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Keywords

Taurine · Coronavirus disease 2019 (COVID-19) · Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) · Oxidative stress · Inflammation · Treatment

Abbreviations

ACE2	angiotensin-converting enzyme 2
ADAM17	a disintegrin and metalloproteinase 17
Ang(1-7)	angiotensin 1-7
Ang II	angiotensin II
ARBs	AT_1R blockers
ARDS	acute respiratory distress syndrome
ATP	adenosine triphosphate
AT_1R	angiotensin II type 1 receptor
BH4	tetrahydrobiopterin
COVID-19	coronavirus disease 2019
CD147	cluster of differentiation 147
CRP	c-reactive protein
DAD	diffuse alveolar damage
EFSA	The European Food Safety Agency
EMMPRIN	extracellular matrix metalloproteinase inducer
eNOS	endothelial nitric oxide synthase
ER	endoplasmic reticulum
ET-1	endothelin-1
GSH	glutathione
HOCl	hypochlorous acid
H_2S	hydrogen sulfide
H_2S_n	hydrogen polysulfides
ICU	intensive care unit
IFN	interferon
IL	interleukin
mACE2	membrane-bound ACE2
MasR	Mas receptor
MAVS	mitochondrial antiviral-signaling proteins
MELAS	mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
MOF	multi-organ failure

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NLRP3	NLR family pyrin domain containing 3
NO	nitric oxide
nsp	nonstructural protein
NETs	neutrophil extracellular traps
$O_2^{\cdot-}$	superoxide
OTD	1.4.5-oxathiazinane-4,4-dioxide
PAI-1	plasminogen activator inhibitor 1
PDH	pyruvate dehydrogenase
PKG	protein kinase G
RAAS	renin-angiotensin-aldosterone system
RdRp	RNA-dependent RNA polymerase
ROS	reactive oxygen species
S	spike
sACE2	soluble ACE2
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TLRs	Toll-like receptors
TMPRSS2	transmembrane serine protease type 2
TNF	tumor necrosis factor
tPA	tissue plasminogen activator
TRD	taurolidine
TRPC3	transient receptor potential channel 3

1 Introduction

Taurine, or 2-aminoethanesulfonic acid, is a semi-essential compound that is produced endogenously in the human body but is also taken up by diet since it is abundantly present in seafood and meat. Although not incorporated into proteins, taurine is classified as an amino acid, where it can be distinguished from "true" amino acids by the presence of a sulfonic acid moiety, instead of a carboxyl one. Taurine is widely distributed in human tissues, residing both intracellularly (especially in leukocytes, platelets, heart, retina, and brain) and extracellularly (Wójcik et al. 2010). In human plasma, concentrations normally range between 65 and 179 mmol/L (8–22 µg/mL) (Ghandforoush-Sattari et al. 2009). Taurine has many physiological functions, including involvement in the conjugation of bile acids, regulation of oxidative stress, mitochondrial membrane stabilization, and osmoregulation, as well as modulation of cardiovascular and neurological functions (Qaradakhi et al. 2020; Wójcik et al. 2010). Considering its versatile biological roles, taurine has been shown to exert promising effects on improving overall health and for treatment purposes in several disease states, such as hypertension and diabetes (Maleki et al. 2020a, b; Schaffer and Kim 2018; Sun et al. 2016). The therapeutic potential of taurine has also recently been implicated for coronavirus disease 2019 (COVID-19), the infectious respiratory disease induced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in December 2019 and rapidly spread worldwide causing millions of deaths (Iwegbulem et al. 2021). Decreased serum taurine levels have been reported in SARS-CoV-2-infected subjects, where taurine levels were half the level compared to that of healthy controls, most notably in patients with moderate-to-high pro-inflammatory interleukin (IL)-6, with higher levels of IL-6 predictive of a severe disease course (Sabaka et al. 2021; Thomas et al. 2020). Furthermore, lower hypotaurine levels, the precursor of taurine, have been associated with an unfavorable prognosis of COVID-19 in an interventional metabolomics study (Danlos et al. 2021). These results have attracted our attention to the potential use of taurine as a beneficial supplement in taurine-depleted SARS-CoV-2-infected patients.

COVID-19 symptomatology ranges from asymptomatic or mild, self-limiting respiratory disease to severe disease, including (typical and atypical) acute respiratory distress syndrome (ARDS) and multi-organ failure (MOF) (Wang et al. 2021a). Some individuals are particularly at risk of developing severe disease, including the elderly (with associated "inflammaging" and "immunosenescence"), males, and those with comorbidities (e.g., diabetes, cardiovascular disease, obesity, chronic respiratory disease, immunodeficiency disorders) (van Eijk et al. 2021; Wang et al. 2021a). Progression of COVID-19 is assumed to result from multiple intertwined pathophysiological mechanisms, including (1)

direct cytopathic effects of SARS-CoV-2 invasion, (2) a hyperactive immune response with hypercytokinemia, (3) an inflammation-driven "oxidative storm," and (4) vascular-related effects, such as thrombotic microangiopathy and endothelial dysfunction (Cumpstey et al. 2021; van Eijk et al. 2021). We propose that the immune-modulating effects of taurine may be beneficial to each of these mechanisms and limit progression to severe disease considering its previously reported antiviral, (indirect) antioxidant, anti-inflammatory, and vascular-related effects.

