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Review article

Cardiovascular protective properties of oxytocin against COVID-19

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ABSTRACT

SARS-CoV-2 infection or COVID-19 has become a worldwide pandemic; however, effective treatment for COVID-19 remains to be established. Along with acute respiratory distress syndrome (ARDS), new and old cardiovascular injuries are important causes of significant morbidity and mortality in COVID-19. Exploring new approaches managing cardiovascular complications is essential in controlling the disease progression and preventing long-term complications. Oxytocin (OXT), an immune-regulating neuropeptide, has recently emerged as a strong candidate for treatment and prevention of COVID-19 pandemic. OXT carries special functions in immunologic defense, homeostasis and surveillance. It suppresses neutrophil infiltration and inflammatory cytokine release, activates T-lymphocytes, and antagonizes negative effects of angiotensin II and other key pathological events of COVID-19. Additionally, OXT can promote γ-interferon expression to inhibit cathepsin L and increases superoxide dismutase expression to reduce heparin and heparan sulphate fragmentation. Through these mechanisms, OXT can block viral invasion, suppress cytokine storm, reverse lymphocytopenia, and prevent progression to ARDS and multiple organ failures. Importantly, besides prevention of metabolic disorders associated with atherosclerosis and diabetes mellitus, OXT can protect the heart and vasculature through suppressing hypertension and brain-heart syndrome, and promoting regeneration of injured cardiomyocytes. Unlike other therapeutic agents, exogenous OXT can be used safely without the side-effects seen in remdesivir and corticosteroid. Importantly, OXT can be mobilized endogenously to prevent pathogenesis of COVID-19. This article summarizes our current understandings of cardiovascular pathogenesis caused by COVID-19, explores the protective potentials of OXT against COVID-19-associated cardiovascular diseases, and discusses challenges in applying OXT in treatment and prevention of COVID-19.

Chemical compounds: Angiotensin-converting enzyme 2 (ACE2); atrial natriuretic peptide (ANP); cathepsin L; heparan sulphate proteoglycans (HSPGs); interferon; interleukin; oxytocin; superoxide dismutase; transmembrane serine protease isoform 2 (TMPRSS2).

1. Introduction

The outbreak of a novel coronavirus (SARS-CoV-2) infection (i.e. COVID-19) has become a worldwide pandemic since December 2019. The number of confirmed cases of COVID-19 in the world is >95.4 million including ~2 million deaths as of January 17, 2021 (https://www.worldometers.info/coronavirus/). The disease carries a high mortality among those who are older, immune-suppressed, or with underlying co-morbidities, predisposing them to acute respiratory distress syndrome (ARDS), cardiovascular (CV) complications, and multi-organ failure [1,2]. Given the medical emergency of a rapidly spreading contagion, its unpredictable nature with continuous viral mutations, lack of effective treatments, and current lack of data for long-term effects of vaccines [3–5], novel strategies to prevent its infection and improve survival rate among infected patients are urgently needed.

Among many potential treatments, oxytocin (OXT), a classical hypothalamic neuropeptide with pleiotropic actions [6], has emerged as a strong candidate against COVID-19. Moreover, evidences have emerged showing the CV protective effects of OXT [7] by targeting many key pathogenetic events in COVID-19. This is critical as CV complications...
contribute to significant morbidity and mortality among COVID-19 patients [8–10]. This article summarizes our current understandings of potential roles of OXT in prevention and treatment of CV complications in COVID-19.

2. Pathogenesis of COVID-19

2.1. Symptoms and clinical manifestations

Despite many asymptomatic cases, those with symptoms often present with fever, cough, fatigue, anosmia or hyposmia, nausea, and anorexia. Factors that are associated with mortality include male sex, advanced age, cytokine storm, ARDS, acute cardiac injury, acute kidney injury and the presence of comorbidities including hypertension, diabetes mellitus, CV diseases, and cerebrovascular diseases [11,12]. Patients often exhibit ground-glass opacity on chest computed tomography [13], troponinemia [14], increased cytokines, and lymphocytopenia [15] as well as hypometabolism in many brain regions including the hypothalamus [16]. All of these findings indicate the involvement of multiple organ systems.

2.2. Immunological disorders

The pathogenesis of COVID-19 involves dysfunction in immunological homeostasis, fibrinolysis, vessel contractility, inflammation, oxidative stress, and vascular permeability, etc. [1]. As reported, COVID-19 patients carry high levels of pro-inflammatory cytokines including interleukin (IL)-6 and tumor necrosis factor-α, atrophy of spleen and lymph nodes, higher neutrophil count and lower number of other types of leukocytes, particularly T-lymphocytes [17]. This compromised immune system causes destruction of pneumocytes following the invasion of SARS-CoV-2, which in turn increases neutrophil infiltration and even leads to the fatal “cytokine storm.” That is, an uncontrolled and excessive release of pro-inflammatory cytokines that causes autoimmune self-destructive response. The cytokine storm contributes to severe ARDS, multiple organ failure and eventually mortality [18]. For instance, IL-1 induces a significant number of metabolic and hematological changes such as hypotension, endothelial dysfunction, macrophage intervention and increased protein leakage from blood vessels, venous thromboembolism and shock [19]. The same importance applies to lymphocytopenia. For example, thymosin α1 supplement significantly reduces mortality of severe COVID-19 patients with the counts of CD8+ and CD4+ T cells in circulation lower than 400/μL and 650/μL, respectively. This is because thymosin α1 reverses T cell exhaustion and improves immune reconstitution by promoting thymus output during SARS-CoV-2 infection [20]. Thus, suppressing sustained release of cytokines and inflammatory response, and promoting T-lymphocyte functions are the essential therapeutic strategy to treat COVID-19 patients.

2.3. SARS-CoV-2 entry of cells

SARS-CoV-2 entry of host cells could involve host cell membrane-bound angiotensin-converting enzyme 2 (ACE2), transmembrane serine protease isofom 2 (TMPRSS2), lysosomal endoproteinase cathepsin L, and membrane bound heparan sulphate proteoglycans (HSPGs) and others [21]. As the receptor for SARS-CoV-2, ACE2 is present on the surface of lung alveolar epithelial cells, enterocytes of the small intestine, renal tubules, heart, arterial and venous endothelial cells, arterial smooth muscle cells, cerebral neurons and monocytes/macrophages [22,23]. Spike proteins give SARS-CoV-2 the ability for cellular infection [24], as human immunodeficiency virus (HIV) does [25]. SARS-CoV-2 enters human ACE2-expressing cells mainly via endocytosis, in which cathepsin L and other components are critical [26]. TMPRSS2 primes the viral spike protein in order to facilitate ACE2-mediated viral entry and extra-pulmonary spread [27]. Besides TMPRSS2, HSPGs are cell surface receptors that assist ACE2 in endocytosis-mediated coronavirus entry [28]. Thus, multiple cellular components are involved in the invasion of SARS-CoV-2 and can be potential targets in the treatment.

