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BRIEF REPORT

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Can intravenous oxytocin infusion counteract hyperinflammation in COVID-19 infected patients?

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ABSTRACT

Objectives: Based on its well-documented anti-inflammatory and restorative properties we propose trials with the natural hormone oxytocin for treatment of hospitalised Covid-19 patients.

Methods: We searched for, retrieved, and commented on specific literature regarding multiple functions of oxytocin with a special focus on its modulation of inflammatory, immune, and restorative functions.

Results: Available data gathered in animals and humans support the anti-inflammatory properties of oxytocin. The multiple anti-inflammatory effects of oxytocin have been demonstrated in vitro and in vivo in various animal models and also in humans in response to intravenous infusion of oxytocin. Furthermore, oxytocin has been documented to activate several types of protective and restorative mechanisms and to exert positive effects on the immune system.

Conclusions: In addition, to being anti-inflammatory, it may be hypothesised, that oxytocin may be less suppressive on adaptive immune systems, as compared with glucocorticoids. Finally, by its restorative effects coupled with its anti-stress and healing properties, oxytocin may shorten the recovery period of the Covid-19 patients.

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Oxytocin; inflammation; anti-inflammatory; immune system; restorative; Covid-19; clinical trials

Introduction

The world is presently experiencing an unprecedented pandemic outbreak with a new coronavirus, the SARS-CoV-2, giving rise to the Covid-19 disease. Presently, the incidence of the disease is stable in most European countries, but the pandemic appears to remain in a progressive phase in United States, South America, India and some third world countries. Not only is the virus highly infective, but also the mortality of the disease is not negligible, particularly in elderly people and individuals with a generally poor health status. The fatal cases are frequently linked to an exaggerated inflammatory reaction to the virus. In the most severe cases, the patients develop acute respiratory distress syndrome (ARDS) characterised by impaired respiration due to lung edoema and alveolar collapse. Hyperinflammation is an important factor in the pathogenesis of ARDS where the inflammation may progress towards a systemic cytokine storm that may cause multiorgan failure (Zhang et al. 2020).

Apart from the hyperinflammation the cellular immune system may be severely affected in the advanced stages of the disease with low T-cell and NK-cell counts. Different types of anti-inflammatory drugs have been introduced in the treatment of critically ill Covid-19 patients to counteract the inflammatory damages of both the organs and the immune system (Zhang et al. 2020). However, such an approach is always a delicate matter as it may further weaken the capability of an already impaired immune system to fight the disease.

More recent data show that prior to the development of ARDS, many patients display hypoxia which may be due to a dysfunctional pulmonary perfusion pattern caused by a disrupted endothelial function (Gattinoni et al. 2020). Hyper-perfusion of hypoxic areas of the lungs may lead to an impaired oxygenation of the blood despite a relatively well-preserved ventilatory capacity. Severe cases of hypoxaemia which may appear at relatively early stages of the Covid-19 disease constitute a bad prognosis, as a blood oxygen saturation $<90\%$ is a strong predictor of mortality (Xie et al. 2020). In such cases, aggressive therapy including respiratory aid is mandatory.

In this urgent situation, immediately available and safe substances with a high potential to antagonise

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inflammation and to restore the endothelial function are called for. Oxytocin is a hormone which promotes uterine contractions during birth but is also involved in the regulation of social behaviour and stress reactions. However, more recently oxytocin has been recognised also to play an important role in the modulation of inflammatory responses and the stimulation of multiple tissue protecting and restorative mechanisms (Buemann and Uvnäs-Moberg 2020).

The use of oxytocin for the treatment of Covid-19 has recently been proposed in a short communication referring to its different protective and anti-inflammatory effects (Soumier and Sirigu 2020). Furthermore, a positive impact of oxytocin against Covid-19 has been suggested based on the clinical observation that morbidity and mortality of the Covid-19 infection appear to be more pronounced in groups of individuals known to have low levels of oxytocin, and thereby supposedly a low function of oxytocin (Diep et al. 2020). In the present paper, we further argue for a potential of oxytocin to alleviate the course of a SARS-CoV-2 infection by referring to several protective effects of oxytocin demonstrated *in vitro* and in animal and human studies.

In clinical practice oxytocin infusion is widely used to promote uterine contractions during labour and to inhibit postpartum bleedings (Uvnäs-Moberg et al. 2019). Both the pharmacokinetics of oxytocin as well as its safety profile are well described (Nielsen et al. 2017). Intravenous (i.v.) infusion of oxytocin has also been tested in human experiments within various contexts including expressions of inflammation in a study performed on healthy men (Table 1).