Although COVID-19 was originally being considered a purely respiratory disease, we currently know that the virus also induces inflammation in and damage to other organ systems (Bourgonje et al. 2020a; van Eijk et al. 2021). Thus, the versatile effects of taurine may be widespread throughout the body. In addition, considering that a substantial subset of patients develop long-term symptoms after SARS-CoV-2 infection – so-called "chronic COVID syndrome," "long-COVID" or "long-haulers" – taurine may also be beneficial in the postinfectious phase (Baig 2021). Herein we aim to clarify the potential role of taurine in COVID-19 by dissecting the various pathophysiological mechanisms of this disease. Finally, we explore the possibilities of taurine as a putative supplementary therapy for COVID-19.

2 SARS-COV-2 Life Cycle and the Antiviral Actions of Taurine

2.1 Animals

SARS-CoV-2 is thought to be primarily transmitted between people through respiratory droplets and aerosols (van Eijk et al. 2021). As shown in Fig. 1, the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) at the cell membrane was found to be essential for viral cell entry (Hoffmann et al. 2020). In addition, transmembrane serine protease type 2 (TMPRSS2) was found to facilitate viral entry via endocytosis and be essential for direct fusion of the viral envelope to the cell membrane (Heurich et al. 2014; Hoffmann et al. 2020; Mahmoud et al. 2020). This route of viral entry matches that of SARS-CoV, the virus that caused an outbreak of severe acute respiratory syndrome in 2002−2004 (Heurich et al. 2014).

ACE2 is expressed in many tissues and cells throughout the human body, including a small population of lung cells – mainly type II alveolar epithelial cells (Wang et al. 2020b; Zou et al. 2020). Comparative studies investigating mRNA levels and protein expression of ACE2 demonstrated that other tissues besides the lung express high levels of ACE2, including the nasopharyngeal mucosa, suggesting that the main entry route of viral invasion is the nasal epithelium (Soni et al. 2021; Wang et al. 2020b). ACE2 was also found to be expressed on the enterocytes of the small intestine, as well as the vascular endothelium and arterial smooth muscle cells in various organs, supporting potential oral and blood-borne infectious routes, respectively (Hamming et al. 2004). In line with this wide tissue distribution of ACE2, the presence of SARS-CoV-2 has been demonstrated in various organs other than the lungs (Bourgonje et al. 2021b; Schurink et al. 2020; Song et al. 2021). For example, a cohort autopsy study examined the systemic SARS-CoV-2 distribution in postmortem organs from 26 COVID-19 patients and found SARS-CoV-2 in, among others, the lungs (92%), hilar lymph nodes (76%), small intestine (31%), colon (23%), heart (19%), and kidneys (15%) (Yao et al. 2021). Moreover, co-localization analysis demonstrated the co-expression of ACE2 and SARS-CoV-2 antigen in multiple organs (including the lungs, trachea, small intestine, heart, kidney, and pancreas), suggesting a potential correlation between membrane-bound ACE2 (mACE2) expression and SARS-CoV-2 tissue tropism (Liu et al. 2021). Alternative viral entry mechanisms include the presence of other viral entry receptors, such as furin, neuropilin-1, and cluster of differentiation 147 (CD147) – also known as extracellular matrix metalloproteinase inducer (EMMPRIN) or basigin – as well as the shedding of ACE2 into a soluble form, which provides a possible mechanism of dissemination of infection from the pri-

