



Potential Antioxidative, Anti-inflammatory and Immunomodulatory Effects of Ghrelin, an Endogenous Peptide from the Stomach in SARS-CoV2 Infection

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Abstract

The current COVID-19 pandemic is one of the most devastating events in recent history. The respiratory effects of this disease include acute respiratory distress syndrome, systemic inflammation, cytokine storm, and pulmonary fibrosis. Ghrelin, an endogenous ligand for the growth hormone secretagogue receptor, is a peptide hormone secreted mainly by the stomach. Interestingly, ghrelin possesses promising antioxidant, anti-and inflammatory effects, making it an attractive agent to reduce the complications of the SARS-CoV-2. In addition, ghrelin exerts a wide range of immunomodulatory and anti-inflammatory effects and can mitigate the uncontrolled cytokine production responsible for acute lung injury by upregulating PPAR γ and down-regulating NF- κ B expression. Ghrelin has also been reported to enhance Nrf2 expression in inflammatory conditions which led to the suppression of oxidative stress. The current opinion summarizes the evidence for the possible pharmacological benefits of ghrelin in the therapeutic management of SARS-CoV-2 infection.

Keywords COVID-19 · Ghrelin · Oxidative stress · Inflammation, NF- κ B · SARS-CoV-2, PPAR γ

Introduction

Coronavirus disease-2019 (COVID-19) is a respiratory infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a new member of the single-stranded RNA virus of the *Coronaviridae* family (Ghasemnejad-Berenji and Pashapour 2020a, b; Hosseini et al. 2020). This viral infection can be related to severe lower respiratory symptoms leading to acute respiratory distress syndrome (ARDS), sudden cytokine storm, inflammation, and subsequent death (Girija et al. 2020). It has been reported that ARDS, which is a serious manifestation of COVID-19, is associated with a complex interplay of multiple signaling pathways such as, activation of mitogen-activated protein kinase (MAPKs) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway, cytokine storm with sudden inflammation (Allawadhi et al. 2020). Moreover, cases with prior severe chronic lung inflammation like emphysema may suffer from pulmonary fibrosis originated by induction of epithelial-to-mesenchymal transition by fibrogenic growth factors like transforming growth factor-beta (TGF- β) (Gharaee-Kermani et al. 2007). It has been revealed that SARS-CoV-2 inter to the

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host cell through the use of angiotensin-converting enzyme 2 (ACE2) as its cellular receptor. ACE2 is a membrane-bound monooxypeptidase found ubiquitously in humans, and expressed predominantly in kidney, heart, intestine and pulmonary alveolar (type II) cells. The entry of SARS-CoV-2 into human cells is mediated by the interaction of a receptor-binding domain in its viral spike glycoprotein ectodomain with the ACE2 receptor (Bourgonje et al. 2020). This viral infection can provoke a cytokine storm, whereby pro-inflammatory chemokines and cytokines and such as IL-1 β , tumor necrosis factor- α , and IL-6 are overproduced by the immune system, resulting in extensive multiorgan injury (Tang et al. 2020). For the management of COVID-19, it is crucial to halt further viral replication as well as provide symptomatic recovery from the systemic complications, especially the respiratory complications (Hassan et al. 2020). Clinically, various antiviral drugs and anti-parasitic drugs have been tried in the past few months. However, the clinically beneficial effects of drugs like, favipiravir (Ghasemnejad-Berenji and Pashapour 2020a, b), hydroxychloroquine, chloroquine and remdesivir have been arguable. Therefore, introducing potential therapeutic targets for COVID-19 can be properly and of greatest importance to ameliorate clinical outcome and reduce mortality (Fakhri et al. 2020; Singh et al. 2020). Ghrelin, a 28-amino-acid acylated peptide produced and secreted predominantly by the X/A-like enteroendocrine cells of the stomach (Fakhri et al. 2020), is a peptide for the growth hormone secretagogue receptor (GHS-R). This endogenous ligand has been shown to possess specific properties that inhibit cell proliferation, oxidative stress, inflammation and, apoptosis (Eid et al. 2018; Prodam and Filigheddu 2014). In this review, we hypothesize that exogenous ghrelin in patients with COVID-19 could alleviate some of the severe symptoms that lead to cytokine storm syndrome and ARDS, via modulation of immune responses such as the NF- κ B pathway and a decrease in cytokine production.