2.4. ACE2 loss and AT II effects

SARS-CoV-2 invasion destroys infected cells and reduces ACE2 activity. Resultantly, the capacity of ACE2 to convert angiotensin II (AT II) into inactive AT 1–7 decreases, which causes elevation of serum AT II levels, neutrophil accumulation, vascular hyper-permeability, and pulmonary edema seen in ARDS [29]. Infusion of ACE2 in ARDS patients can decrease AT II and IL-6 levels, and increase surfactant protein, thereby exerting protective functions [30]. Blocking viral endocytosis and excessive AT II actions are alternative measures for controlling the pathogenesis.

3. COVID-19 and CV complications

3.1. CV complications

CV disease represents a common comorbidity predisposing COVID-19 patients to high mortality [8–10]. The complications include acute cardiac injury, myocarditis, fibrosis, fulminant myocarditis rapidly evolving into depressed systolic left ventricular function, arrhythmias, hypercoagulable state, venous thromboembolism, and cardiomyopathies mimicking ST-elevation myocardial infarction [14,31]. Acute cardiac injury is commonly observed in severe cases and is strongly associated with mortality [11]. It is important to note that COVID-19 patients often carry pre-existing CV comorbidities. Among 45 studies including 14,358 adult participants, prevalent comorbidities are hypertension (19.1%), CV disease (17.9%), and diabetes (9.2%) [13]. Patients with pre-existing conditions may face a greater risk of developing into the severe condition. Thus, old and new CV complications are worthy of special attention in COVID-19 patients.

3.2. Dissemination via endothelium of blood vessels

In the dissemination of SARS-CoV-2 from the lung to multiple organs, endothelial dysfunction of the CV system is a common cause. After infecting respiratory epithelial cells, SARS-CoV-2 gets into the circulation through endothelial cells of blood vessels in the lung and then enters tissues through the endothelial cells in capillaries again. COVID-19 patients exhibit abnormalities in the vascular endothelium, which alter the blood flow, and evoke platelet function abnormalities and hyper-viscosity [32]. The endothelial dysfunction and damage cause release of procoagulant components, which together with hypoxia, immune reactions and hypercoagulability contributes to thrombogenesis [33]. Thus, endothelium is a critical barrier in COVID-19 transmission and dissemination.

3.3. Mechanisms underlying CV injuries

CV injuries from viral infection are also mediated by ACE2 and cathepsin L [34]. In adult human heart, pericytes with high-expression of ACE2 serve as target cardiac cells for SARS-CoV-2. Infection in periocytes results in dysfunction of capillary endothelial cells and microvascular dysfunction. Patients with heart failure show increased ACE2 expression at both mRNA and protein levels [35]. Among patients with diabetes and CV disease, the expression levels of TMPRSS2 are elevated significantly in comparison to healthy individuals. Additionally, expression of viral entry-related genes is increased in the settings of hypertension across target organ systems [21]. Thus, if infected by the virus, these patients may have higher risk of CV complications and progression to critically-ill condition.

The etiology of CV injuries seems to be multifactorial including direct viral myocardial damage, hypoxia, hypoperfusion, enhanced
inflammatory state, ACE2 down-regulation, drug toxicity, endogenous catecholamine adrenergic status and others [36]. In SARS-CoV-2 infected human, pluripotent stem cell-derived cardiomyocytes, double-stranded viral RNA and viral spike protein expressions are detected in intracellular space. In addition, viral spike protein and particles are present in living human heart slices after infection with SARS-CoV-2, which induces cytotoxic and proapoptotic reaction and abolishes cardiomyocyte activities. The subsequent virus-mediated myocardial injury is closely related to inflammatory hyperactivity. For example, cardiac injury is significantly associated with inflammation biomarkers such as IL-6, C-reactive protein, hyperferritinemia, and leukocytosis along with elevated troponin I levels [31]. Direct cardiac injury following viral entry through ACE2 receptors is closely associated with cytokine storm [37]. One of the currently used treatments, remdesivir, has been shown to inhibit viral infection of cardiomyocytes [34,38]. These findings highlight the key role of viral injury in initiating the CV pathogenesis in COVID-19 patients.

Further study also reveals that lung pathology can cause CV malfunctions. Clinical and experimental observations have shown that loss of ACE2 function aggravates pulmonary hypertension while restoring ACE2 function exerts protection on cardiopulmonary circulation. In addition, SARS-CoV-2 tropism and its interaction with the renin-angiotensin-aldosterone system (RAAS), through ACE2 receptor, may enhance inflammation response and cardiac aggression [31]. Lastly, SARS-CoV-2 infection can lead to right heart dysfunction by inducing pulmonary hypertension, pulmonary embolism, and ARDS.

4. Effects of OXT on CV activity

OXT, a nonapeptide synthesized in hypothalamic magnocellular neuroendocrine cells in the supraoptic and paraventricular nuclei (SON and PVN), is a well-known humoral factor regulating parturition and lactation [6,39]. In the brain, OXT terminals are found on large intracerebral arteries [40]. OXT-containing neural fibers are present in pia-arachnoids, blood vessels at the base of the brain and over the dorsal surface [41]. Thus, OXT can regulate cerebral blood flow directly. Moreover, OXT and OXT receptor (OTR) are identified in the pulmonary artery, vena cava and aorta of rats, dogs and sheep [42] as well as cardiac cells in rats [43] and endothelial cells of human umbilical vein endothelial cells [44]. They allow OXT to regulate CV activity at peripheral sites as well.

4.1. General effects of OXT on CV activity

OXT can modulate CV activity including the development of cardiomyocytes, ionotropic and chronotropic effects, dual role in cardiac output, endocrine activity (e.g. secretion of atrial natriuretic peptide, ANP) and direct cardioprotection [7].

In general, OXT exerts negative chronotropic and ionotropic effects on cardiac activity. OXT can reduce heart rate and cardiac contractility by activating intrinsic cardiac cholinergic neurons of the vagus and promoting nitric oxide (NO) production. This is because atropine and NO synthase inhibitor, L-NAME, can significantly inhibit this OXT effect [45]. Consistently, in OXT knockout mice, there were mild hypotension,
higher sympathetic tone and higher heart rate [46], indicating activation of sympathetic outflow. At higher concentrations, OXT can directly reduce left ventricle pressure and heart rate in isolated rat hearts and decrease mean artery pressure in rats, which could involve the action of ANP [47]. Thus, OXT participates in the maintenance of tonic blood pressure and suppression of sympathetic reserve.

OXT can protect the CV system from social stress damages or the brain-heart syndrome via neural and endocrine approaches. Social stress is important etiology of CV malfunctions because it can disrupt normal behavior, neuroendocrine, and autonomic responses. By facilitating positive social interactions, suppressing sympathetic outflow and reducing fear and anxiety, OXT can counteract the deleterious effects of social stress and its associated unhealthy life-style, hypertension, and coronary artery diseases [48,49].

Another approach for OXT protection is its influencing the secretion of many cytokines [50,51]. For example, in rats with myocardial infarction, OXT infusion dose-dependently increases plasma ANP concentration as much as 4-fold after 20 min. ANP produced in the right atrium can prevent reperfusion arrhythmia and maintain ATP production in ischemic tissue while facilitating Na+ excretion to reduce after-load and blood pressure [52]. Moreover, OXT can suppress the activity of hypothalamic-pituitary-adrenocortical axis [53], and reduce the release of stress hormone. Through these approaches, OXT can reduce heart rate and blood pressure while increasing the reserve of cardiac output, thereby exerting CV protective effects.