In the present work we further investigated the possible potential of oxytocin to mitigate the course of SARS-CoV-2 infection. As part of our literature retrieval we performed a search in PubMed applying the search profile:

> (Oxytocin[Title]) AND ((inflammation[Title/Abstract]) OR (inflammatory[Title/Abstract]) OR (macrophage[Title/Abstract]) OR (immune[Title/Abstract]) OR (lymphocyte[Title/Abstract]) OR (covid[Title/Abstract]) OR (injury[Title/Abstract]) OR (damage[Title/Abstract]) OR (endothelial[Title/Abstract]) OR (endothelium[Title/Abstract]) OR (cytokine[Title/Abstract]) OR (PPAR[Title/Abstract]) OR (TNF[Title/Abstract]) OR (protective[Title/Abstract])).

In this search, we retrieved 468 articles of which 35 are cited in the present paper. The remaining were excluded as review articles or having a focus on behaviour, pain, atherosclerosis, diabetes, energy balance or reproduction.

Anti-inflammatory effects of oxytocin

Numerous in vitro and in vivo animal studies documented a capacity of oxytocin to exert anti-inflammatory and anti-oxidative effects by a plethora of pathways summarised in Box 1 involving direct receptor mediated mechanisms (Tables 2 and 3). Furthermore, observations in rats of an increased plasma oxytocin level during early stages of sepsis may point to a down-regulatory role of oxytocin on e.g. the innate (unspecific) immune system (Oliveira-Pelegrin et al. 2013).

Table 1. Human studies using i.v. infusion.

Reference	Study group	Administration	Achieved max plasma concentration	Assessed outcome
Clodi et al. (2008)	10 healthy younger men	600 μIU/kg/min over 90 min. 5,4 μg in total at 60kg	170 pg/ml ∼ approx. 4x basal level	Attenuated response of diff. inflammatory cytokines and body temp. to bacterial toxin.
Nielsen et al. (2017)	33 healthy postmenopausal women	Single dose of oxytocin, 10 IU ∼ 16,7 μg or infusion of 10 IU in 5 hours	>1000 pg/ml or Approx. 130 pg/ml	Pharmacodynamic parameters
Burt et al. (1963)	20 healthy post-labour women.	Single dose of oxytocin, 10 IU ∼ 16,7 μg per kg body weight	not reported	Plasma: NEFA ↑, glucose ↓
Hollander et al. (2003)	14 male + 1 female with autism spectrum disorders.	14 IU in total during 4h incremental protocol	Not reported	Behavioral parameters Increased social competence
Legros et al. (1984)	6 younger men	0,016 IU/min over 30 min ∼ 0,8 μg in total	29,5 pg/ml	Plasma ACTH ↓, cortisol ↓
Page et al. (1990)	6 lean younger men	0,111 IU/min over 4h ∼ 44,5 μg in total	133,6 pg/ml	Ablated response of ACTH to CRH. Other adenohypophysal hormones unaffected
Ohlsson et al. (2004)	14 healthy women	20–40 mIU/min over 90 min ∼ 3–6 μg in total.	not roproted	Colonic antegrade peristaltic contractions ↑

Table 2. Animal studies on the anti-inflammatory, antioxidative and restorative effects of oxytocin.