Ghrelin Structure and Its Function in the Body

Ghrelin is a hormone primarily expressed by the X/A-like cells of the stomach. The ghrelin gene encodes a 117 amino acid peptide, known as pre-pro-ghrelin, which is subsequently cleaved into the mature 28 amino acid form in which it is secreted. Therefore, human ghrelin contains 28 amino acids, and a total molecular mass of 3370.9 Dalton and a molecular formula of C₁₄₉H₂₄₉N₄₇O₄₂ (Sato et al. 2012). During its maturation in the gastric mucosa and before secretion in the blood, the proghrelin is first cleaved and part of the proghrelin is octanoylated on its N-terminal 3rd serine residue, in the endoplasmic reticulum lumen. The stomach

enzyme involved in ghrelin octanoylation is called ghrelin O-acyltransferase (Gutierrez et al. 2008). Ghrelin-producing cells are not only present on the stomach, but also in the pancreas, duodenum, jejunum, lungs, pancreatic islets, gonads, adrenal cortex, placenta, and kidney. It has also been observed that ghrelin is produced locally in the brain (Ferrini et al. 2009). This hormone could enhance the growth hormone secretion. In addition, ghrelin has been found to be a potent inducer of food intake and also increases adiposity. During states of hunger, acylated ghrelin is released from the stomach into the circulation where it is transported into the brain affecting the feeding centers within the hypothalamus to induce sense of hunger (Delporte 2013). Ghrelin can act in the hypothalamus to regulate food intake, in the hippocampus to regulate neurogenesis, and in the olfactory bulb to regulate food-seeking behaviours. It has been determined that the primary signaling receptor for ghrelin, the growth hormone secretagogue receptor (GHSR), mediates the transport of ghrelin from blood to the brain. Ghrelin has also been reported to influence a number of other biological actions, including effects on glucose homeostasis, reproductive organ functions, sleep, memory, cardiovascular function, hormone secretion, gastrointestinal motility, neurogenesis, pancreatic function, cell proliferation and survival, bone metabolism, gastric emptying, and gastric acid secretion (Dixit and Taub 2005; Stengel and Taché 2012). Furthermore, several studies have demonstrated a role for ghrelin in regulating inflammation and inflammatory cytokine expression in rodents and humans both in vivo and in vitro as well as in T-cell development (Stengel and Taché 2012; Baatar et al. 2011; Dixit et al. 2004; Lin et al. 2016).

Ghrelin and Its Anti-inflammatory Effects

The anti-inflammatory effects of the endogenous peptides have received much attention in recent years. For example, recently TAT CARMIL1 a combination of two naturally occurring peptides that, when combined, work together to penetrate a cell's membrane in order to dampen an acute inflammatory response. The leucine-rich domains (LRR) of CARMIL1 interacts with IL-1 signaling proteins to facilitate IL-1-mediated matrix degradation. Degradation of the extracellular matrix is fundamental to IL-1-driven inflammatory diseases (Wang et al. 2020a, b, c). Previous studies reported that ghrelin inhibits mononuclear cell binding, proinflammatory cytokine production, and NF- κ B activation in human endothelial cells in vitro, as well as endotoxin-induced cytokine production in vivo. This suggests an anti-inflammatory function for ghrelin (Li et al. 2004; Wu et al. 2007a, b). There is a lot of evidence that ghrelin plays a key role in regulating immune function and inflammation. Also, ghrelin or its receptor, GHS-R, may have considerable roles