4.2. Suppressing pathogenesis underlying CV diseases by OXT

OXT is a well-documented hormone of CV protection [54,55]. For example, in rats with myocardial infarction, OXT infusion results in suppression of inflammation by reducing neutrophils and macrophages, depressing the expression of tumor necrosis factor-α and IL-6, promoting transforming growth factor-β and reducing apoptosis and fibrotic deposits [56]. In rabbits of myocardial infarction and reperfusion, OXT treatment significantly improves left ventricular function, reduces infarct size, and increases the number of CD31-positive microvessels. These effects are associated with increased expression of OTR, pro-survival signals, and anti-fibrotic and angiogenic signals like phosphorylated-Akt protein kinase, phosphorylated-endothelial NO synthase, and vascular endothelial growth factor [57]. In addition, OXT can reduce oxygen consumption by its negative chronotropic and inotropic effects and protect the heart from ischemia/reperfusion injuries. These facts support that OXT can be a potential treatment in patients with CV complications.

The protective effects of OXT can also be achieved through central approach. In a rat model of trans-ascending aortic constriction-induced left ventricular hypertrophy and heart failure, chronic activation of hypothalamic OXT neurons in the PVN to elevate parasympathetic tone can improve cardiac function, reduce IL-1β expression and lower myocardial collagen density (an indicator of cardiac fibrosis) as well as heart rate sensitivity to β-adrenergic stimulation [58]. Intracerebroventricular infusion of OXT or centrally released OXT can induce a preconditioning effect in ischemic-reperfusion rat heart via brain OTR [59].

In OXT protection of the CV system, endothelial cells are an important target. OXT can elicit mesenchymal cells to express endothelial cell markers [60] and promote proliferation and migration of human dermal microvascular endothelial cells [61]. OXT is necessary for the formation of neovascular interface in the pituitary by affecting endothelial morphogenesis [62]. In the posterior pituitary, OXT-containing axonal terminals express vascular endothelial growth factor A that can cause active proliferation of endothelial cells [63]. By protecting endothelial cells in blood vessels and stabilizing anticoagulant heparan [64], OXT could reduce the formation of thromboembolism and atherosclerosis while blocking pathogen invasion. Fig. 1 summarizes the CV protective effects and potential involvement of OXT in COVID-19-associated CV diseases.

5. OXT functions against COVID-19-associated CV injuries

The OXT-secreting system is considered as the higher neuroendocrine regulation center of the immune system [50,51] and key protective factor of CV system. Interruption of this system by COVID-19 partially accounts for the CV complications while reviving the OXT-secreting system or supplying OXT becomes a feasible strategy of inhibiting the pathogenesis of CV manifestations in COVID-19.

5.1. Evidence suggesting OXT involvement in COVID-19

The pathological changes in CV system of COVID-19 patients could result from dysfunction of the OXT-secreting system. In epidemiology, the decline in OXT and OTR with aging is likely responsible for the increased incidence of CV diseases since weakened OTR signaling can accelerate inflammatory and oxidative injuries, particularly among menopausal women [53,65]. In aged man, OXT secretion is also reduced, which is in parallel with increased incidence of hypertension, coronary artery disease, diabetes and cerebrovascular diseases. These diseases are also the common comorbidities that increase susceptibility to COVID-19 [11]. Consistently, plasma OXT level experiences a 3-fold decline in aged mice compared with young, and this decline is accompanied by similar decrease in OTR levels in muscle stem cells [66]. By contrast, exogenous estrogen application can increase OXT secretion, OTR mRNA expression in mouse brain [67], and intracardiac OTR signaling [68], which simulates the physiology of young women who are less susceptible than menopausal women to COVID-19. In addition, melatonin, a pineal hormone that has remarkable anti-inflammatory effects and can antagonize various viral infections including COVID-19 [69], can also regulate OXT release [70]. Thus, the susceptibility to COVID-19 is highly correlated with the activity of the OXT-secreting system.

In COVID-19 patients, there is also evidence indicating involvement of the hypothalamic-pituitary system. In two SARS-CoV-2 infected patients, the mammillary bodies and hypothalamus carried T2-hyperintensity, the pituitary gland was enlarged, and the upper pituitary stalk seemed globular in sagittal fluid-attenuated inversion recovery [71]. Since the mammillary bodies function as the upstream center of OXT neuronal activity, particularly its release in a pulsatile pattern [72], viral infection of the mammillary bodies unavoidably changes the downstream OXT neuronal activity and OXT secretion. In COVID-19 patients, many brain areas innervated by olfactory bulbs including the hypothalamus showed hypometabolism in 18F-FDG positron emission tomography scans [16], suggesting low activity of olfaction-associated hypothalamic hyperprolactinemia processes. It is also reported that activation of ACE2 in the PVN increases neuronal NO synthase and NO production, which can increase sympatho-inhibitory GABA activity and decrease sympatho-excitatory AT II signaling and glutamate activity [73]. ACE2 can reduce oxidative stress and cyclooxygenase-mediated neuroinflammation, increase antioxidant and NO signaling, and attenuate the development of neurogenic hypertension [74]. Studies on pathological changes in the hypothalumus of SARS-CoV-associated diseases also support the involvement of the hypothalamic neuroendocrine system in COVID-19. For example, in autopsies of 8 SARS patients, SARS-CoV was identified in the cytoplasm of numerous neurons in the hypothalamus and cortex [75]. In post-mortem tissues from HIV patients, OXT immunoreactivity in hypothalamic neurons decreased significantly [76]. Since these viruses use the same mechanisms of cellular infection and disruption as SARS-CoV-2 does, disruption of endogenous OXT production could be one etiology leading to the progression of COVID-19.

Involvement of the neuroendocrine hypothalamus is also supported by findings of endocrine disorders in COVID-19 patients as well. Testosterone and estrogen can increase the expression of ACE2, whereas
immunological disorders among COVID-19 patients. OXT has the potential to further clarify this association. It is likely that SARS-CoV-2 enters the brain from the nose to the olfactory bulbs, and then infects neurons in the hypothalamus via the olfactory nerve [16]. The olfactory bulb involvement is supported by the high rates of anosmia or hyposmia in patients with COVID-19 [81] and by neural connections between the olfactory bulb and SON [82]. Alternatively, SARS-CoV-2 in the blood can enter the hypothalamus and pituitary through fenestrated capillaries of blood-brain barrier around the third ventricle and pituitary [83]. Direct evaluation of plasma OXT levels and examination of hypothalamic histology of COVID-19 patients are needed to further clarify this association.

5.2. Suppression of immunological disorders by OXT

Cytokine storm and lymphocytopenia are two major features of immunological disorders among COVID-19 patients. OXT has the potential to suppress cytokine storm. Diffuse pneumocyte and alveolar damage with pulmonary edema, proteinaceous exudate, inflammatory cell infiltrates, and release of pro-inflammatory cytokines can lead to cytokine storm [84]. This process can be suppressed by OXT administration. As shown in animal studies, exogenous OXT can decrease levels of IL-1β, IL-6, IL-18, and myeloperoxidase as well as incidence of acute lung injury in mice induced by lipopolysaccharide, an endotoxin [85]. OXT can downregulate neutrophil chemotactic molecules and myocardial neutrophil infiltration, and prevent myocardial injury by reducing inflammatory reaction, reactive oxygen species, and apoptosis caused by neutrophils [86]. In both smooth muscle and vascular endothelial cells, OXT can inhibit oxidative stress and pro-inflammatory cytokine release [87,88], thereby attenuating the cytokine storm and inflammation.