Reference	Study group	Stimulation	Oxytocin manipulation	Organ	Assessed outcome
İşeri et al. (2005a)	Rats	Caecal ligation puncture induced sepsis	2 × 1 mg/kg subcutaneously	Colon, uterus, and liver	Myeloperoxidase (Neutrophile infiltration) ↓ TNF-α plasma levels ↓ Glutathione ↑ Collagen levels in organs ↓
İşeri et al. (2005b)	Rats	Acetic acid in colon	0.5 mg/kg 2x daily for 4 days.	Colon	Tissue damages ↓ Malondialdehyde (Lipid peroxidation) ↓ Glutathione ↑ Myeloperoxidase (Neutrophile infiltration) ↓ TNF-α ↓
Jankowski et al. (2010)	Rats	Ischaemia/reperfusion	25 ng/kg/h subcutaneously for 3 or 7 days	Heart	Neutrophil infiltration ↓ TNF-α and IL-6 ↓ Necrosis, apoptosis and fibrosis ↓ Proliferating cell nuclear antigen (PCNA) ↑ Post-infarction contractability ↑
Biyikli et al. (2006)	Rats	E. coli into the renal medulla	1 mg/kg/day intraperitoneally	Kidney	TNF-α ↓ Neutrophile infiltration ↓ Glutathione ↑ Malondialdehyde (Lipid peroxidation) ↓
Petersson et al. (2001)	Rats	Carrageenan injection	One dose 100 μg/kg subcutaneously	Hind paw	Edoema ↓ comparable to that of dexamethasone.
Abood and Alghamdi (2017)	Rats	None (old compared to young)	3 mg/kg body weight intraperitoneally for 5 days	Whole body	Serum IL-1β, IL-6 and TNF-α ↓ Particular TNF-α went down to a level comparable to that of the young.
Rashed et al. (2011)	Rats	Cisplatin injected intraperitoneally	Single dose of 1 mg/kg intraperitoneally.	Kidney	Gene expression of NADPH oxidase and P38 MAPK ↓ GSH and SOD ↑ Histology normalised
Tang et al. (2019)	Mice	Dextran sulphate sodium salt in drinking water	OXR knock-out of myeloid cells	Intestine	Epithelial destruction ↑, Pro-inflammatory phenotype of macrophages ↑.
Garrido-Urbani et al. (2018)	Obese mice	None	50 μg/day subcutaneously daily for 2 weeks	Adipose tissue	TNF-α ↓
An et al. (2019)	Mice	LPS injected intraperitoneally	0.1 mg/kg intraperitoneally	Lung	Pro-inflammatory cytokine and NF-κB gene expression in lung tissue ↓ Index of edoema ↓ Pathological injury ↓ Myeloperoxidase as a marker of neutrophil infiltration ↓
Lin et al. (2019)	Rats	Heat stress	5-80 μg/kg intravenously	Lung	Index of edoema ↓ Pathological injury ↓ Myeloperoxidase (neutrophil infiltration) ↓ Markers of oxidative stress ↓ Time of survival ↑
Chen et al. (2015)	Mice and rats	Whole body irradiation (10 Gy) or Dextran sulphate sodium salt in drinking water	1 mg/kg intraperitoneally daily for 2 weeks.	Intestine	Protection of mucosal structure (villi and crypts) and primordial cells with both treatments.
Düşünceli et al. (2008)	Rats	Ischaemia/reperfusion	500 μg/kg 24h, 12h before ischaemia and immediately before reperfusion	Liver	Serum TNF-α and liver enzymes ↓ Tissue malondialdehyde (Lipid peroxidation) ↓ Myeloperoxidase (neutrophil infiltration) ↓ Fibrosis ↓
Houshmand et al. (2009)	Rats	Ischaemia/reperfusion	0.0001, 0.001, 0.01, 0.1 or 1 μg intraperitoneally.	Heart	Infarct size ↓ Plasma levels of creatine kinase-MB isoenzyme (CK-MB) and lactate dehydrogenase (LDH) ↓ Greatest effect at 0.1 μg.
Senturk et al. (2013)	Rats	Ischaemia/reperfusion	0.5 μg/kg intraperitoneally	Bladder	Tissue malondialdehyde (Lipid peroxidation) ↓ GSH ↑ Mast cell count in mucosa ↓ Improved histopathology

(*continued*)

Table 2. Continued.