in various inflammatory disease states (Pereira and Silva 2017). Recently, ghrelin and its specific receptors have been detected in lung tissue, indicating that the peptide may play an important role in respiratory system regulation (Li et al. 2015; Zhang et al. 2019). It has been indicated that ghrelin interacted with proinflammatory cytokines and led to systemic inflammation in chronic obstructive pulmonary disease (Itoh et al. 2004; Miki et al. 2012). Ghrelin is also able to decrease basal and tumor necrosis factor α (TNF- α)-induced chemotactic cytokine production and mononuclear cell adhesion in human vascular endothelial cells (Hedayati et al. 2009). Furthermore, ghrelin and GHS-R are expressed in human monocytes and T lymphocytes; and activation of GHS-R by this peptide specifically subsides the expression of proinflammatory cytokines such as IL-6, IL-1 β , and TNF- α (Dixit et al. 2004). Apart from those 2 cell types, it has been found that ghrelin inhibited endotoxin-induced IL-6 production and reduced nitrite and nitrate release from peritoneal macrophages in vitro (Abrehdari et al. 2014). In addition, cecal ligation model of sepsis in rats, ghrelin showed an ameliorative effect via NF- κ B-dependent pathway (Peng et al. 2012). The downregulation of the brain levels of IL-6 and TNF- α by ghrelin has also been indicated after traumatic brain injury in rats (Qi et al. 2012). Ghrelin also significantly suppressed TNF- α and IL-1 β in the infarcted border of cardiac tissue in rats that underwent coronary ligation to induce MI (Yuan et al. 2009). Some examples of published studies and the inflammatory parameters measured after ghrelin administration are shown in Table 1.

Ghrelin and Its Protective Effects Against Acute Lung Injury Models

Ghrelin and its receptors have been detected in lung tissue, indicating that the peptide may play a role in respiratory regulation. Recent studies indicate that ghrelin has protective effects in acute lung injury models. The biological effects of ghrelin are mediated through the ghrelin receptors in the human lung pulmonary artery wall and parenchyma (Wu et al. 2007a, b; Imazu et al. 2011; Li et al. 2017). According to previous reports, treatment with ghrelin improved morphologic damage, pulmonary parameters, and decreased serum proinflammatory cytokine levels in pancreatitis-induced acute lung injury model. It has been shown that ghrelin could significantly improve the lung architecture in sepsis induced acute lung injury while administration of a specific ghrelin receptor antagonist worsens the survival rate in experimental animals (Zhou and Xue 2010). Furthermore, the ameliorative effect of ghrelin on lipopolysaccharide-induced acute lung inflammation by suppressing the proinflammatory cytokine production in lung macrophages has been observed (Chen et al. 2008).

Clinical Trials on the Use of Ghrelin in Respiratory Inflammatory Disorders

Despite a plethora of animal studies supporting the therapeutic anti-inflammatory potential of ghrelin, only a few human trials have been conducted on the use of ghrelin in inflammatory disorders. Kodama and colleagues reported that three-week administration of ghrelin to patients with chronic respiratory infection reduced neutrophil density and air sputum inflammatory cytokine levels, as well as increased exercise tolerance (Kodama et al. 2008). In a randomized double-blind placebo-controlled trial, three weeks of ghrelin treatment in patients with COPD similarly improved respiratory symptoms and respiratory strength (Miki et al. 2012). More recently, a randomized trial showed ghrelin treatment to reduce inflammation and pulmonary complications during the postoperative period following esophagectomy (Takata et al. 2015).

Preparation of Human Ghrelin and Way of Administration

In the study of Kodama et al. the synthetic human ghrelin was dissolved in water containing 4% D-mannitol. This solution was sterilized. The sterilized ghrelin solution was stored in 2-mL vials, each containing 120 μ g of ghrelin. All vials stored at -30 °C until administration. This solution was administered (2 μ g/kg, 20 mL solution) intravenously for 3 weeks to 7 cachectic patients with chronic respiratory infection to confirm ghrelin's effects on airway inflammation (Kodama et al. 2008).