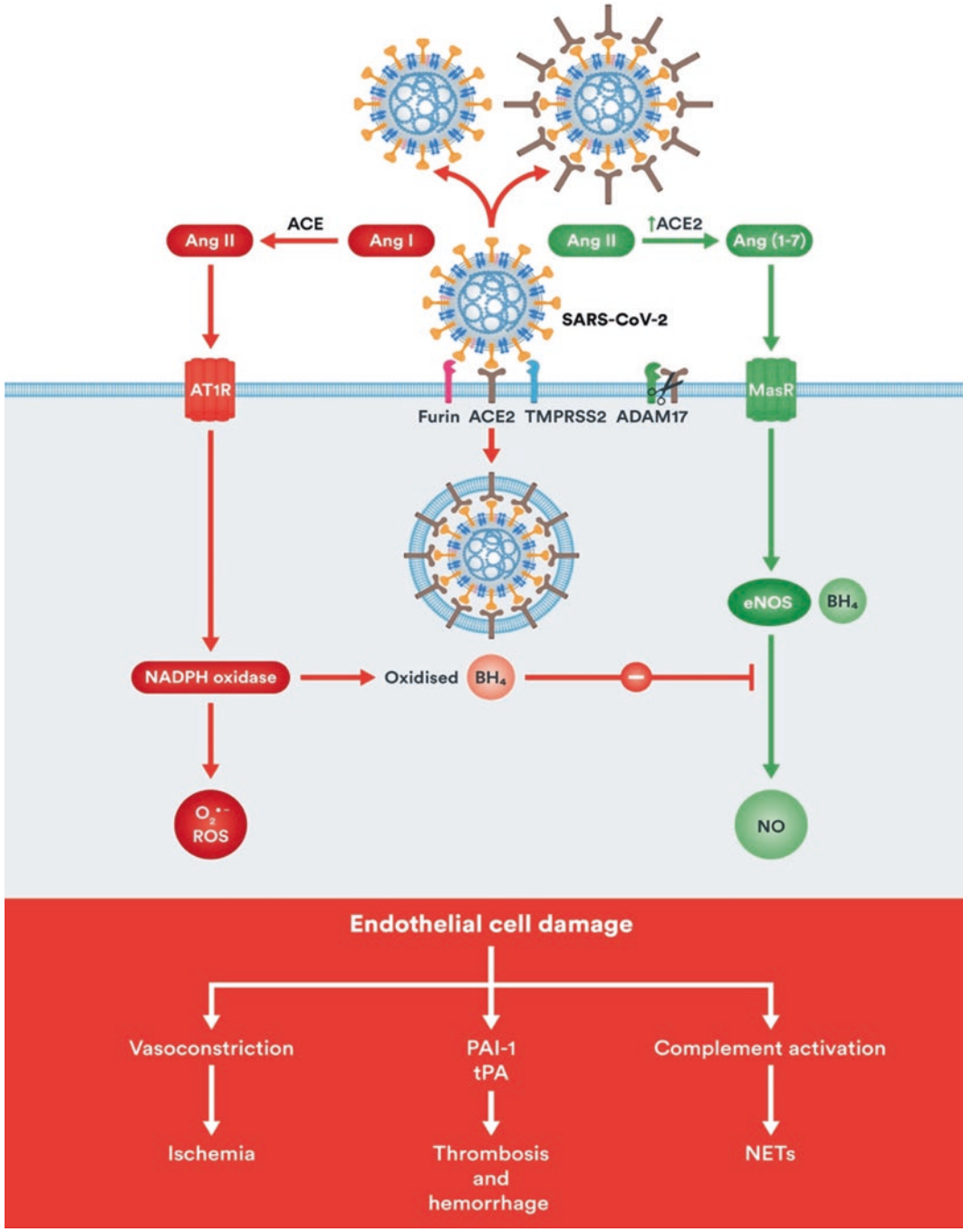

Fig. 1 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry and the involvement of angiotensin II (AngII) signaling in oxidative stress and inflammation in coronavirus disease 2019 (COVID-19). SARS-CoV-2 binding to ACE2 leads to viral entry into the host cell, which may be facilitated by transmembrane serine protease type 2 (TMPRSS2) and furin, among others. ADAM17 is a major sheddase of ACE2, resulting in soluble ACE2 that may bind to viral particles and potentially facilitate viral cell entry. Taurine stimulates ACE2, which functions as converter of Ang II into angiotensin 1-7 (Ang(1-7)) that in turn activates the Mas receptor (MasR). Ang(1-7)/MasR signaling stimulates endothelial nitric oxide synthase (eNOS) – in conjunction with its essential cofactor tetrahydrobiopterin (BH4) – to produce anti-inflammatory nitric oxide (NO). However, angiotensin II – converted from angiotensin I by angiotensin-converting enzyme (ACE) – activates the angiotensin II type 1 receptor (AT_1R), which stimulates NADPH oxidase to oxidize BH4, thereby inducing eNOS to produce superoxide instead of NO. The production of reactive oxygen species (ROS) may cause endothelial dysfunction that contributes to COVID-19-related vascular pathology in various ways, including vasoconstriction-induced ischemia, dysregulated fibrinolysis, and the formation of NETs via complement activation

mary site of infection to peripheral locations (Kyrou et al. 2021; Yeung et al. 2021). Although CD147's definite involvement in SARS-CoV-2 cell entry has not been established (Shilts et al. 2021), it was found to play a potential role in SARS-CoV-2 infection, either as a viral entry receptor (specifically in immune cells that do not express ACE2) or by reducing the expression of ACE2, which underscores a potential two-way contradictory effect of CD147 (Fenizia et al. 2021; Wang et al. 2020a).

A major sheddase of ACE2 is a disintegrin and metalloproteinase 17 (ADAM17), previously found to be activated when TMPRSS2 was not (Heurich et al. 2014). Notably, soluble ACE2 (sACE2) retains an intact interaction site for binding to SARS-CoV-2, which has recently been shown to form complexes with the SARS-CoV-2 spike protein (S) in a human kidney cell line (Yeung et al. 2021). In this study, the sACE2-S complex (either with or without interaction with vasopressin) facilitated cell entry via binding to angiotensin II type 1 receptor (AT_1R) (or AVPR1B in case of vasopressin interaction), resulting in receptor-mediated endocytosis. These findings indicate a potential role for sACE2 as a co-receptor required for viral entry in cells lacking mACE2 and additionally highlight the involvement of the renin-angiotensin-aldosterone system (RAAS) in this cell entry mechanism.

SARS-CoV-2 infection is assumed to downregulate mACE2 either via shedding or endocytosis of the virus/ACE2 complex (Vieira et al. 2021). Normally, at the cell membrane, ACE2 converts angiotensin II (Ang II) – the main effector of RAAS causing blood pressure elevation – into angiotensin 1-7 (Ang(1-7)), which has opposing effects through binding to the Mas receptor (MasR), inducing the production of nitric oxide (NO) which lowers blood pressure. SARS-CoV-2-induced downregulation of ACE2 shifts this balance toward Ang II, which exerts its effects via AT_1R. Apart from its main function as a regulator of blood pressure, Ang II also exerts pro-oxidative, pro-fibrotic, and pro-inflammatory effects (Benicky et al. 2009; Bourgonje et al. 2020a; Ruiz-Ortega et al. 2002). Interestingly, a study on neurogenic hypertension showed that Ang II-AT_1R signaling promotes ACE2 internalization into the cell and subsequent lysosomal degradation (Deshotels et al. 2014). This finding supports the hypothesis that the endocytosis of the SARS-CoV-2/mACE2 complex is AT_1R-mediated too, also considering the common occurrence of systemic hyperinflammation and the potential positive effects of AT_1R blockers (ARBs) on the prognosis of COVID-19 – although still under debate (Baral et al. 2021; Duarte et al. 2021; Jarcho et al. 2020; Singh et al. 2021a). In this case, viral cell entry would not solely depend on surface ACE2 expression, but also on its endocytosis induced by Ang II-AT_1R signaling. Taurine has previously been shown to upregulate mACE2 – albeit its magnitude still unknown – and attenuate the actions of Ang II (Lv et al. 2017; Schaffer et al. 2000). Taurine may therefore, in theory, impede viral cell entry by attenuating AT_1R-mediated endocytosis of the SARS-CoV-2/ACE2 complex, thereby preserving ACE2 protective functions, primarily by converting Ang II to Ang1-7. High-risk groups for severe COVID-19 (e.g., the elderly, cardiovascular disease, diabetes, etc.) could especially benefit from these protective effects of taurine, as they tend to show decreased ACE2 expression and activity (Bourgonje et al. 2020a; van Eijk et al. 2021). However, the question remains whether taurine may also affect mACE2-independent viral cell entry. Albeit an inhibitory effect of taurine on CD147 has been reported, and its effect on other potential viral entry receptors or sACE2 requires further examination (Jin et al. 2018).