Reference	Study group	Stimulation	Oxytocin manipulation	Organ	Assessed outcome
Stadnikov et al. (2011)	Albino rats	Intratracheal injection of E. coli bacteria after 11 days foot-shock stress	0,02 IU/mL intramuscularly daily for 7 days	Lung	Number of apoptotic cells ↓ Bcl-2, clara cell protein (CC-16) ↑
Tuğtepe et al. (2007)	Rats	Ischaemia/reperfusion	1 mg/kg intraperitoneally 30 min prior to ischaemia and immediately before reperfusion	Kidney	Serum TNF-α ↓ Tissue malondialdehyde (Lipid peroxidation) ↓ Tissue GSH ↑
Akdemir et al. (2014)	Rats	Ischaemia/reperfusion	80 IU/kg intramuscularly	Ovaria	Tissue malondialdehyde (Lipid peroxidation) ↓ Edoema and follicular degeneration ↓
Erkanli et al. (2013)	Rats	Ischaemia/reperfusion	0.5 ml/kg intraperitoneally	Skeletal muscle	Tissue malondialdehyde (Lipid peroxidation) ↓ Number of apoptotic cells ↓ GSH ↑ Improved histopathology
Hekimoglu et al. (2013)	Rats	Renal ischaemia/ reperfusion	500 μg/kg subcutaneously	Liver	Tissue malondialdehyde (Lipid peroxidation) ↓ Improved histopathology
Kobayashi et al. (2009)	Rabbits	MI by 30 min coronary artery occlusion	10 mg/kg subcutaneously daily for 5 days	Heart	Infarct size after 14 days ↓ Myocardial activation of prosurvival signals (phosphorylation of STAT3, ERK, eNOS) after 2 days ↑ Expression of the anti-apoptopic and anti-necrotic factor Bcl-2↑ Expression of angiogenetic factors VEGF ↑ Expression of the antifibrotic factor MMP ↑
Polshekan et al. (2019)	Rats	30 min ischaemia / 100 min reperfusion	0.12 nmoles/min perfused for 40 min pre-ischaemia or 15 min post-ischaemia	Perfused isolated heart	Number of apoptotic cells ↓ Infarct size ↓ Lactate dehydrogenase activity ↓ Arrhythmias ↓
Karelina et al. (2011)	Mice	Ischaemia/reperfusion	20 ng intracerebro-ventricular daily for 3 days	Brain	Cerebral IL6 ↑ Infarct size after 3 days ↓
Zhang et al. (2007)	Rats	Ischaemia/reperfusion	20, or 100 μg intraperitoneally	Stomach	Mucosal damage ↓ Gastric pH ↑ Gastric fluid output ↓
Erbaş et al. (2013)	Rats	Caecal ligation puncture induced sepsis	0.8 mg/kg intraperitoneally	Nerve function	EMG deteriorations ↓ TNF-α plasma levels ↓ Plasma malondialdehyde (Lipid peroxidation) ↓
Işeri et al. (2008)	Rats	Skin burns	5 μg/kg subcutaneously shortly after and 24h following treatment	Stomach and skin	Damage on skin and gastric mucosa ↓ Neutrophile infiltration in stomach ↓ Malondialdehyde (Lipid peroxidation) in stomach ↓ Serum TNF-α ↓
Vitalo et al. (2009)	Rats	Skin burns	10 mg/kg intraperitoneally	Skin (inflicted wounds)	Improved healing
Xiong et al. (2020)	Rats	Ischaemia/reperfusion	0.1 μg/kg, intraperitoneally prior to I/R	Heart	Infarction size ↓ Arrhythmias ↓ Improved hemodynamics Mast cell degranulation ↓
Yuan et al. (2016)	Mice	LPS injected intraperitoneally	Nasal administration	Brain	Inflammatory morphology changes of microglia cells in prefrontal cortex ↓ Protein and gene expression in prefrontal cortex of TNF-α, IL-1β, iNOS and COX-2↓
Sorg et al. (2017)	Mice	Dorsal surgical wound	1 mg/kg or 10 mg/kg intraperitoneally	Skin (inflicted wounds)	No effects of oxytocin on healing processes
Erbas et al. (2014)	Rats	Cisplatin 2 mg/kg 2x per week for 5 weeks	200 μg/kg intraperitoneally daily during the same period	Kidney	Improved glomerular and tubular histopathology. Tissue TGF- β and CRP ↓

(*continued*)

Table 2. Continued.

Reference	Study group	Stimulation	Oxytocin manipulation	Organ	Assessed outcome
Erbas et al. 2017	Rats	Diabetes induced by single dose of streptozotocin	80 μg/kg or 160 μg/kg intraperitoneally for 4 weeks	Nerve function	EMG deteriorations ↓ Muscle strength ↑ with high dose. Perineural fibrosis ↓ with high dose. Plasma GSH ↑ Plasma malondialdehyde (Lipid peroxidation) ↓

Table 3. *In vitro* and *in situ* studies on the anti-inflammatory and antioxidative effects of oxytocin.