Ghrelin and NF- κ B Signaling Pathway

The NF- κ B signaling pathway plays a crucial role in regulating the transcription of cytokine-encoding genes and has been considered a novel promising therapeutic target for inflammatory lung disease (Liu et al. 2017; Park and Christman 2006). Under inactivating conditions, NF- κ B dimers are bound to I κ B-inhibitory proteins, which sequester NF- κ B in the cytoplasm. Once activated, the I κ B kinase complex phosphorylates I κ B proteins, triggering I κ B ubiquitination and proteasomal degradation, releasing NF- κ B dimers to translocate to the nucleus to induce gene expression (Giridharan and Srinivasan 2018). It has been demonstrated that activation of the NF- κ B pathway plays a significant role in the development of acute lung injury (ALI) during the inflammatory responses (Zhang et al. 2019). The ameliorative effect of exogenous ghrelin

Table 1 Several examples of ghrelin-mediated regulation of proinflammatory cytokine expression in animal models and humans

Cytokine(s) suppressed by ghrelin	Animal/model	Mechanism/target	References
TNF- α , IL-1 β	Mice/acetetic acid-induced colitis	NA	Matuszyk et al. (2016)
TNF- α , IL-6	Rats/cecal ligation sepsis	Activation of vagus nerve (cholinergic stimulation)	Wu et al. (2007a, b)
IL-8, TNF- CRP, soluble ICAM-1	Cachectic patients with chronic respiratory infections	NA	Kodama et al. (2008)
TNF- α , IL-6	Rats/gut ischemia	Cholinergic stimulation	Wu et al. (2008)
TNF- α , IL-6	Rats/sepsis by cecal ligation and puncture	Stimulation of the vagus nerve	Wu et al. (2007a, b)
Pooled levels of proinflammatory cytokines (IL-1 β , TNF- α , IL-6, etc.)	Rats/nephrectomy, chronic renal failure model	NA	Wang et al. (2009)
IL-1 β , TNF- α	Rats/intratracheal instillation LPS	Increase in NO production	Chen et al. (2008)
TNF- α , IL-1 β	Rats/cardiac ischemia	Suppression of NF- κ B activation	Chang et al. (2004)
TNF- α , IFN- γ , IL-6, IL-1 α , IL-1 β	Mice, colitis	NA	Wu et al. (2008), Gonzalez-Rey et al. (2006)
TNF- α , IL-6	Rats/burn injury	NA	Şehirli et al. (2008)
TNF- α , IL-1 β	Rat, subarachnoid hemorrhage model	NA	Erşahin et al. (2010)
TNF- α	Rats, acetaminophen induced liver injury	NA	Jahromi et al. (2010)
IL-6	Dopaminergic SN4741 cell-line derived from the mouse substantia nigra	NA	Beynon et al. (2013)
TNF- α	Balb/c mice/Traumatic brain injury	Vagal Stimulation	Bansal et al. (2012)
TNF- α , IL-6	Rats/high-fat diet for inducing non-alcoholic fatty liver disease	LKB1/AMPK and PI3 K/Akt pathways	Li et al. (2013)
IL-1 β , IL-6	RAW264.7, NHEK cells	Antagonizing TNF- α /NF- κ B signaling pathways	Qu et al. (2019)
TNF- α , IL-1 β , and MCP-1	Rat/ unilateral ureteral obstruction model	Suppressing the TGF- β 1/Smad3/ NF- κ B signaling pathways	Sun et al. (2015)
L-1 β , IL-6, TNF- α and IL-18	Mice/ traumatic brain injury-induced acute lung injury	Pyroptosis/NF- κ B pathway	Shao et al. (2020)
TNF α and IL-6	Mouse endotoxemia model	NA	Nikitopoulou et al. (2020)

INF Interferon, *IL* interleukin, *LPS* lipopolysaccharide, *MCP-1* monocyte chemoattractant protein-1, *NA* not analyzed, *NF- κ B* Nuclear factor kappa B, *NO* nitric oxide, *TNF* tumor necrosis factor

in sepsis-induced ALI and its effect on reduction of pulmonary levels of proinflammatory cytokines is mediated by preventing NF- κ B activation (Wu et al. 2007a, b; Peng et al. 2012). It has been reported that ghrelin inhibits NF- κ B activity by modulating the expression of an upstream activator, nucleotide-binding oligomerization domain2 (NOD2), which transmits signals to receptor interacting protein (Rip2) to activate NF- κ B. Ghrelin has also been reported to down-regulate NF- κ B and TLR-4 expression in ventilator-induced lung injury in rats (Zheng et al. 2019). In a study by Zhang et al. (2019). Furthermore, ghrelin seems to exert anti-inflammatory effects in contact dermatitis and psoriasis by barring activation of the NF- κ B signaling pathway (Qu et al. 2019).