2.2 Viral Replication

Next to potentially limiting host cell entry of SARS-CoV-2, taurine may also exert antiviral actions during the process of viral replication. Upon entering the cell, viral uncoating follows, in which SARS-CoV-2 is disassembled to release its genomic RNA. After primary translation, the process of transcription and replication is initiated, mediated by the RNA-dependent RNA polymerase (RdRp, or nonstructural protein [nsp] 12). This is followed by translation of structural proteins, which assemble and encapsulate the newly formed genomic RNA, thereby generating

new viral particles that are released from the host cell by exocytosis (V'Kovski et al. 2021). RdRp forms a complex with two nonstructural proteins, nsp7 and nsp8, which catalyze RNA synthesis, together forming a potential therapeutic target to inhibit SARS-CoV-2 replication. For instance, the antiviral actions of RdRp inhibitors (e.g., remdesivir) and hydrogen sulfide (H_2S) donors (e.g., N-acetylcysteine) are thought to be mediated by acting on the RdRp/nsp7/nsp8 complex (Bourgonje et al. 2021a). Taurine has previously been shown to increase endogenous H_2S levels and may therefore indirectly inhibit viral replication by inhibiting RdRp (Sun et al. 2016; Zhao et al. 2018).

When viruses exploit the hosts' cellular machinery for their own replication, stress in cellular organelles such as the endoplasmic reticulum (ER) and mitochondria is induced, while host response mechanisms are inhibited (Ajaz et al. 2021; Li et al. 2015). Viral replication also requires large quantities of ER-produced proteins and lipids, which accumulate and induce ER stress whenever the amount exceeds the post-translational process of protein folding (Li et al. 2015). ER stress was found to promote viral replication as was previously demonstrated for reovirus and hepatitis B virus, which potentially also relates to SARS-CoV-2 (Choi and Song 2019; Li et al. 2015). In fact, research on coronavirus-induced ER stress has been suggested to provide new targets for treating COVID-19 (Sureda et al. 2020). Previous studies have demonstrated that taurine inhibits ER-stress and its downstream effects, including apoptosis and activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome (Bian et al. 2018; Liu et al. 2019; Men et al. 2010).

Furthermore, taurine enhances mitochondrial function that may result in decreased viral replication due to its stimulating effect on interferon (IFN) production – which is initially compromised in COVID-19 (vide infra) (Bender et al. 2015; van Eijk et al. 2021). Mitochondrial antiviral-signaling proteins (MAVS), located on the outer mitochondrial membrane, peroxisomes, and the mitochondria-associated membrane of the ER, lead to the production of IFNs (Bender et al. 2015). A recent study on COVID-19 demonstrated that SARS-CoV-2 evades the antiviral type I IFN response by targeting MAVS (Wang et al. 2021b). These literature-based hypotheses on the antiviral effects of taurine provide a rationale for conducting future research (e.g., in SARS-CoV-2-infected cell lines) to test the actual effects of taurine on SARS-CoV-2 uptake and replication.

Finally, modulation of lipid metabolism by taurine could potentially interfere with the viral life cycle, considering lipids are the essential components of the SARS-CoV-2 envelope and double-membrane vesicles in the host cell involved in viral cell entry, viral replication, and viral propagation (Abu-Farha et al. 2020; Caterino et al. 2021). Taurine may modify the structure of the phospholipid bilayer through inhibition of phospholipid N-methyltransferase – an enzyme that regulates the ratio of phosphatidylethanolamine (PE) and phosphatidylcholine (PC) (Schaffer et al. 2010). As PE is normally situated on the outer side and PC on the inner side of the membrane, one can imagine that alterations in their ratio would influence the membrane's structure and function (Schaffer et al. 2010). Other potential taurine-mediated effects on lipid-dependent viral replication include the modulation of molecules that impact lipids, such as cholesterol. Indeed, taurine modulates cholesterol metabolism with cholesterol-lowering effects, which may be explained through various mechanisms, including improved LDLR-binding capacity and increased formation of fecal bile acid via upregulating CYP7A1, among others (Chen et al. 2012).

3 Age-Related Mitochondrial Dysfunction in COVID-19 and the Indirect Antioxidant Actions of Taurine

There are multiple age-related contributors to the increased risk of severe disease in COVID-19, including (among others) an increased incidence of comorbidities in older patients, a decline in immune function affecting innate and adaptive

immune responses ("immunosenescence"), and a chronic pro-inflammatory profile ("inflammaging") (van Eijk et al. 2021). As seen in Fig. 2, inflammaging is associated with the deterioration of mitochondrial function, which entails mitochondria that are incompetent to produce sufficient amounts of adenosine triphosphate (ATP) to meet metabolic demands, while producing an excessive amount of reactive oxygen species (ROS), causing oxidative stress to the cell, resulting in chronic inflammation in the elderly. Mitochondrial dysfunction affecting immune cells is associated with immunosenescence, thereby contributing to excessive inflammation (with increased activation of NLRP3, NF-κB, and increased levels of IL-6) and impaired adaptive immunity as seen in COVID-19. Inflammation itself goes along with immune cell infiltration that generates and releases ROS, which normally function in cell signaling pathways important to their immunological functions (Bourgonje et al. 2020b). However, COVID-19 promotes the overproduction of ROS with antioxidant systems being overrun, causing harmful oxidative stress with resulting tissue damage and ongoing inflammation (Ganji and Reddy 2020).