Reference	Organ, tissue, cells	Stimulation	Oxytocin administration	Assessed outcome
Oliveira-Pelegrin et al. (2013)	Rat peritoneal macrophage culture	*In vivo:* Caecal ligation puncture induced sepsis followed by *In vitro* LPS-stimulation.	1 or 100 pM in medium	Production of nitrite, TNF-α and IL-1 ↓
Ghadrdan et al. 2016	Subcutaneous pouch in rats	carrageenan injection	4.25, 8.5 and 17 μg into the pouch	Exudate volume, leukocyte accumulation, VEGF and IL-1ß in the pouch ↓
Deing et al. (2013)	Cultured human fibroblasts and keratinocytes	UV irradiation	Oxytocin receptor knockdown by siRNA	Response of ROS production ↑ and IL 6, CCL5 and CXCLIO release ↑
Szeto et al. (2008)	Cultured human vascular cells, THP-1 monocytes, and macrophages	LPS to macrophages TNFα to endothelial cells	10 or 100 pM to medium	NADPH superoxide production ↓ IL-6 secretion ↓
Szeto et al. (2017)	Cultured human macrophages	LPS added to the medium	100 pM to medium	IL-6 secretion ↓
Garrido-Urbani et al. (2018)	Cultured mouse macrophages	None	?	M1/M2 ratio ↓ TNF-α ↓
Cho et al. (2019)	Cultured dermal fibroblasts from young humans	Medium conditioned by senescent fibroblasts	10 nM to medium	Senescent phenotype acquiring ↓
Karelina et al. (2011)	Cultured microglia from mouse brain	LPS added to the medium	0.1 or 1 μM to medium	MHC class II expression as measure of microglial reactivity ↓
Ross et al. (2013)	Cultured human monocytes and macrophages	LPS added to the medium	10–1000 pM to medium	Absent effect of oxytocin on inflammatory cytokine response
Clodi et al. (2008)	Isolated human peripheral blood mononuclear cells	LPS added to the medium	10 pM–10 nM to medium	Absent effect of oxytocin on TNF-α and IL-6 responses
Inoue et al. (2019)	Cultured mouse microglia cells	LPS added to the medium	1 μM to medium	TNF-α ↓ IL-6 and TNF-α gene expression ↓
Yuan et al. 2016	Cultured mouse microglia cells	LPS added to the medium	1 μM to medium	Protein and gene expression of TNF-α, IL-1β, iNOS and COX-2↓

Patients with severe Covid-19 are characterised by an elevated neutrophil-to-lymphocyte ratio compared to those being less affected (Lagunas-Rangel FA 2020) indicating that hyperactivity of these most abundant leucocyte plays a pivotal role in the severe pathogenesis of the disease. Autopsies from patients who had died from a Covid-19 infection demonstrate extensive neutrophil infiltration in pulmonary capillaries accompanied by fibrin deposition. Furthermore, aberrant neutrophil activity could in part explain the micro-thrombotic condition in Covid-19 patients (Barnes et al. 2020).

Oxytocin has been shown to dampen the inflammatory response of neutrophils in multiple animal models. Multi-organ damages caused by sepsis have been reported to be ameliorated by oxytocin in rats together with decreased tissue inflammatory cell infiltrations (Işeri et al. 2005a). At the same time, the neutrophil response in the different tissues assessed by myeloperoxidase activity was blunted. Oxytocin has also been reported to reduce the neutrophil response to acetic acid infused in the colon and to renal E coli infection, which was accompanied by an amelioration of tissue injuries with less inflammatory cell infiltration,

Box 1. Summarised probable anti-inflammatory mechanism of oxytocin.

- NADPH oxidase expression ↓ → ROS production ↓
- NF-κB signaling ↓ → Number of macrophages with a pro-inflammatory phenotype ↓ → production of pro-inflammatory cytokines including TNFα ↓
- PPAR-ϒ receptor expression ↑ → sensitivity to anti-inflammatory PPAR-ϒ-agonists ↑
- Parasympathetic activity ↑ → cholinergic stimulation of immune cells ↑
- Stimulation of mesenchymal stem cells → tissue anti-inflammatory mechanisms ↑

reduced oxidative stress and an attenuated response of pro-inflammatory cytokines (Işeri et al. 2005b, Biyikli et al. 2006). A reduced neutrophil response with less tissue damages as a result of oxytocin treatment has also been found in rats with ischaemia–reperfusion experiments of the liver (Düşünceli et al. 2008) and kidney (Tuğtepe H 2007) as well as myocardial infarction (Jankowski M 2010). Furthermore, less neutrophil activity was seen in the hind paw where inflammation was introduced by injection of carrageenan if oxytocin had been given subcutaneously (Petersson et al. 2001). In that study, the attenuating effect on the edoema by oxytocin administered in moderate doses was comparable to what could be achieved by dexamethasone. The dampening effect by oxytocin on the neutrophil activity may involve a downregulation of the toll-like receptor-4 (Mou et al. 2020) which is essential for the capacity of these cells to infiltrate tissues, as demonstrated in lung tissue (Hu et al. 2010).

In macrophages, oxytocin may attenuate their transition into a pro-inflammatory phenotype by upregulation of β-arrestin 2 (Tang et al. 2019). This is associated with an inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling, as demonstrated in lipopolysaccharide stimulated macrophages (Tang et al. 2019). NF-κB is a prominent transcription factor for a pro-inflammatory immune response including production of pro-inflammatory interleukins and TNF-α. When NF-κB is antagonised, it may therefore result in a decreased release of TNF-α from different cell types as observed with oxytocin treatment in a study on mice (Garrido-Urbani et al. 2018). A pivotal role of oxytocin as a modulator of the innate immune response is further supported by findings that the oxytocin receptor gene is increased 10-fold when monocytes differentiate into macrophages (Szeto et al. 2008). Interestingly, oxytocin may, by exerting such an inhibitory effect on inflammatory activity, have the capacity to be part of a negative cellular feed-back mechanism on inflammatory responses. This is supported by observations showing that the expression of the oxytocin receptor gene in human macrophages is upregulated during inflammation by a NF-κB dependent mechanism (Szeto et al. 2017).