Ghrelin and Immunomodulatory Effect

Ghrelin, like the expression of several other endogenous gut peptides, is found in immune cells encompassing monocytes and natural killer cells as well as B and T cells (Hattori et al. 2001). In addition, also the ghrelin receptor is expressed on rodent immune cells and has subsequently also been detected on human T cells and monocytes (Hattori 2009). The expression of GH in immune cells is stimulated by ghrelin. This peptide modulates phagocytosis, enhances thymopoiesis and T cell development, which would be beneficial for patients with immunodeficiency due to glucocorticoid therapy, bone marrow transplantation, and HIV-1 infection. Ghrelin and ghrelin agonists have an immunomodulatory protective

effect under conditions of acute endotoxemia resulting in reduced tissue infiltration by immune cells and decreased mortality (Kasımay et al. 2006). This could be mediated directly via the interaction with immune cells since ghrelin reduces the mRNA and protein production of the proinflammatory cytokines such as IL-1 α , IL-6, IL-1 β , and TNF- α after an immune challenge (Dixit et al. 2004). Ghrelin affects both the Th1 and the Th2 pathways as demonstrated by the suppression of IL-2 and interferon- γ and IL-4 and IL-10 respectively in mice (Xia et al. 2004). Conversely, when ghrelin expression is knocked down in T cells by silencing RNA, levels of proinflammatory cytokines such as IL-17 and interferon- γ were severely increased giving rise to a physiological role of endogenous ghrelin in regulating the inflammatory immune responses (Dixit et al. 2009).

Ghrelin and PPAR- γ

Peroxisome proliferator-activated receptor-gamma (PPAR- γ) is a transcription factor belonging to the nuclear hormone receptor superfamily. Various evidence indicates that PPAR- γ exerts a broad range of effects on cardiovascular disease and activation of PPAR- γ was beneficial to delay the pathological change of fibrosis. Furthermore, PPAR γ agonism in resident alveolar macrophages significantly promotes host recovery and limits pulmonary inflammation following respiratory viral infections (Chen et al. 2016; Huang et al. 2019a, b, c). As it has been demonstrated during acute pneumonia, alveolar macrophage largely expresses PPAR γ (Huang et al. 2019a, b, c). PPAR γ activation is also responsible for the control of cytokine over-production with consequent amelioration of the tissue damage (Esposito et al. 2020). It has been reported that the adipogenic effects of ghrelin are mediated through the activation of PPAR- γ (Chabot et al. 2014). Several studies have indicated that ghrelin decreases myocardial fibrosis by upregulating PPAR- γ expression (Wang et al. 2018; Zhao et al. 2008).

Ghrelin and Oxidative Stress

The protective effects of ghrelin on oxidative stress-induced injuries in different organs such as the heart, kidney, brain, lung, gastrointestinal tract, and testis have been reported in several studies (Chang et al. 2004; Imazu et al. 2011; Huang et al. 2019a, b, c; Kheradmand et al. 2009; Suzuki et al. 2010). Ghrelin administration ameliorates experimental paclitaxel-induced neuropathy by increasing mitochondrial number and suppressing mitochondrial reactive oxygen species (ROS) production (Ishii et al. 2018). Studies on the effects of exogenous ghrelin on testicular ischemia have indicated that administration of this peptide increases

antioxidant enzyme activities and reduces the lipid peroxidation in the testicular tissue exposed to I/R (Taati et al. 2015, 2016). Furthermore, studies on the effect of ghrelin on cardiopulmonary bypass-induced myocardial injury has shown that ghrelin could exert cardioprotective effects by attenuating oxidative stress (Sukumaran et al. 2018). In addition, it has been reported that ghrelin attenuates sepsis-induced acute lung injury in rats by decreasing pulmonary oxidative stress (Zeng et al. 2015).