Additionally, OXT has the potential to block SARS-CoV-2 infection of cells and reduce SARS-CoV-2 loads. OXT can induce γ-interferon expression as shown in mouse spleen cell cultures [89]. Interferons can reduce viral infections by producing γ-interferon-inducible lysosomal thiol reductase that restricts the entry of selected enveloped RNA viruses via disrupting cathepsin L metabolism [90]. This potential of OXT is supported by the fact that at 24-h following weaning of suckling when OXT levels and pulsatility reduce, cathepsin L and cell apoptosis increase dramatically in mouse mammary glands [91]. Another potential approach of OXT blocking SARS-CoV-2 infection is its blocking HSPG-mediated viral infection. OXT can induce the expression of extracellular superoxide dismutase [92], an antioxidant enzyme that has been shown to protect tissues from reactive oxygen species-induced heparin and heparan sulphate fragmentation, and thus the subsequent neutrophil chemotaxis [93]. Importantly, heparin and heparan sulphate can antagonize the binding of SARS-CoV-2 to HSPGs and block their cellular internalization [94]. Through these approaches, OXT has the potential to prevent SARS-CoV-2 entry and disruption of cells.

OXT can also reduce viral load by reversing lymphocytopenia. As reported, OXT acts on OTR in the thymus to promote the differentiation of T-lymphocytes [94]. OXT elicits a functional intracellular [Ca^{2+}] response in T-lymphocytes to activate resident T-lymphocytes [95]. In women infected with HIV that has spike proteins highly homologous to COVID-19, high-level of OXT was associated with a positive correlation between stress and CD4 cell counts [96]. In a recent study, OXT was found to be more effective than hydroxychloroquine or lopinavir in modulating inflammation, and enhancing T-lymphocyte activation [97]. These findings suggest that OXT can prevent or alleviate lymphocytopenia in COVID-19 patients and thus reduce SARS-CoV-2 load, making OXT an ideal candidate for treatment of COVID-19.

5.3. Alleviating CV pathogenesis by increasing endothelial integrity

Besides immunological modulation, OXT may reduce CV injury from COVID-19 by increasing cellular integrity, particularly endothelium. First, OXT can prevent ACE2 loss by increasing T-lymphocytes that can in turn reduce SARS-CoV-2 viral load and cellular injuries [98]. Second, OXT maintains cell integrity by reducing neutrophil-mediated inflammatory injury and cardiac apoptosis [99]. Third, OXT may protect endothelial cells by increasing vascular endothelial growth factor [57] and promoting angiogenesis [44]. Fourth, OXT antagonizes the adverse effect of AT II on the CV system by increasing ANP production [7]. ANP can reduce renin and thus AT II activity in the RAAS, thus reducing damages in endothelial, pulmonary, and CV systems from COVID-19 [79]. Fifth, OXT can activate brainstem vagal neurons to increase parasympathetic output while reducing RAAS activity [100] driven by sympathetic outflow [101] that are activated during COVID-19 [102]. Lastly, OXT can inhibit carbonic anhydrase activity that is associated with hypoxic pulmonary vasoconstriction, pulmonary hypertension right ventricle hypertrophy and fibrosis among COVID-19 patients [103]. While direct evidence on OXT modulation of ACE2 and AT II remains to be collected, OXT can be used to antagonize AT II effects in COVID-19 patients.

5.4. Suppression of COVID-19-associated CV injuries

CV system is a major target of COVID-19 that causes myocardial infarction, fulminant myocarditis, heart failure, arrhythmias, venous thromboembolism, and cardiomypathies [14,31,104,105]. OXT exerts cardioprotective functions by reducing inflammation and cardiac fibrosis, improving left ventricular function, enhancing pro-survival kinases, elevating parasympathetic tone, reducing the infarct size, and protecting the heart from myocardial injury [7]. For example, OXT pre-treatment inhibits the degranulation of cardiac mast cells induced by ischemia and reperfusion injury, and down-regulates the expression of inflammatory factors [106]. OXT also functions as an anti-arrhythmic agent. For example, acute myocardial ischemia is accompanied by a rapid increase in electrical instability and often fatal ventricular arrhythmias. OXT can cause a significant and biphasic dose-dependent reduction in ectopic heart activity and arrhythmia score [107]. Intranasal application of OXT significantly reduces brain infarction and maintains the integrity of the blood-brain barrier in mice [108] and rats [109] undergoing transient middle cerebral artery occlusion. Additionally, OXT can promote angiogenesis, regeneration of cardiomyocytes, resistance to apoptosis and cardiac fibrosis [58]. For these reasons, OXT is able to increase the integrity of endothelial cells and thus, reduce the occurrence of thromboembolism. Furthermore, OXT significantly suppresses oxidized low-density lipoprotein-induced attachment of spontaneously immortalized THP-1 monocytes to human brain microvascular endothelial cells by reducing the expression of adhesion molecules, such as vascular cell adhesion protein 1 and E-selectin [110]. Thus, OXT carries the capacity to protect CV functions at all levels from COVID-19 injuries.
Many COVID-19 patients have pre-existing comorbidities including hypertension, CV disease, endocrine disorder and diabetes. These comorbidities, particularly CV diseases, increase the morbidity and mortality of COVID-19 [3,11,104,111]. Inhibiting or improving these pre-existing conditions is important for reducing COVID-19 morbidity and mortality and thus, we further discuss the role of OXT in stabilization of these conditions.

### 5.5.1. Prevention of obesity, atherosclerosis and their complications

Metabolic and immunological disorders are essential etiologies underlying obesity, atherosclerosis and the associated diseases, such as hypertension, coronary artery disease and ischemic stroke [112]. OXT does not only carry anti-inflammatory effects as stated above but also reduces hyperlipidemia, an essential metabolic disorder for obesity and atherosclerosis. As reported, serum OXT levels were low in obese person [113]; OXT- or OTR-deficient mice developed late-onset obesity [114]. In response to subcutaneous injection of OXT, cholesterol levels decreased in rats [115]. Chronic OXT application also reduced weight gain in diet-induced obese mice and rats; chronic subcutaneous or intranasal OXT treatment was sufficient to elicit body weight loss in obese humans [116]. Thus, OXT may reduce individual susceptibility to COVID-19 by suppressing obesity, atherosclerosis and its complications.

### 5.5.2. Prevention of hypertension

OXT has the potential to inhibit the development of hypertension. In hypertensive rats, OXT and OXT mRNA expressions are reduced in the hypothalamus whereas, OXT injected subcutaneously or intracerebroventricularly for 5 days can significantly decrease blood pressure in rats [117]. Centrally released OXT can significantly reduce blood pressure and heart rate and antagonize acute stress-induced CV responses [118]. Moreover, chronic activation of OXT neurons restores the release of OXT from PVN neural fibers in the dorsal motor nucleus of the vagus, and prevents chronic intermittent hypoxia-evoked hypertension [119]. Based on these findings, we believe that OXT can exert anti-hypertensive effects through both central and peripheral approaches.