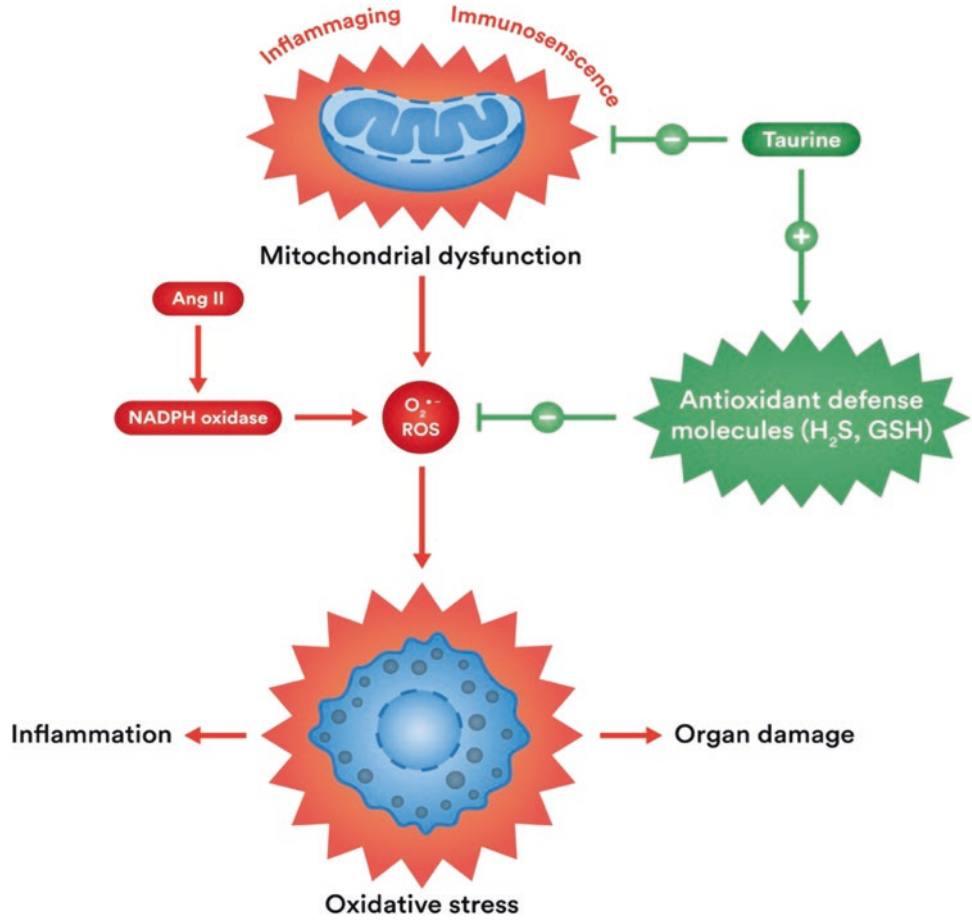

Fig. 2 Interrelationships between age-related mitochondrial dysfunction, oxidative stress, and taurine. Age-related inflammaging and immunosenescence are associated with mitochondrial dysfunction, leading to excessive amounts of reactive oxygen species (ROS). In addition, ROS is promoted by angiotensin II (Ang II) through the activation of NADPH oxidase. ROS in turn cause oxidative stress to the cell, resulting in tissue damage and ongoing inflammation. These effects may be alleviated by taurine because of its indirect antioxidant effects, including its stimulating effect on mitochrondrial functions and by enhancing endogenous hydrogen sulfide (H_2S) and glutathione (GSH) availability

Ang II promotes ROS through the activation of NADPH oxidase, which is counteracted by conversion of Ang II into Ang(1-7) by ACE2 (Gwathmey et al. 2010; Rabelo et al. 2011). Notably, taurine was found to protect against oxidant-induced lung injury and pulmonary fibrosis (Gurujeyalakshmi et al. 2000; Schuller-Levis et al. 1994, 2003). Conversely, taurine concentrations were repeatedly observed to be decreased in oxidative stress-mediated disorders and during aging (Ito et al. 2012; Yoshimura et al. 2021). Although taurine does not appear to have inherent antioxidative capacity, it indirectly increases antioxidation by improving mitochondrial functions (by enhancing electron transport chain activity), thereby attenuating mitochondrial ROS production (Barbiera et al. 2020). Furthermore, taurine displays indirect antioxidant activity through the enhancement of endogenous H_2S and glutathione (GSH) – a tripeptide synthesized from cysteine – availability, both of which are major antioxidants (Bourgonje et al. 2021a). H_2S exerts its antioxidant effects through multiple mechanisms, including the direct scavenging of ROS, increasing levels of other antioxidant defense molecules (such as GSH), and by desulfuration generating sulfane sulfur species (Bourgonje et al. 2021a; Corsello et al. 2018). Finally, taurine is known to neutralize hypochlorous acid (HOCl), which is a major toxic oxidant generated by the myeloperoxidase-halide system within activated leukocytes and is involved in multiple age-related diseases (Casciaro et al. 2017; Chorazy et al. 2002; Goud et al. 2021).

