathology enhancement mechanisms [14]. OXT is a potent nine peptide neurohormone produced primarily in the hypothalamus, where it is transported to the posterior pituitary gland and released into the systemic circulation. OXT has a broad range of pro-health and immune system enhancing effects throughout the entire body [15]. Some probiotic gut bacteria [16] are known to positively modulate OXT production via the vagus nerve. This pathway suggests a neuroendocrine based health enhancing opportunity involving OXT that could be applied to long-COVID patients and help reverse viral damage via neuroendocrine re-activation of the parasympathetic system. Our paper compares long-COVID pathology with OXT mechanisms in light of advances in neuroendocrinology and the proposed use of OXT as an acute antiviral for COVID-19 [4, 17–19]. We elaborate the literature of OXT mechanisms that may be implemented in treating long-COVID symptoms and conditions, and then discuss therapeutic relevance and methods of administration.

Long-COVID symptoms

Long-COVID pathologies may have always been with us, hiding under the surface, going by other names such as Chronic Fatigue Syndrome-like illnesses, idiopathic diseases and even psychiatric illnesses [20]; the overlap between long-COVID and some of these states make them indistinguishable from long-COVID. Also, it does seem that some factors associated with more severe COVID-19 such as old age and co-morbidities also increase the risk of long-COVID [21]. At present, globally defined diagnostic criteria for long-COVID have not been agreed upon. Indeed, the number of proposed symptoms and signs may be greater than 50 and the frequency of this diagnosis may be as high as 80% if broad and generous criteria are used (e.g. one symptom for a duration of two weeks) [22]. However, if stricter criteria for symptoms and duration are applied this may drop significantly to around 5% or lower [21].

It will be interesting to see, with hindsight, whether the current criteria are too broad and too generous to properly define long-COVID. For example CFS which has overlapping symptoms and signs has more rigid criteria as defined by the Centers for Disease Control and Prevention (CDC): “three symptoms and at least one of two additional manifestations”, “for six months” [23].

Some of the numerous symptoms and signs that have been attributed to long-COVID include, in brief and not exhaustively [21,22]: general fatigue, weakness, and sleep disorders; continuing headaches; protracted loss or change of smell and taste; psychiatric illnesses; inflammatory disorders such as myalgia; respiratory, cardiovascular, gastrointestinal, hepatic and renal dysfunction; and skin rashes.

The symptoms and conditions are legion and seem to be increasing as more data accumulates.

OXT vs. long-COVID symptoms and related disorders

OXT has beneficial mechanisms for treating disorders involving fatigue, weakness, and sleeplessness; symptoms seen in long-COVID. Brain inflammation due to mitochondrial, mast cell [24] and vagus nerve [25] dysfunction have been implicated as contributing factors behind CFS. OXT is known to mediate health enhancing effects via the vagus nerve [16]. It can inhibit mast cell degranulation in rats [26], and positively modulate both energy metabolism [27] and mitochondrial function [28]. OXT ameliorates weakness as it can regenerate muscle [29] and reduce age related declines in strength [30] in mice. OXT can induce release of the “sleep hormone” and potent anti-oxidant melatonin [31] in rats, probably via a breakdown product of OXT, melanocyte-inhibiting factor (MIF-1) [32]; it is reasonable to speculate that this mechanism is presently functional within humans.

OXT is neuroprotective and stimulates neurogenesis in rats and mice [33, 34]. In rats it can protect against diabetic neuropathy [35] and help recovery of damaged nerves [36].

OXT has a strong role in taste and smell, in both murine [37, 38] and human olfactory functions [39]. Stimulating neurogenesis even under stress [40] could affect the recovery of these senses after loss during acute COVID-19 infection. There is growing data to show the importance of OXT in depression and other areas of mental health [41]. It appears to have a role in anxiety and post traumatic stress [42] and has been highlighted as of great significance in terms of the psychological sequel of COVID-19, isolation and social distancing [43, 44].

OXT has numerous anti-inflammatory properties which may ameliorate the generalized inflammation seen in COVID-19 [4, 45, 46]. It has been shown that female patients suffering from fibromyalgia, a neuropathic pain disorder, have lower OXT levels [47]. OXT modulates pain and has been used as a treatment for headaches [48, 49]. OXT is known to have anti-pain and anti-nociceptive mechanisms [50–52] some of which may be through cannabinoid [53], opioid [53, 54] and vanilloid (capsaicin) [55] receptors.

Respiratory system damage is one of the major complications of COVID-19 and remains a risk for long-COVID sufferers. OXT can protect against lung inflammation [56] and damage [57]. OXT is known to increase nitric oxide [58, 59] which is present in the airways [60] and improves oxygenation [61], healing and repair [62] and has antiviral properties against SARS-CoV [63] therefore presumably against SARS-CoV-2.

OXT is considered a substantial cardiovascular hormone [64], associated with cardioprotective propensities and supportive mechanisms that combat obesity [65], atherosclerosis [66], inflammation and cardiac failure [67]. It has been highlighted as a potential cardioprotective agent for COVID-19 [68], and may serve well to ameliorate long-COVID cardiovascular symptoms.