### 5.5.3. Anti-diabetic effects

Population with diabetes mellitus has high prevalence of CV diseases [120] and high susceptibility to COVID-19. In patients with type 2 diabetes mellitus, serum OXT levels are relatively low [113]. In a mouse model of type 2 diabetes mellitus, OXT, OTRs, ANP, and endothelial NO synthase gene expressions in the heart are low [121]. In fasting men, intranasal OXT application can attenuate the peak excursion of plasma glucose [122]. Mechanistically, OTR signaling attenuates the death of beta cells in pancreatic islets exposed to cytotoxic stresses [123] and increases beta-cell response to the glucose challenge [122]. Furthermore, OXT can promote glucose uptake in cultured cardiomyocytes from newborn and adult rats [124], in myocardial cells during hypoxia [125] and in mesenchymal stem cells [126]. These facts indicate that OXT plays a significant role in the regulation of glucose metabolism and can prevent development and progression of diabetes mellitus. Thus, OXT could be used to reduce COVID-19 morbidity through glycemic control and stabilization.

### 5.5.4. Anti-social stress

Anxiety and panic are common responses in COVID-19 patients especially with ARDS [127]. OXT can reduce the expression of panic-related behaviors (e.g. fear and escape) by acting on the medial amygdala and the dorsal periaqueductal gray as previously reviewed [51]. OXT is positively associated with diminished stress among securely attached participants and can attenuate perception of stress due to adverse life events in old age [128]. In stroke, social pairing in adult mice enhances hypothalamic OXT gene expression and leads to smaller infarct size by reducing neuroinflammation and oxidative stress [112].

OXT can reduce stress-elicited neuroendocrine, autonomic, and behavioral responses [53], which can be used to prevent the brain-heart syndrome [129]. In addition, OXT also has anti-depressive effects [130] and may be used to relieve social isolation-associated depression in COVID-19 patients [48]. Thus, OXT/OTR signaling contributes to cardio-protection through diverse approaches in COVID-19.

### 5.6. Further questions about CV protective potential of OXT in COVID-19

In prevention and treatment of COVID-19, particularly the CV complications, OXT or OTR agonist is an ideal candidate for clinical trials. The following questions should be considered before its trials in management of COVID-19.

#### 5.6.1. Platelet aggregation and thrombosis

Some observations suggest that OXT can promote platelet aggregation. For example, inducing labor by using OXT tends to increase platelet aggregation and decrease disaggregation [131]; synthetic polyphosphate can inhibit OXT-induced platelet aggregation by reducing platelet Ca\(^{2+}\) levels and inhibiting the thromboxane A2 signaling pathway [132]. Notably, OXT has different effects on ADP-induced platelet aggregation at different reproductive states. That is, the aggregation is potentiated at low (≤200 nM) and inhibited at high (>400 nM) ADP concentrations in nonpregnant women; in pregnant women, OXT does not modulate ADP-induced platelet aggregation [133]. Since most of these observations are associated with parturition and depending on the doses of OXT applied, the pro-coagulation effect of OXT may facilitate homeostasis during parturition. In contrast, OXT generally protects endothelial cells from immunological injuries [110], increases anticoagulant heparan sulphate stability, and reduces adhesion molecules [110], and thus could reduce the formation of thrombosis. These facts support the possibility that OXT may reduce the pro-thrombotic state in non-pregnant COVID-19 patients.

#### 5.6.2. Biomarker or inducer of CV injuries

While OXT exhibits extensive protective potentials for CV complications in COVID-19, there are some observations showing controversial results about OXT protection of CV system. For example, left coronary artery ligation-induced myocardial infarction in rats increased OXT release, which was inhibited by melatonin [134], an agent having CV protective function. Acute myocardial infarction can increase brain release of OXT in the PVN which mediates sympahto-excitatory responses and the production of proinflammatory cytokines in rats [135]. Various stressors can provoke sudden CV effects and trigger the release of OXT in rats. However, administration of exogenous OXT on the ischemic-reperfused isolated heart of rats still reduced infarct size, levels of creatine kinase MB isoenzyme and lactate dehydrogenase in coronary effluent, and severity of ischemia and reperfusion injury [136]. As for the inhibition of OXT level by the CV protective melatonin [137], this effect is likely due to dose-dependent effects of melatonin on OXT secretion [70]. Taken together, these findings support that OXT is critical in immunologic surveillance [50] and the increased OXT levels function as a compensatory reaction to the acute hypoxia injury.

Another question is whether cardiac-specific over-expression of OTR is beneficial to myocardial functions. In mice with cardiac-specific over-expression of OTR, the left ventricular function was reduced, end-diastolic volume was larger and mortality was high along with cardiac fibrosis, atrial thrombus, and increased expression of pro-fibrogenic genes [138]. Interestingly, in rat dams separated from her pups, hypothalamic OXT secretion increased; however, plasma OXT levels were low. This is due to that over-activation of OTR signaling causes post-excitation inhibition and a subsequent reduction of the secretory activity of OXT neurons [139]. Thus, it is possible that over-expression...
or over-activation of OTR exerts an effect opposite to the physiological effect although normal OTR signaling is essential for CV protection.

The third question is about the effect of OXT on renin secretion. In denervated kidney, direct infusion of OXT can significantly increase renin secretion from the kidneys in association with the activation of β-adrenoceptors [140]. This effect is likely due to that the denervation of sympathetic nerve increases the expression of β-adrenoceptors or its sensitivity to adrenergic agonist, which amplifies a weaker OXT effects on renin secretion without the antagonism of secondary ANP release from the atrium and inhibition of sympathetic outflows from the PVN by OXT in vivo. As a whole, OXT increase during acute CV injuries can be viewed as a biomarker of cardiac stresses and a compensatory reaction of body defense system, but not an inducer of CV injuries.

### 6.3. Characteristics of OXT Effects on the CV System

OXT in the blood could differentially modulate CV activities, depending on the amount and pattern of its secretion from the posterior pituitary. This is because the effects of OXT on its targets are time-, dose- and pattern-dependent [141].

That is, longer and higher dose of OXT stimulation can cause inhibition of target cells following initial excitation [142,143]; OXT released in bolus can cause stronger response than the same amount of OXT in lower dose for longer time [144]. In the CV system, the same characteristics are also present. For example, in isolated hearts, 10⁻⁵ M OXT caused 10% reduction of left ventricle pressure, but 10⁻¹⁰ to 10⁻⁸ M concentrations had no effects while diastolic pressure raised and heart rate fell only with 10⁻⁵ M OXT [47].

Relative to the physiological levels of plasma OXT in 10⁻¹² to 10⁻¹¹ M [145,146], the negative ionotrop effects of OXT are clearly based on pharmacological mechanism. For example, the pressor effect of high-dose OXT is actually mediated by vasopressin receptors [147].

Under different conditions, expressions of OXT and OTR are also different [43], which make OXT effects on CV system different following changes in CV activity, such as the effect of cardiac-specific over-expression of OTR in mice [138].