4 COVID-19 Immune Response and the Immune-Related Actions of Taurine

A maladaptive immune response is a hallmark of COVID-19, consisting of a hyperinflammatory innate immune response along with an inadequate adaptive response, eliciting both local and systemic tissue damage (van Eijk et al. 2021). Autopsy data show evidence of an extensive inflammatory response in various organs, including the lungs, kidneys, heart, brain, and liver (Schurink et al. 2020). The type and magnitude of the immune response highly depend on the phase of the disease course. The interstitial infiltrate in the lungs of patients with exudative diffuse alveolar damage (DAD), for example, was found to be CD4+-T-lymphocyte-mediated, whereas in patients with proliferative DAD, this response was primarily CD8+-T-lymphocyte-mediated (Schurink et al. 2020). Furthermore, early COVID-19 is characterized by a more pronounced viral presence and increased neutrophil infiltration, whereas increased macrophage and lymphoplasmacytic infiltration are more often observed when the disease progresses (Nienhold et al. 2020; Rendeiro et al. 2021). The disconnection between viral presence in early disease and inflammatory pathology in late COVID-19 underscores the role of self-perpetuating immunopathology in causing severe disease when the virus usually can no longer be detected.

Similar to other viral infections, the immune response against SARS-CoV-2 starts with the activation of pattern recognition receptors, such as Toll-like receptors (TLRs) that lead to the activation of transcription factors, ultimately resulting in the production of IFN-I, which exerts antiviral actions (Kumar et al., 2021). COVID-19 is characterized by an initial delay in IFN-I response, allowing the virus to replicate and disseminate uncontrollably within the infected host, thereby stimulating a strong activation of the immune response, which promotes hyperinflammatory injury during later stages of COVID-19 (van Eijk et al. 2021). SARS-CoV-2-induced activation of NLRP3 inflammasome was also shown to contribute to this hyperinflammation (Pan et al. 2021). The overactivation of the immune response is characterized by extensive hypercytokinemia – the so-called cytokine storm (Henderson et al. 2020). High serum levels of IL-6, IL-8, and tumor necrosis factor (TNF) at the time of hospitalization were found to be strongly and independently predictive of mortality (Del Valle et al. 2020). Furthermore, the change in ratio of pro-inflammatory IL-6 to anti-inflammatory IL-10 taken 4 days apart, called the Dublin-Boston score, was found to be of prognostic value in COVID-19 (McElvaney et al.

2020). Administration of taurine may be effective in reducing IL-6 and increasing IL-10, either directly or indirectly by affecting other inflammatory modulators, such as NLRP3 (Lak et al. 2015; Liu et al. 2019). Conversely, the SARS-CoV-2 infection especially in patients with moderate to high pro-inflammatory IL-6 levels was associated with decreased taurine levels (Thomas et al. 2020). This decrement could be potentially related to reduced taurine biosynthesis in COVID-19. For example, oxidative stress oxidizes the active form of vitamin B6, pyridoxal-5'-phosphate (PLP), which is involved as cofactor in endogenous taurine synthesis (Mahootchi et al. 2021). Another potential explanation to decreased serum taurine levels includes a shift in taurine distribution with increased body requirements due to its function as conjugator. This hypothesis is supported by a study in which increased levels of taurine were measured in peripheral blood mononuclear cells (PBMCs), where it can neutralize HOCl, thereby favoring anti-oxidation and anti-inflammation (Chorazy et al. 2002; Singh et al. 2021b). Other pro-inflammatory mediators have been shown to be inhibited by taurine, including Ang II, AT_1R, TLR4, IL-1β, NADPH oxidase, and the NLRP3-inflammasome (Han et al. 2016; Liu et al. 2019; Schaffer et al. 2000; Younis et al. 2021). At the same time, taurine can increase anti-inflammatory ACE2 and Ang(1-7), in addition to IL-10 (Lv et al. 2017; Schaffer et al. 2000). Supplementation dosages vary greatly across human studies reporting on the effect of taurine supplementation on inflammatory markers. For instance, studies on obesity (3 gram/day for 8 weeks), type 2 diabetes (1000 mg 3 times/day for 8 weeks), and traumatic brain injury (30 mg/kg/day for 2 weeks) resulted in decreased levels of C-reactive protein (CRP), both TNF-α and CRP, and IL-6 respectively (Maleki et al. 2020b; Rosa et al. 2014; Vahdat et al. 2021).

The aforementioned downregulation of ACE2 with subsequent disrupted orchestration of the Ang II:Ang(1-7) ratio may contribute to the excessive inflammatory response in COVID-19 patients. Ang II binding to AT_1R for instance induces the activation of pro-inflammatory mediators, including TLR4, IL-6, Il-1β, NF-κB, NADPH oxidase, and NLRP3-inflammasome (Fazeli et al. 2012; Wen et al. 2016). Together, these mediators induce the production of superoxide ($O_2^{\cdot-}$), increase vascular permeability, and facilitate leukocyte and thrombocyte adhesion as an excessive response to the infection (Jin et al. 2020; Mittal et al. 2014). The inhibition of Ang II/AT_1R-signaling by taurine may prevent the ACE2-bound virus from entering the cell, limit the pro-inflammatory response, and facilitate anti-inflammation. During a moderate innate immune response, Ang(1-7) activates the MasR, which induces endothelial nitric oxide synthase (eNOS) to produce anti-inflammatory NO (Sampaio et al. 2007). Interestingly, taurine has been found to increase eNOS expression and phosphorylation (Guizoni et al. 2020). Ang II/AT_1R-signaling, however, activates superoxide-producing NADPH oxidase, which causes oxidation of the essential eNOS cofactor tetrahydrobiopterin (BH4), inducing eNOS to produce $O_2^{\cdot-}$ rather than NO – a process called eNOS uncoupling (Bowers et al. 2011; Fazeli et al. 2012). Inhibition of NADPH oxidase by taurine may therefore limit $O_2^{\cdot-}$ production, thereby resulting in an increased availability of BH4 for the activation of eNOS to produce anti-inflammatory NO (Myojo et al. 2014).