OXT has been shown to be lower in children with recurrent abdominal pain [69]. Elevated levels of the neuropeptide improve symptoms of irritable bowel especially when associated with depression [70, 71] as well as reduce colonic inflammation [72, 73] and stress-aggravated colitis [74] in mice and rats, and could serve to reduce the gastrointestinal disturbances seen in long-COVID. OXT has been shown to rejuvenate the liver [29] and to protect the kidney from inflammation [75] in rats. It has been shown to modulate the stress responses in human skin cells [76] and to improve skin healing [77, 78] in rats. Mast cells are important in the development of skin rashes, and OXT has been shown to inhibit mast cell degranulation [26]. OXT has positive effects on stem cells [79] which may be of great help in overall recovery from COVID-19 and prevention of long-COVID.

In effect, this explicit interplay of therapeutic mechanisms could help treat acute COVID-19 and long-COVID. In addition, COVID-19 patients who have had prolonged periods in intensive care units may benefit from OXT's potent therapeutic effects; as it improves muscle atrophy, post-traumatic stress, wound healing and possibly pressure ulcers [77, 78].

Hypothetical OXT dysregulation in COVID-19 and long-COVID

Previous research into viral infection of the hypothalamus and OXT neurons provides convincing data regarding the ability for viruses to affect OXT. An animal study has shown that the antiviral immune response is, at least in part, regulated by the hypothalamus-pituitary-adrenal axis [80]. Further, viral infection of the hypothalamus has been identified, including in SARS [11] HIV [13] and Zika virus [81]. A study reported that an HIV patient was shown to have CMV infection in the hypothalamus, expressing a reduction in vasopressin neurons leading to diabetes insipidus, and also a significant reduction in OXT neurones [12]. Hypopituitarism can be caused by viral infection and this has been identified for Hantaviruses [82, 83]. In terms of coronaviruses, SARS-CoV can infect hypothalamic neurons [11] and this can lead to hypothalamic dysfunction [84]. In addition to the reduction in OXT output, viral infection has also been shown to down regulate OXT receptors [14]. Another possible mechanism of OXT dysregulation is via vagus nerve dysfunction. The vagus nerve can be considered part of the OXT pathway and vagus nerve stimulation increases OXT [85]. In addition, the gut microbiome can increase OXT via the vagus nerve [16]. It has been proposed that chronic fatigue syndrome is due to vagus nerve infection [25] and indeed it has been shown that viral infection of the vagus nerve can occur [86, 87]. More specifically, it is plausible that the vagus nerve can be infected by SARS-CoV-2 [88].

Therefore, the mechanism of SARS-CoV-2 infection leading to long-COVID is hypothesized to be in the suggested order of consecutive events (Figure 1):

(1) SARS-CoV-2 infects the hypothalamus and specifically OXT neurons as both ACE2 and TMPRSS2 are most likely co-localized on OXT neurons [89].
(2) This will lead to cytopathic effects on the OXT neurons which will reduce their function or possibly lead to some degree of neuronal death.
(3) Therefore, OXT production will be reduced leading to decreased systemic plasma OXT levels.

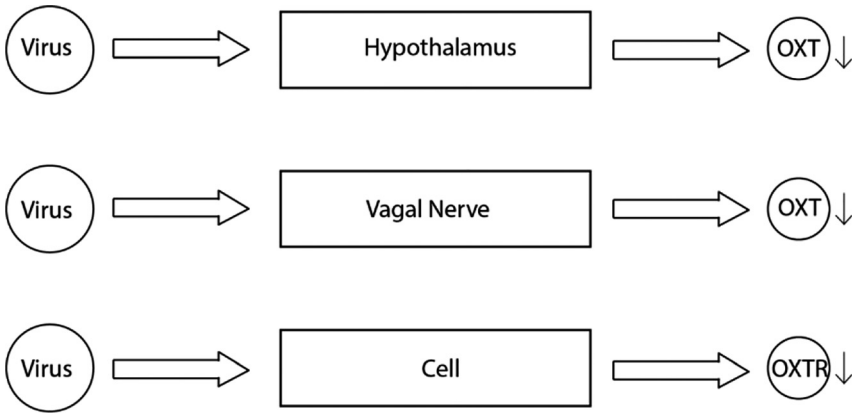

Figure 1: Proposed routes of viral infection leading to oxytocin (OXT) and OXT receptor (OXTR) down-regulation.

(4) In addition, down-regulation of OXT receptors would lead to further OXT system dysfunction.
(5) Vagus nerve dysfunction will lead to an additional OXT dysfunction.
(6) This will most likely lead to a significant reduction in the potent protective and healing effects of OXT and subsequently exacerbate the effects of long-COVID.

This seems plausible but there are some difficulties and limitations to the hypothetical mechanism for reduced OXT in COVID-19. At least seven come to mind.

First, proof of SARS-CoV-2 infection of the nervous system, as hypothesized above, needs to be acquired from sources such as post-mortems.