In addition, the action of OXT is tissue-specific. In isolated dog carotid arteries, OXT causes vasoconstriction of human basal artery [41], likely by acting on smooth muscle cells [148]. It is also reported that OXT in 10⁻¹¹ to 10⁻⁷ M levels causes relatively weaker contraction of the basal artery compared to vasopressin and has no effects on mesenteric arteries in rats [149]. Intramuscular injection of OXT decreases uterine blood flow during uterine contractions in puerperal dairy cows [150], which occurs at postpartum day 2 but not day 5. Lastly, patterns of OXT actions are also important for its effect. For example, pulsatile but not tonic secretion of OXT plays the role of anti-precancerous lesions of the mammary glands in rat dams [151]; social desirability and milk transferred from the mother to the baby are largely dependent on OXT pulsatility [152]. Thus, in application of OXT, it is necessary to consider the location of target tissue- and organ-specific effect, the time- and dose-dependent effects as well as the patterns of application.

### 7. Strategies of OXT Application in COVID-19

#### 7.1. Clinical Trials of OXT in COVID-19 Patients

In management of COVID-19, many drugs have been considered, such as ACE2 blockers, anti-inflammatory drugs, antibiotics against IL-1 and anti-IL-6, remdesivir, dexamethasone, hydroxychloroquine and vaccines [153]. In clinical studies, their efficacies are either under further evaluation or proved to be ineffective. For instance, COVID-19 patients’ sera have only limited cross-neutralization [26], suggesting that recovery from one infection might not protect against the other. In patients with COVID-19, the hypothalamic-pituitary-adrenocortical axis is likely inhibited as stated above, which makes corticosteroid critical for prevention of cytokine storm [154]; however, corticosteroid delays virus clearing but does not convincingly improve survival or reduce hospitalization duration and the use of mechanical ventilation [155].

Hydroxychloroquine previously used to treat COVID-19 is known to prolong the QT interval and can have a proarrhythmic propensity [36]. Right now it is not given to COVID-19 patients as it is considered to be ineffective [156,157]. Lastly, COVID-19 vaccines have been developed extensively; however, their safety and efficacy profiles remain to be established. Notably, at 6 months after acute infection, COVID-19 survivors are troubled with fatigue, sleep difficulties, anxiety or depression and even severe impaired pulmonary diffusion capacities and abnormal finding on pulmonary imaging tests [158]. So far, there are currently no known specifically effective treatments for COVID-19. OXT, with broad-spectrum anti-COVID-19 potential, is relatively safe compared to anti-viral drugs and corticosteroids, and inexpensive relative to antiviral therapies [5,111], and thus is worthy of clinical trial to validate its efficiency.

In treatment of CV diseases, many approaches of applying OXT have been proposed [7]. These considerations are also viable for treating CV complications in COVID-19. In brief, OXT or its agonists can be used exogenously by intravenous infusion, intramuscular injection or intranasal application. OXT can be used in a continuous low dose to minimize potential CV disturbances, or in bolus to maximize the efficiency without desensitizing OTR. OXT can also be used in nasal approach to activate the OXT-secreting system. Special caution should be taken for pregnant women around parturition, particularly for those who are allergic to OXT or have high basal AT II levels. As reported, acute systemic administration of low-dose OXT exerts a protective role; however, chronic subcutaneous administration of low-dose OXT (20 or 100 ng/kg, for 28 days) can enforce AT II-induced hypertension, cardiac hypertrophy, and renal damage in rats although OXT itself does not have these effects [159].

Future laboratory study and clinical trial of OXT usages are critical in translating its therapeutic potentials into reality, not only for COVID-19 but also for other unexpected viral infections.

#### 7.2. Prevention of COVID-19 through Mobilization of Endogenous OXT

Besides the needs for treatment, prevention of COVID-19 is another irreplaceable potential of OXT. Human-to-human transmission via droplets and contaminated surfaces has been described, from both symptomatic and asymptomatic individuals. Correspondingly, wearing mask and social distance have been adopted as common prevention measures. While these measures are effective in reducing COVID-19 morbidity, they also raise concerns for massive social isolation and long-term psychological effects [160] that decrease immunological defense [50,51] and thus can increase COVID-19 susceptibility. It is known that social isolation can cause CV complications [161] while disrupting normal OXT secretion [162–164]. Importantly, application of OXT can alleviate social isolation-induced atherosclerosis and adipose tissue inflammation [165].

Currently, newly developed specific vaccines face the challenge of continued mutations in SARS-CoV-2 and immune evasion [166,167] while complete social isolation is difficult to achieve, which leave majority of the population remaining under the threats of COVID-19. Thus, strengthening the basic immunologic function is a measure that universally fits our human society, particularly for aged population who have reduced immunologic function and OXT production [168]. For this purpose, mobilization of endogenous OXT can be an optimal approach to improve our resistance to COVID-19 by blocking SARS-CoV-2 entry, reducing viral load, and reducing pre-existing comorbidities.

OXT is a “social hormone” and can be elicited by many types of healthy behavior via increasing vagal inputs and by conditioned reflex, such as massage [169], listening to music [170], brief mindfulness session [171], light therapy [172], and physical exercise [172,173]. Although the integrity of our human society can be disrupted by self-isolation and social distancing, mobilizing endogenous OXT functions can help us to rebuild it by giving individuals of high immunologic defense capacity and lower susceptibility to COVID-19 in the “re-

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8. Conclusion

CV protective potentials of OXT allow reversal of lymphocytopenia, suppression of cytokine storm, prevention of ARDS, and reversal of multiple organ failures. While blocking SAR-CoV-2 infection, OXT also has the potential to treat CV complications in COVID-19 patients through multiple mechanisms (Fig. 2). For this reason, we should repurpose OXT for treatment and prevention of COVID-19.

CRediT authorship contribution statement

SCW conceived the study and wrote the first draft; YFW conceived the study and made the final revision.

Declaration of competing interest

The authors declare that they have no competing interests.

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References

[1] P. Libby, T. Lucher, COVID-19 is, in the end, an endothelial disease, Eur. Heart J. 41 (2020) 3038–3044.

[2] A. Alharthy, F. Faqih, Z.A. Memish, D. Karakitsos, Fragile endothelium and brain dysregulated neurochemical activity in COVID-19, ACS Chem. Neurosci. 11 (2020) 2159–2162.

[3] J. Zhang, L. Zhou, Y. Yang, W. Peng, W. Wang, X. Chen, Therapeutic and triage strategies for 2019 novel coronavirus disease in Fever clinics, Lancet Respir. Med. 8 (2020) e11–e12.

[4] A. Barlow, K.M. Landolf, B. Barlow, S.Y.A. Yeung, J.J. Heavner, C.W. Claassen, M.S. Heavner, Review of emerging pharmacotherapy for the treatment of coronavirus disease 2019, Pharmacotherapy 40 (2020) 416–437.

[5] D. Macirow, S.Z.E. Idrissi, Y. Gupta, B.J. Medernach, M.B. Burns, D.P. Becker, R. Duvansula, P. Kempiash, A review of the preclinical and clinical efficacy of remdesivir, hydroxychloroquine, and lopinavir-ritonavir treatments against COVID-19, SLAS Discovery 25 (2020) 1108–1122.