Taurine also inhibits TLR4, which has the dual function of initially activating a pro-inflammatory response by way of pro-inflammatory cytokines and an anti-inflammatory response after it is endocytosed into the cell (Kim et al. 2013). Inside the cell, TLR4 activates anti-inflammatory cytokines, such as IL-10, after which TLR4-signaling is ended (Chang et al. 2009; Guven-Maiorov et al. 2015; Kim et al. 2013). In leukocytes, taurine traps and reacts with HOCl to produce taurine chloramine, which inhibits the generation of inflammatory mediators, such as IL-6 and TNF-α (Chorazy et al. 2002). Finally, alteration of the gut microbiota (with its immunomodulatory potential) in response to SARS-CoV-2 infection has been linked to increased levels of inflammatory markers and more severe COVID-19 (Yeoh et al. 2021). Taurine has a modulatory role on the gut

microbiota by potentiating the production of sulfide, an inhibitor of pathogen respiration key to viral invasion into the host, thereby enhancing the resistance against viral infection (Stacy et al. 2021).

5 COVID-19 Vascular Pathology and the Vascular-Related Actions of Taurine

5.1 Prothrombotic State

COVID-19 predisposes individuals to a prothrombotic state, characterized by elevations in D-dimer and fibrinogen levels, both correlates of a poor outcome (Di Micco et al. 2020; He et al. 2021). Consistent with this prothrombotic state, both pulmonary and extrapulmonary microthrombotic and thromboembolic complications are common among severely affected COVID-19 patients, findings which are thought to contribute to disease symptomatology and MOF (Fahmy et al. 2021). For example, microthrombi in the lungs could lead to pulmonary vascular redistribution, thereby contributing to the gas exchange abnormalities observed in COVID-19 (Thillai et al. 2021). The microvascular thrombi have been shown to contain neutrophil extracellular traps (NETs) associated with platelets and fibrin, indicating inflammation as an underlying mechanism for the observed thrombotic complications in COVID-19 – a process also known as "dysregulated immunothrombosis" (Ackermann et al. 2021; Nicolai et al. 2020). Although intravascular microthrombosis is not specific to COVID-19 as it may also occur in sepsis-induced disease states, it was previously shown to occur more frequently in COVID-19-induced respiratory failure when compared to patients with influenza by a ninefold increase (Ackermann et al. 2020). The pathophysiology of the observed thrombosis is complex and assumed to result from an interplay between various underlying mechanisms, including endothelial damage, platelet dysfunction, complement activation associated with the formation of thrombogenic NETs, hypercytokinemia (including IL-6-mediated platelet abnormalities and thrombogenesis), and abnormal blood flow (e.g., due to hyperviscosity or impaired microcirculation in response to hypoxia) (Ackermann et al. 2021; Ahmed et al. 2020; van Eijk et al. 2021).

Taurine may be protective in thrombotic complications of COVID-19 by acting on these different underlying mechanisms. For example, the vasorelaxant functions of taurine (vide infra) may restore hypoxia-induced impaired microcirculation, thereby attenuating thrombosis induced by abnormal blood flow (Ahmed et al. 2020; Nishida and Satoh 2009). Furthermore, the above-described anti-inflammatory effects of taurine will likely attenuate thrombosis associated with the cytokine storm. In COVID-19, cytokine-induced (and possibly virus-induced) endothelial damage, as well as increased Ang II/AT_1R signaling, may stimulate the release of plasminogen activator inhibitor 1 (PAI-1), an inhibitor of fibrinolysis and a risk factor of thrombosis, from primarily endothelial cells lining the blood vessels (Ahmed et al. 2020). Elevated PAI-1 levels have previously been observed among intensive care unit (ICU)-admitted COVID-19 patients, and impaired fibrinolytic activity has further been demonstrated by prolonged clot lysis time in critically ill COVID-19 patients (Nougier et al. 2020; Wright et al. 2020). In ARDS, elevated PAI-1 levels have been shown to be an independent risk factor for poor outcomes and appear to play a role in fibrin deposition leading to fibrosis (Whyte et al. 2020). Taurine may hamper PAI-1 release (e.g., possibly through attenuating cytokine-induced endothelial damage or inhibiting AT_1R), as was previously demonstrated in animal studies, and could therefore restore the fibrinolytic shutdown in severe COVID-19 (Lee et al. 2005; Ruan et al. 2016). Simultaneously, due to its stimulating effect on ACE2, taurine favors the Ang(1-7)/Mas pathway, activation of which leads to the inhibition of platelet adherence and aggregation via the release of NO (Ahmed et al. 2020). Furthermore, ACE2 itself has antithrombotic effects, partly through the activation of tissue plasminogen activator (tPA), a serine protease found on endothelial cells involved in fibrinolysis (Ahmed et al. 2020). Paradoxically, a recent study in 118 hospitalized COVID-19 patients found elevations in not only PAI-1 levels but also tPA levels, findings that are similar to sepsis-induced coagulopathy (Schmitt