Some *in vitro* studies on isolated monocytes and macrophages did not find an attenuated pro-inflammatory cytokine response to bacterial lipopolysaccharide endotoxin (LPS) when preincubated with oxytocin (Clodi et al. 2008, Ross et al. 2013). The diminished innate immune response to different immune challenges associated with oxytocin treatment on organ and whole-body level (Tables 1 and 2) may therefore depend on effects on other immune cells e.g. neutrophils, or involve central mechanisms.

The dampening impact of oxytocin on the inflammatory activity of different immune cells may involve an upregulation of peroxisome proliferator-activated receptor gamma (PPAR-ϒ). PPAR-ϒ is an important transcription factor inhibiting the inflammatory response and is therefore a target for several anti-inflammatory drugs. PPAR-ϒ receptor agonists are also used to attenuate the inflammatory activity during viral lung infections, however, PPAR-ϒ may be downregulated in alveolar macrophages by viral lung infections (Huang et al. 2019). In rat adipose tissue, PPAR-ϒ gene expression has been found to be upregulated after two weeks of oxytocin treatment (Eckertova et al. 2011). If oxytocin also upregulates PPAR-ϒ in some types of immune cells in the lungs it might reinforce the effects of anti-inflammatory treatment with PPAR-ϒ receptor agonists.

The anti-inflammatory effect of oxytocin may also involve a suppression of the gene expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. This enzyme is responsible for the inflammation induced superoxide production and thereby the formation of Reactive Oxygen Species (ROS). Such an effect of oxytocin was demonstrated in kidney homogenate from rats being treated with intraperitoneal injection of cisplatin (Rashed et al. 2011). In the same study, the gene expression of p38 mitogen-activated protein kinase (MAPK), an enzyme involved in the apoptotic pathway, was also reduced by oxytocin. The latter effect may protect the tissue against further destruction. These observations are in line with findings of a decreased basal and stimulated NADPH-dependent superoxide activity in human vascular cells, monocytes, and macrophages when the cells were

incubated with oxytocin at physiological levels (Szeto et al. 2008).

Does oxytocin counteract ARDS-development by defending endothelial integrity? Endothelial cells achieved from different kinds of blood vessels including pulmonary arteries express oxytocin receptors and produce nitric oxide (NO) when stimulated by oxytocin (Thibonnier et al. 1999). This release of NO by oxytocin is a result of the stimulation of endothelial nitric oxide synthase (eNOS) probably partly mediated by the protein kinase B (Akt)-pathway (Gonzalez-Reyes et al. 2015). An increased endothelial NO production may counteract the adherence of neutrophils to the endothelium and formation of platelet-neutrophil aggregates in a state of hyperinflammation (Khan et al. 2010). The anti-inflammatory adipokine omentin acting similarly to oxytocin in this regard has been demonstrated to protect the endothelial barrier in the lungs in mice with LPS-induced ARDS where the development of edoema was counteracted (Qi et al. 2016). The claim that NO is involved in pulmonary vascular protection during lung inflammations is supported by a decrease of pulmonary edoema in a study where rats were treated with adipose tissue derived stem cells after an acute lung injury was introduced by LPS (Gao et al. 2013). This effect was accompanied by an increased eNOS expression. A protective NO mediated effect of oxytocin on the vascular endothelium in the lungs may therefore be hypothesised.

Furthermore, the Covid-19 patients show signs of a damaged endothelial function caused by a disruption of the angiotensin system. This may be a result of the virus binding to the ACE-2 receptor causing elevations of angiotensin 2, which in turn, leads to vascular inflammation and an increased coagulation activity (Leisman et al. 2020). In this situation, a protective effect by oxytocin on the vascular endothelium in the lungs may be very beneficial. This may also apply to the inhibition of platelet aggregation by endothelium-derived NO.