[6] H.P. Yang, L. Wang, L. Han, S.C. Wang, Nonocclusive functions of hypothalamic oxytocin, ISRN Neurosci 2013 (2013) 179272.

[7] P. Wang, S.C. Wang, H. Yang, L. Lv, S. Jia, X. Liu, X. Wang, D. Meng, D. Qin, H. Zhu, Y.F. Wang, Therapeutic potential of oxytocin in atherothrombotic cardiovascular disease: mechanisms and signaling pathways, Front. Neurosci. 13 (2019) 454.

[8] G.D. Duerr, A. Heine, M. Hamko, S. Zimmer, J.A. Luetkens, J. Nattermann, G. Rieke, A. Iisaik, J. Jehle, S.A.E. Feld, J.C. Wasmuth, M. Wittmann, C. P. Strassburg, P. Brosmis, M. Colburn, H. Teedle, G. Nickenig, C. Kurts, M. Velten, Parameters predicting COVID-19-induced myocardial injury and mortality, Life Sci. 260 (2020) 118400.

[9] J.A. Luetkens, A. Iisaik, S. Zimmer, J. Nattermann, A.M. Sprinkart, C. Boesecke, G. J. Rieke, C. Zachoval, A. Heine, M. Velten, G.D. Duerr, Diffuse myocardial inflammation in COVID-19 associated myocarditis detected by multiparametric cardiac magnetic resonance imaging, Circulation Cardiovascular Imaging 13 (2020), e010897.

[10] D. Lindner, A. Fitzek, H. Brauningger, G. Aleshcheva, C. Edler, R. Meisner, K. Scherschel, P. Kirchhof, F. Escher, H.P. Schultheiss, S. Blankenberg, K. Pusche, D. Westermann, Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases, JAMA Cardiol. 5 (2020) 1281–1285.

[11] M. Madjid, R. Nafisi, S. Solomon, O. Vardeny, Potential effects of coronaviruses on the cardiovascular system: a review, JAMA Cardiol. 5 (2020) 801–810.

[12] C. Gebhard, V. Regitz-Zagrosek, H.K. Neuhauser, B. Morgan, S.L. Klein, Impact of sex and gender on COVID-19 outcomes in Europe, Biol. Sex Differ. 11 (2020) 29.

[13] S. Bennett, J. Tafuro, J. Mayer, D. Darlington, C. Wai Wong, E.A. Muntean, N. Wong, C. Mallen, C. Shing Kwok, Clinical features and outcomes of adults with COVID-19: a systematic review and pooled analysis of the literature, International journal of clinical practice (2020), e13725.
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14. M. Bansal, Cardiovascular disease and COVID-19, Diabetes & metabolic syndrome 14 (2020) 247–250.

15. D. Huang, X. Li, X. Song, H. Ma, Z. Lian, Y. Liang, T. Qin, W. Chen, S. W. Wang, Clinical features of severe patients infected with 2019 novel coronavirus: a systematic review and meta-analysis, Annals of translational medicine 8 (2020) 579–586.

16. E. Guedj, M. Million, P. Dudouet, H. Tissot-Dupont, F. Bregeon, S. Cammilleri, Structural insights on the role of antibodies in HIV-1 vaccine and therapy, Cell 156 (2014) 633–649.

17. M. Bansal, Cardiovascular disease and COVID-19, Diabetes 156 (2020) –151.

18. D. Mendelowitz, M.W. Kay, Chronic activation of hypothalamic oxytocin neurons improves cardiovascular function: studies in oxytocin-deficient mice, Am. J. Physiol. Heart Circ. Physiol. 300 (2011) H969–H986.

19. J. Kuzawa, W.H. McNab, R.C. Starling, Heart failure and COVID-19, Heart Fail. Rev. 26 (2020) 1–10.

20. J. Heijl, K.G. Tornkvist, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R. W. Finberg, K. Dierberg, V. Tapson, L. Hietsch, T.F. Patterson, R. Paredes, A. Sweeney, W.R. Short, G. Toufentou, D.C. Lye, N. Ohmagari, M.D. Oh, M. Ruiz-Palacios, T. Benitez-Patino, H. S. Boger, H. Kortepeter, R.L. Atmar, C. B. Creek, J. Lundgren, A.G. Babiker, S. Pett, J. D. Neaton, T.H. Burgess, T. Bonnet, M. Green, M. Makowski, A. Osnisui, S. Saya, D.C. Lane, A.-S. G. Members, Remdesivir for the treatment of COVID-19 – final report, N. Engl. J. Med. 383 (2020) 1813–1826.

21. Z.V. Johnson, L.J. Young, Oxytocin and vasopressin neural networks: implications for social behavioral diversity and translational neuroscience, Neurosci. Biobehav. Rev. 37 (2013) 87–98.

22. G.M. Abrams, G. Nilaver, L.R. Rech, J. Haldar, E.A. Zimmerman, Hypothalamic oxytocin: a cerebrovascular modulator in man? Neurology 35 (1985) 1046–1049.

23. M. Jankowski, D. Wang, F. Hajjar, S. Mukkadah-Daher, S.M. McCaun, J. Gutowska, Oxytocin and its receptors are synthesized in the rat vasculature, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 6205–6211.

24. A. Wool, K. Kasaravelu, M. Kuch, K. Gala, A. Cudnoch-Jedrzejewska, Increased activity of the intracardiac oxytocinergic system in the development of postinfarction heart failure, Biomed. Res. Int. (2016) 3652068.

25. J. Zhu, H. Wang, X. Zhang, X. Yao, Regulation of angiogenic behavior by oxytocin receptor through GII-induced transcription of HIF-1alpha in human umbilical vein endothelial cells, Biomed. Pharmacol. 97 (2019) 928–934.

26. S. Mukkadah-Daher, Y.L. Yin, J. Roy, J. Gutowska, R. Cardinal, Negative impact of chronic and chronic progressive HIV-1 infection on the cytokine storm in COVID-19, challenges and hopes, Life Sci. 257 (2020) 118054.

27. E. Guedj, M. Million, P. Dudouet, H. Tissot-Dupont, F. Bregeon, S. Cammilleri, Immunologic activity, J. Neuroimmunol. 289 (2015) 152–161.

28. Y. F. Wang, Oxytocin-secretion system: a major part of the neuroendocrine center regulating immunologic activity, J. Neuroimmunol. 289 (2015) 152–161.

29. Y.-F. Wang, Center role of the oxytocin-secretin system in neuroendocrine immune network revisited, Journal of Clinical & Experimental Neuroimmunology 1 (2016) 102.

30. H. Iishi, T. Amato, T. Matsubara, T. Murohara, Pharmacological intervention for prevention of left ventricular remodeling and improving prognosis in myocardial infection, Circulation 118 (2008) 2710–2718.

31. V.U. De Melo, R.R. Saldanha, C.R. dos Santos, Cruz J. De Campos, V.A. Lira, V. Santana-Filho, L.C. Michelini, Oxytocin hormone deprivation reduces oxytocin expression in paraventricular nucleus of male rats and correlates with baroreflex impairment in rats. Front. Physiol. 7 (2016) 461.

32. C. Viero, I. Shibuya, N. Kitamura, A. Verkhratsky, H. Fujihara, A. Katoh, Y. Ueta, D. Raoult, (18)F-FDG brain PET hypometabolism in post-SARS-CoV-2 infection: a systematic review and meta-analysis, Annals of translational medicine 8 (2020) 11592–11599.