Ghrelin and Nrf2 Signalling Pathway

Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is an important endogenous modulator of ROS over-production by initiating antioxidative defense pathways. The Nrf2 transcription factor is expressed and present in various organs and tissues, including the kidney, muscle, lung, heart, liver, and brain. The Nrf2 transcription factor is tightly regulated by the repressor protein, Keap1 (Kelch-like ECH-associated protein 1). Under oxidative stress conditions, Nrf2 dissociates from Keap1, translocates to the nucleus, and consequently activates several cytoprotective genes to combat oxidative stress (Ma 2013). A recent study on the effects of ghrelin against the secondary brain injury following intracerebral hemorrhage has shown that ghrelin exerts its protective effect by activating the Nrf2 signaling pathway (Jiang et al. 2017). Furthermore, it has been reported that in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- Parkinson's disease model, ghrelin markedly enhanced Nrf2 expression which led to the suppression of oxidative stress and protection against MPTP induced cytotoxicity (Wang et al. 2020a, b, c).

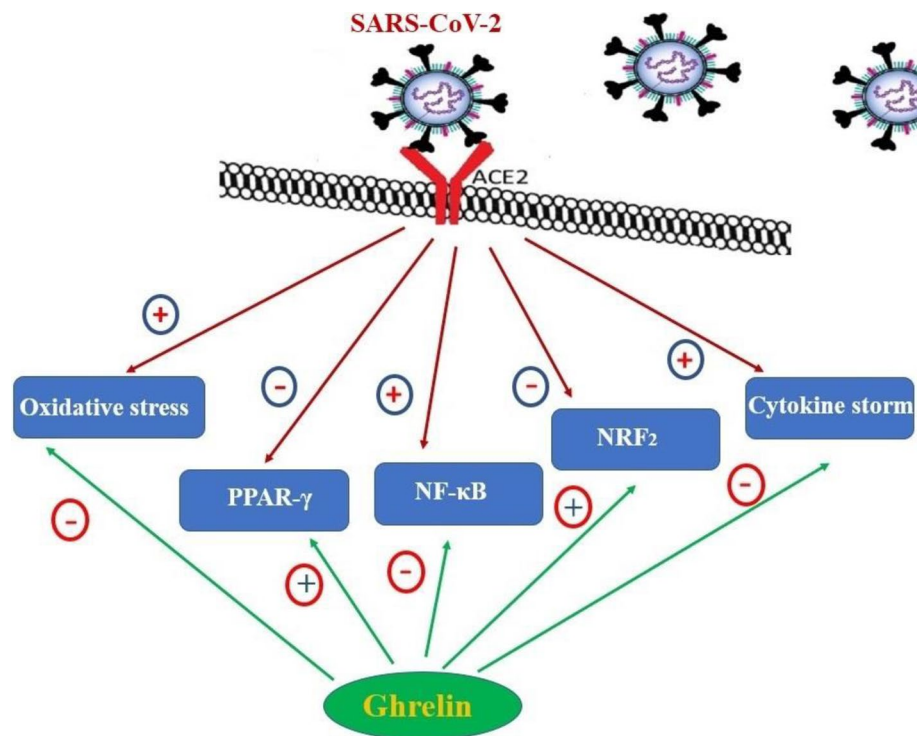
Ghrelin and the Potential Beneficial Effects on COVID-19

ARDS is a predictable severe complication of COVID-19 (Wang et al. 2020a, b, c). It is mediated by a complex interplay of multiple pathways like activation of NF κ B pathway, enhanced inflammation, cytokine storm, and oxidative stress (Wang et al. 2020a, b, c; Schönrich et al. 2020; Zhang et al. 2020). Although there is absence of basic, and clinical evidence on therapeutic effects of ghrelin on COVID-19 infection and the associated severe complications, preclinical studies to date demonstrated that this peptide is able to ameliorate the severity of ALI by reducing lung fluid accumulation, hypoxemia and cytokine secretion which occur in COVID-19-associated ARDS (Zheng et al. 2019). In addition to directly causing an improvement in lung dynamics, ghrelin could significantly counteract the onset of the cytokine storm from resident macrophages.