Second, measurement of plasma OXT is technically demanding [90]. In addition, OXT release is not stable and constant; it is pulsatile, being released approximately every half hour [91].

Third, OXT can stimulate vasopressin receptors and vice versa [92], therefore, assessment of OXT function needs to take into consideration vasopressin to some extent.

Fourth, OXT receptor function cannot be assessed by measuring the OXT peptide in the plasma, which means that even with normal or high levels of plasma OXT the pathway may still be dysfunctional.

Fifth, this does not take into account epigenetic influences on OXT function [93].

Sixth, OXT is produced and released from other tissues of the body such as muscle [94] and it is unknown how this affects overall OXT levels and function.

Seventh, and most importantly, to our knowledge, plasma OXT levels have not been directly measured in COVID-19 patients. However, Liu et al. investigated the association between the nasopharyngeal microbiome and metabolome in COVID-19 patients and identified down-regulation of the OXT signaling pathway; thus providing indirect but tantalizing evidence of reduced OXT levels [95].

Social isolation reduces OXT [43]. The pandemic has led to a significant disruption in normal social interaction [96]. If OXT is indeed a treatment for long-COVID then this has implications for social isolation measures. It may be that social isolation and thus reduced OXT levels, can be mitigated to some extent by actions that raise endogenous production of OXT, such as increasing aerobic capacity [97], singing [98], touch [99, 100], sex and bonding [101]. Interestingly, vitamin D probably up-regulates production of OXT and up-regulates the OXT receptor [102] and melatonin has been shown to increase nocturnal OXT release [103]. Maybe simple everyday actions such as getting sufficient sunlight (vitamin D) and sleep (melatonin) are part of the foundation for healthy OXT function, and by extrapolation, important for long-COVID recovery.

If there is incapacitated endogenous OXT output, then treatment with exogenous OXT may ameliorate the aforementioned ailments. It would be prudent to begin administration of OXT at low doses, on a gradually increasing scheme if required and if adverse effects are not evident. However, a limitation is that the half-life of OXT is in the range of minutes, up to approximately 30 min [4]. Another limitation is that the usual route, intravenous (IV) exogenous administration, would not be easily available at home. Acute high doses of exogenous OXT can cause unwanted cardiovascular effects [104] and can lead to down-regulation of the OXT receptor [105]. Higher than optimal levels of a hormone or a drug can have negative effects (endogenous or exogenous, natural or synthetic). Indeed, high levels of endogenous OXT can be released during stress responses [106] but chronic administration of exogenous OXT can also induce anxiety [107].

In addition, OXT does not cross the blood brain barrier passively [108], therefore IV exogenous administration is

unlikely to reach the brain. This limits its positive effects on neuroinflammation and neuroprotection. Also, this reduces the possibility of stimulating endogenous central release of OXT [109].

Interestingly, avoiding the IV route may actually be advantageous as OXT is known to be pulsatile in its release and therefore intermittent administration, such as via intranasal spray, may be more effective. Intranasal OXT is well tolerated and has a good safety profile; however it is not heat-stable and requires refrigeration. A likely benefit is that this mode of delivery can reach the brain and can probably stimulate central release [109].

More recently a dry inhaler has been available which does not require refrigeration. Inhaled OXT is also unlikely to be able to cross the blood brain barrier. However, it would be able to reach the lungs directly which would be advantageous in reducing any ongoing lung pathology. Unfortunately, there is little data on the most effective dose of intranasal and inhaled OXT.

Conclusions

This paper has compared the symptoms of long-COVID with evidence of OXT's use for these symptoms within other disorders. We have identified a potential mechanism for long-COVID that involves OXT dysfunction. The circumstantial evidence provided is broad and correlates with many areas of long-COVID symptoms and conditions. However, the evidence has its limitations; much of the data is experimental and based on animal models and thus have not been confirmed through formal clinical trials in humans. The following data is incomplete or missing from the literature, and there is need for further clinical research:

(1) OXT plasma levels for different demographic and susceptibility groups
(2) OXT plasma levels in acute COVID-19 patients
(3) Periodic monitoring of OXT plasma levels over days to weeks

It may be advantageous to focus treatment on patients with low OXT, identified through demographic and predisposing risk factors, and by direct measurement of plasma OXT. Raising OXT levels in the acute phase either by endogenous induction or exogenous administration may help mitigate the frequency and severity of long-COVID due to OXT's multi-target protective mechanisms.

Ultimately, the "love hormone", OXT, may be our great hope: it could be the post-pandemic panacea that has been hiding in plain sight.

Highlights

- A comparison of long-COVID pathology with OXT therapeutic mechanisms was performed
- Following advances in neuroendocrinology and proposed use of OXT as an acute antiviral for COVID-19; we elaborate OXT mechanisms in treating long-COVID, via therapeutic relevance and methods of administration.
- Further demonstration of OXT levels for different demographic and susceptibility groups, acute levels in COVID-19 patients and periodic monitoring of OXT levels is warranted.

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