33. G. Ronconi, E. Toniato, IL-1 induces throboxane-A2 (TxA2) in COVID-19 myocardial ischemic index, Life Sci. 257 (2020) 118065.
D. Li, M. Grima, J.-S. Jang, J.-Y. Helwig, J.L. Imbs, M. Barthelmès, Oxytocin-receptor driven mictions in rats with pup deprivation, ASN Neuro 12 (2020), 1759091420944658.

J. Gour, C. Michot, J. Ciosek, J. Drobnik, Function of the hypothalo-neurohypophysial system in different modes of administration of PGF2alpha in obstetrics and gynecology, Lactation 452 (2021) 13–25.

E.K. Ailamazyan, N.N. Petrishchev, E.V. Vivulanets, L.V. Maryutina, I. A Wsol, A Cudnoch-Je drzejewska, E Szczepanska-Sadowska, S Kowalewski, M. Petersson, K. Uvnas-Moberg, Postnatal oxytocin treatment of spontaneously hypertensive rats with myocardial infarction is modified by melatonin, Pharmacol. Rep. 64 (2012) 441.

Y.F. Wang, G.A. Tonio, G.I. Hatton, Autofeedback effects of progressively rising oxytocin concentrations on suprarenal oxytocin neural activity in slices from rat heart, Am J Physiol Regul Integr Comp Physiol 290 (2006) R1119–R1180.

Y.F. Wang, G.I. Hatton, Dominant role of beta-gamma subunits of G-proteins in oxytocin-evoked burst firing, J. Neurosci. 27 (2007) 1902–1912.

J.B. Wakeley, G. Clarke, A.J. Summerlee, Milk ejection and its control, in: M. Kobli, J.D. Neill (Eds.), The Physiology of Reproduction, Raven, New York, 1994, pp. 1131–1177.

C. Binay, C. Pakseti, S. Guzel, N. Samanci, Serum irisin and Oxytocin as Predictors of metabolic Parameters in Obese Children, Clin Res Pediatr Endocrinol 9 (2017) 16–31.

M.R. Lee, K.B. Scheidweiler, X.X. Xiao, F. Akhlaghi, A. Cummins, M.A. Huestis, L. Leggio, B.B. Averbeck, Oxytocin by intranasal and intravenous routes reaches the cerebrospinal fluid in rhesus macaques: determination using a novel oxytocin assay, Mol. Psychiatry 25 (2020) 117–122.

M.A. Petty, R.E. Lang, T. Unger, D. Ganten, The cardiovascular effects of oxytocin in conscious male rats, Eur. J. Pharmac. 112 (1985) 203–210.

P. D’Orleans-Juste, S. Dion, J. Mizrahi, D. Regoli, Effects of peptides and non-peptides on isolated arterial smooth muscles: role of endothelium, Eur. J. Pharmac. 114 (1985) 9–21.

C. Szabo, J.E. Hardebo, Regional differences in the contractile activity of neuropeptide Y, endothelin, oxytocin and vasopressin: comparison with non-peptidergic constrictor responses, Acta Physiol Hung. 79 (1992) 264–277.

H. Jameson, R. Bateman, P. Byrne, J. Dyvanyanali, X. Wang, V. Jain, D. Mendedolowitz, Oxytocin neuron activation prevents hypothermia that occurs with chronic intermittent hypoxia/hypocapnia in rats, Am. J. Physiol. Heart Circ. Physiol. 310 (2016) H1549–H1557.

M. Lehrke, N. Marx, Diabetes mellitus and heart failure, Am. J. Cardiol. 120 (2017) S37–S47.

J. Gurtowski, T.L. Broderick, D. Bogdan, D. Wang, J.M. Lavoie, M. Jankowski, Downregulation of oxytocin and natriuretic peptides in diabetes: possible implications in cardiomyopathy, J. Physiol. 587 (2009) 4725–4736.

J. Klement, V. Ott, K. Rapp, S. Brede, F. Piccinini, C. Cobelli, H. Lehmann, M. Hallischmid, Oxytocin improves beta-cell responsiveness and glucose tolerance in healthy men, Diabetes 66 (2017) 517–525.

S. Watanabe, F.Y. Wei, T. Matsunaga, N. Matsunaga, T. Kaituska, K. Tomizawa, Oxytocin protects against stress-induced cell death in murine pancreatic beta-cells, Sci. Rep. 6 (2016) 25185.

M. Florian, M. Jankowski, J. Gurtowski, Oxytocin increases glucose uptake in neonatal rat cardiomyocytes, Endocrinologie 151 (2010) 482–491.

T. Shiio, P.M. Kang, P.S. Douglas, J. Hampe, C.M.P. Ybane, J. Lawitts, L.C. Cantley, S. Irimo, The conserved phosphoinositide-3-kinase pathway determines heart size in mice, EMBO J. 19 (2000) 2527–2534.

N. Noisieux, M. Borie, A. Desnoyers, A. Menaouar, L.M. Stevens, S. Mansour, B. A. Danalache, D.C. Roy, M. Jankowski, J. Gurtowski, Preconditioning of stem cells by oxytocin to improve their therapeutic potential, Endocrinologie 153 (2012) 5361–5372.

H. Javelot, L. Weiner, Panic and paradigm: narrative review of the literature on the links and risks of panic disorder as a consequence of the SARS-CoV-2 pandemic, J. Psychosom. Obstet. Gynaecol. 19 (1998) 291–304.

R.T. Emery, D. Huber, M. Bidlingmaier, M. Reinecke, G. Klug, K.H. Ladwig, Oxytocin-induced coping with stressful life events in old age depends on attachment: findings from the cross-sectional KORA Age study, Psychoneuroendocrinology 56 (2015) 152–162.

X. Yang, W. Pei, X. Hu, The brain-heart connection in Takotsubo syndrome: the links and risks of panic disorder as a consequence of the SARS-CoV-2 pandemic, J. Psychosom. Obstet. Gynaecol. 19 (1998) 291–304.

H. Li, C. Chen, F. Hu, J. Wang, Q. Zhao, R.P. Gale, Y. Liang, Impact of corticosteroids use during SARS-CoV-2 infection, J. Endocrinol. Investig. (2020) 339–343.

F. Ferrau, F. Cecatto, S. Cannavo, C. Scarroni, What we have to know about corticosteroids use during SARS-CoV-2 infection, J. Endocrinol. Investig. (2020) 1–9.

H. Li, C. Chen, F. Hu, J. Wang, Q. Zhao, R.P. Gale, Y. Liang, Impact of corticosteroids use during SARS-CoV-2 infection, J. Endocrinol. Investig. (2020) 1–9.

A. Danalache, D.C. Roy, M. Jankowski, J. Gutkowska, Preconditioning of stem cells by oxytocin to improve their therapeutic potential, Endocrinologie 153 (2012) 5361–5372.

H. Javelot, L. Weiner, Panic and paradigm: narrative review of the literature on the links and risks of panic disorder as a consequence of the SARS-CoV-2 pandemic, J. Psychosom. Obstet. Gynaecol. 19 (1998) 291–304.