Oxytocin may potentiate the adaptive immune response

In addition to exerting anti-inflammatory and restorative effects, oxytocin may also support the adaptive immune system by stimulating cellular maturation and differentiation of lymphocytes. In this regard, oxytocin may act on receptors on different types of T lymphocytes and support their differentiation and survival (Hansenne et al. 2005). Moreover, oxytocin may potentiate the adaptive immune response by enhancing the proliferation of lymphocytes when they are exposed to antigens (Macciò et al. 2010). Furthermore, oxytocin may protect lymphocytes during oxidative stress combined with hypercortisolemia (Stanić et al. 2016). Taking these protective and stimulatory effects on the immune system into account, oxytocin differs from many other types of anti-inflammatory treatments by at the same time being anti-inflammatory and exerting some positive effects on the adaptive immune response.

Protective and restorative effects of oxytocin

Oxytocin has been reported to mitigate tissue damages in different inflicted injury models. This includes sepsis (Işeri et al. 2005a) and global thermal trauma in rats (Işeri et al. 2008) and different local intestinal injury models in mice (Chen et al. 2015). Moreover, oxytocin has been shown to reduce sepsis induced polyneuropathy in rats (Erbaş et al. 2013). Pertaining particularly to inflammation in the lungs, oxytocin has recently been reported to reduce the severity of bacterial LPS-induced acute lung injury in mice showing less damages and edoema of the tissue (An et al. 2019). Furthermore, the treatment with oxytocin attenuated the responses to LPS regarding gene expression and appearance of pro-inflammatory cytokines in the lungs. Accordingly, the elevation in the expression of NF-κB was ablated. Oxytocin has also been demonstrated to alleviate the consequences of a heat stroke elicited acute lung injury in rats (Lin et al. 2019). A blunted inflammatory response was also seen in this case together with an improved survival.

Reduced tissue damages associated with lung infections imposed by E. coli bacteria have been demonstrated. In one study, stressed rats were given a lung infection by intratracheal injection of an E. coli suspension (Stadnikov et al. 2011). In that study, intra-muscular injections of oxytocin resulted in a reduction of the apoptotic cells in the lungs after 11 days. In another study, E. coli bacteria were injected into the renal medulla and the animals were examined after one or 7 days (Biyikli et al. 2006). In this case, the elevations of oxidative stress markers in the tissue observed after 7 days was antagonised by oxytocin as was the response in plasma TNF-α.

It is not an uncommon phenomenon that the myocardium is affected by Covid-19, which may lead to a fatal outcome particularly in patients, who suffer from heart comorbidities (Kochi et al. 2020). Oxytocin has been demonstrated to possess potent cardioprotective properties in different models. Thus, in situ ischaemia/

reperfusion and infarct experiments with isolated hearts have shown an improved resilience to transient hypoxia of the myocardium with less injuries following administration of oxytocin (Houshmand et al. 2009, Xiong et al. 2020, Jankowski et al. 2010). As inflammatory reactions are involved in the organ damages attributable to hypoxaemia (Wei et al. 2016), the anti-inflammatory impact of oxytocin may play a protective role in such conditions being accompanied by an increased activation of anti-apoptotic and restorative pathways (Kobayashi et al. 2009, Polshekan et al. 2019). Moreover, a protective effect of oxytocin against damages caused by transient hypoxia has been confirmed in a number of ischaemia/reperfusion experiment in a variety of other organs (Table 2) including a study where damages inflicted on the liver by ischaemia/reperfusion of the kidney was alleviated by oxytocin (Hekimoglu et al. 2013) indicating this mechanism also may act on a systemic level.

The tissue protective role of oxytocin may not be limited to anti-inflammatory and anti-apoptotic mechanisms; more direct healing and regenerative effects on tissues may also be exerted by oxytocin. The capacity of oxytocin to promote the function of stem cells (Noiseux et al. 2012) may be part of the restorative function of oxytocin. In this context the capacity of mesenchymal stem cells to repair ischaemic heart damage in rats has been reported to be enhanced after preconditioning with oxytocin (Kim et al. 2012). Stem cells may also contribute to the cardio-protective effect of oxytocin as demonstrated in diabetic rats (Plante et al. 2015). A general stimulatory effect of oxytocin on stem cells might also be of significance in the alveolar tissue as such cells may promote restoration, in addition to attenuating pulmonary inflammation (Mei et al. 2010). An over-all 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 (Vitalo et al. 2009, Petersson et al. 1998, Xu et al. 2017). Concordantly, wound healing was accelerated in mice receiving an oxytocin promoting probiont, which stimulates the release of oxytocin, an effect which was absent in oxytocin gene knockout mice (Poutahidis et al. 2013). Oxytocin has also been found to restore striated muscles and therefore counteract sarcopenia in rats (Elabd et al. 2014). These observations suggest a global restoring potential of oxytocin that may involve most types of tissues. Oxytocin might therefore be applied to improve the chance for a general successful recovery of damaged organs in the severely affected Covid-19 patient.