Therefore, ghrelin may potentially block acute effects of COVID-19, and its beneficial effects may extend to protecting other organs from the cytokine storm and reducing mortality (Yorulmaz et al. 2017). Another possible beneficial effect of ghrelin on COVID-19 could be related to the ability of this peptide on upregulating PPAR- γ expression. PPAR- γ acts on the transcription of the upstream inflammatory genes, thus preventing the cytokine over-production and becoming an attractive target for immunomodulatory. It has been reported that stimulation of PPAR- γ can exert a regulatory role on the cytokine storm induced by viral infections (Wang et al. 2018; Zhao et al. 2008). Reductions in PPAR- γ from SARS-CoV-2 may be an important effector of pulmonary inflammation and mechanistically involved in the pathogenesis of acute lung injury (Ciavarella et al. 2020). As such, use of the ghrelin may serve a useful therapeutic role by helping to reverse the inflammatory changes induced by SARS-CoV-2. Viral infections could evoke “cytokine storm” that leads to lung capillary endothelial cell activation, increased oxidative stress, and neutrophil infiltration (Morris et al. 2020). ARDS, characteristic of severe hypoxemia, is usually accompanied by uncontrolled severe inflammation, extensive oxidative injury, and damage to the alveolar-capillary barrier (Meng et al. 2019). Increased oxidative stress is a major insult in pulmonary injury including ALI and ARDS, two clinical manifestations of acute respiratory failure with substantially high morbidity and mortality (Chow et al. 2003). Oxidative stress is the result

of an imbalance between oxidant production and antioxidant mechanisms that leads to oxidative damage, including lipid peroxidation and DNA oxidation (Jafari et al. 2020; Yazdani et al. 2019). In addition to the neutrophil infiltration and release of ROS, viral infections are associated with a decrease in antioxidant defenses (Camini et al. 2017). Exposure to pro-oxidants usually leads to nuclear translocation of the master redox-sensitive transcription factor NRF₂, which activates antioxidant defenses; however, respiratory viral infections have been associated with inhibition of NRF₂-mediated pathways and NF- κ B signaling activation, which can promote inflammation and oxidative damage during these infections (Ahmed et al. 2017; Rahman and McFadden 2011; Wardyn et al. 2015). Hence the ameliorative effect of ghrelin on oxidative stress-induced injuries could be the other potential beneficial effect of this peptide on COVID-19 (Prodam and Filigheddu 2014; Suzuki et al. 2010; Ercan et al. 2013; Neamati et al. 2011). Several studies have shown that ghrelin could down-regulate NF- κ B and upregulate Nrf2 expression in inflammatory states (Zhang et al. 2019; Wang et al. 2020a, b, c; Cheng et al. 2020). Furthermore, a recent study has indicated that Nrf2 activation downregulates ACE2 expression, and its deficiency up-regulates the ACE2 receptor. It has been revealed that Nrf2 knockout mice present an enhancement in ACE2 expression (Zhao et al. 2018). Since ghrelin represses the inflammatory process by reducing oxidative stress and cytokine production; it might play a similar role in protecting against lung injury associated with COVID-19 (Fig. 1).

Fig. 1 The potential of ghrelin in SARS-CoV2 infection. Ghrelin recognizes several receptor targets and displays a multifaceted anti-oxidative, anti-inflammatory and immunomodulatory activity that could limit the severity of SARS-CoV2 infection: ghrelin could down-regulate NF- κ B and upregulate PPAR- γ and Nrf2 expression which lead to repression in cytokine storm and oxidative stress



Conclusions

In conclusion, we suggest that, in parallel to finding compounds for direct blockade of the SARS-CoV-2 penetration, introducing new safe therapeutic strategies for reducing the SARS-CoV-2 induced inflammation and oxidative stress should be paid particular attention. The possible beneficial effects of ghrelin as adjuvant use in COVID-19 in anti-inflammation, anti-oxidation, immune response regulation has been repeatedly demonstrated in respiratory disorder models. Herein, based on preclinical evidence, we hypothesize that according to the unique pharmacological properties, ghrelin might be an attractive preclinical candidate to reduce the complications of COVID-19. Further, it may be used as a prevention or treatment strategy in combination with other drugs.

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Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

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