Human studies

Oxytocin has also in humans been shown to exert anti-inflammatory, antioxidant and restorative effects. Intravenous infusion of oxytocin (1 ng/kg/min for 90 min) was reported to blunt the febrile response and the response of several proinflammatory cytokines, including that of TNF-α, caused by a bolus injection of LPS in healthy men (Clodi et al. 2008). In another study an anti-inflammatory effect of oxytocin was demonstrated in human skin, as knockdown of the oxytocin receptor (OXTR) in cultured skin cells was found to increase levels of reactive oxygen species (ROS) and reduce the level of glutathione (GSH). Moreover, the OXTR-depleted keratinocytes exhibited an increased release of the pro-inflammatory cytokines IL6, CCL5 and CXCL10 (Deing et al. 2013). Local intravaginal application of oxytocin for one week rejuvenated the vaginal mucosa by increasing the number of cell layers and the maturation of the cells (Jonasson et al. 2011) (Al-Saqi et al. 2015). Together these data indicate that oxytocin also in humans can exert anti-inflammatory, antioxidant and restorative effects.

Clinical considerations

Based on the in vitro mechanistic experiments and the in vivo animal and human studies presented above we find it conceivable that administration of oxytocin could be helpful in the treatment of Covid-19 and should be tested in clinical trials.

In connection with birth, oxytocin is given in doses from 1–32 mIU/min over several hours. After birth often 5 or 10 IU are given as a bolus to prevent bleedings. Side effects are rare, but water intoxication has been shown to occur in response to infusion of extremely high doses of oxytocin. Bolus administration of 10 IU has been observed to influence heart rate and blood pressure in rare cases (Uvnäs-Moberg et al. 2019).

The pharmacokinetics of oxytocin are well studied, and the half-life is around 30 minutes (Nielsen et al. 2017). Oxytocin levels increase by 1-2 pg/ml in response to an increased rate of infusion by 1 mIU/min and when the rate of oxytocin infusion is doubled, the oxytocin level in the circulation is also doubled both in women during labour and in healthy males (Uvnäs-Moberg et al. 2019, Legros et al. 1984). Infusion rates up to 10 mIU/min reflect levels seen during normal physiological labour. We assume that oxytocin may be less tolerated in elderly and Covid-19 weakened patients and therefore low doses of oxytocin should be given. Based on these considerations we

suggest that oxytocin should be infused at low infusion rates, gradually being increased from 1-10 mIU/min for some hours, during monitoring of the cardiovascular function.

Treatment with intranasal oxytocin may be an option in less sick individuals to prevent the development of inflammation. The pharmacokinetics are not as well described, and the administration is not as easily monitored as for intravenous infusion of oxytocin.

The direct beneficial effects of increasing circulating oxytocin levels by i.v. infusion may be potentiated by an enhancement of the endogenous oxytocin activity. Enhanced levels of oxytocin in the circulation may, via activation of afferent sensory nerves, stimulate oxytocin release from nerves within the brain that emanate from the hypothalamus (Velandia 2012). Afferent vagal fibres may be involved in a reciprocal feed-back signal of blood oxytocin to the brain (Iwasaki et al. 2015), but other sensory nerves may also be involved (Uvnäs-Moberg et al. 2014). This may lead to neural release of oxytocin into several important regulatory areas of the brain including the dorsal vagal complex in the brainstem (Uvnäs-Moberg et al. 2014). Subsequently, vagal tone may be increased promoting the cholinergic anti-inflammatory pathway (Borovikova et al. 2000). In addition, the neural release of oxytocin into different parts of the brain may be associated with an attenuation of stress, fear and pain (Uvnäs-Moberg et al. 2014).

Conclusion

Oxytocin is a natural, safe and well-known drug with a substantial anti-inflammatory and anti-stress potential. In addition, in comparison with glucocorticoids, oxytocin may promote rather than suppress the adaptive immune response due to its putative stimulatory effects on lymphocytes. Finally, the restorative properties of oxytocin may promote recovery and shorten the time period of patient's hospitalisation. Oxytocin is readily available, as it is presently being used in most hospitals. Infusion regimens, pharmacokinetic properties and safety are well established. In the present situation with a worldwide progression of the Covid-19 pandemic that challenges the entire global health resources, it is urgent to identify inexpensive and safe agents that can relieve the course of the disease. We therefore propose that i.v. infusion of oxytocin should be tested in hospitalised Covid-19 patients.

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Statement of interest

None to declare.

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