et al. 2019; Zuo et al. 2021). These results indicate that fibrinolytic homeostasis in COVID-19 is complicated and provide an explanation for the enhanced bleeding risk among critically ill patients, in addition to the well-known enhanced thrombotic risk (Al-Samkari et al. 2020). An animal study exploring the effect of taurine in combination with delayed tPA on embolic stroke found that this treatment prevented tPA-associated hemorrhage, as well as fibrin/fibrinogen and platelet deposition in (micro)vessels, which could be linked to the inhibition of CD147 by taurine (Jin et al. 2018). Thus, taurine may be protective by regulating fibrinolytic activity, preventing both hemorrhage and thrombosis, through its inhibitory effect on CD147. In addition to improving microvascular patency, the inhibitory effects of taurine on CD147 may potentially limit SARS-CoV-2 uptake and COVID-19-associated hyperinflammation, considering its role in increasing inflammation and fibrosis after a pro-inflammatory insult (Fenizia et al. 2021; Jin et al. 2019; Wang et al. 2020a; Zhu et al. 2014). Although most data come from animal models, the antithrombotic properties of taurine have also been demonstrated in human studies (Santhakumar et al. 2013; Franconi et al. 1995; Ijiri et al. 2013). Findings included a decrease platelet aggregation (Santhakumar et al. 2013; Franconi et al. 1995), a prolongation in prothrombin clotting time (Santhakumar et al. 2013), and an increase in endogenous thrombolytic activity (Ijiri et al. 2013).

5.2 Vasoconstriction

As the endothelial cell layer is a key regulator of vascular homeostasis through its production of vasodilators (e.g., NO, prostaglandins, and endothelium-derived hyperpolarizing factor) and vasoconstrictors, including endothelin-1 (ET-1), endothelial damage in COVID-19 could lead to a prothrombotic and pro-inflammatory state of vasoconstriction (Varga et al. 2020). Release of ET-1 and platelet-activating factor shift the vascular equilibrium toward more vasoconstriction, leading to a reduction in tissue perfusion with resultant ischemic-related tissue damage, thereby further activating inflammation and cytokine release (Eltzschig and Carmeliet 2011; Indranil Biswas 2019). Interestingly, concentrations of ET-1 and ET-1-receptor expression are increased by Ang II, resulting in an increased production of ROS by NADPH oxidase (Lin et al. 2014; Loomis et al. 2005; Moreau et al. 1997). Prevention of conversion of Ang II into Ang(1-7) due to ACE2 deficiency may limit the activation of eNOS via Ang(1-7)/MasR signaling, thereby inhibiting the production of vasodilatory NO. Furthermore, hypoxia is a common feature in severe COVID-19, which itself induces impaired microcirculation in affected organs. For example, hypoxic pulmonary vasoconstriction (i.e., contraction of the vascular smooth muscle of small intrapulmonary arteries in response to hypoxia) likely is a partial contributor to the impaired gas exchange in COVID-19 (Thillai et al. 2021).

Taurine may be beneficial in COVID-19-related vascular dysfunction due to its known modulatory role in homeostatic function of vascular smooth muscle. Through its attenuating effect on Ang II signaling, taurine is assumed to target the vasoconstrictive effects that Ang II exerts via the AT_1R (Schaffer et al. 2000). Furthermore, the increased production of NO as a result of taurine not only exerts anti-inflammatory effects but is also assumed to cause vasorelaxation. NO may interact with H_2S to generate inorganic hydrogen polysulfides (H_2S_n) that activate protein kinase G (PKG)1α, which has vasorelaxant functions (Bourgonje et al. 2021a). NO could also induce relaxation of vascular smooth muscle cells via activation of guanylate cyclase, which is downregulated by increased levels of intracellular Ca2+ (Murad et al. 1987; Serfass et al. 2001). Depending on cellular Ca2+ concentrations, taurine either promotes vasoconstriction to maintain blood pressure or exerts vasodilatory actions during hypoxia, thereby increasing tissue perfusion (Nishida and Satoh 2009). In a study on individuals with prehypertension (i.e., an early stage in the development of hypertension), administration of taurine significantly improved endothelium-dependent and endothelium-independent vasodilation (Sun et al. 2016). Therein, experimental studies on hypertensive rats showed that administration of taurine inhib-

ited transient receptor potential channel 3 (TRPC3) expression in the vasculature, whereas TRPC3 antagonist treatment enhanced H_2S donor-induced vascular relaxation, indicating that taurine exerts vascular relaxation by targeting TRPC3-mediated calcium influx, which is regulated by AT_1R (Sun et al. 2016; Yamaguchi et al. 2018). Next to smooth muscle in the vasculature, taurine has previously been shown to exert a vasorelaxant effect on pulmonary smooth muscle in rats (Ammer et al. 2013). This finding may be especially interesting for long-COVID-19 patients, in which bronchodilators have been suggested as a treatment option to facilitate breathing – even in patients without concomitant obstructive lung disease (Maniscalco et al. 2021).

6 Taurine as Putative Supplementary Therapy for COVID-19

The role of taurine as an immunomodulator has been well-described in the literature. Considering its antiviral, anti-inflammatory, and vascular modulatory effects, as well as its favorable safety profile, taurine could be regarded as a putative beneficial supplement in taurine-deficient patients with COVID-19. To date, no clinical trials of taurine as a treatment for COVID-19 have been conducted. However, other researchers have previously suggested the therapeutic potential of taurine and its derivatives in COVID-19 (Iwegbulem et al. 2021). Potentially suitable derivatives that were mentioned by the authors included taurolidine (TRD) and 1.4.5-oxathiazinane-4,4-dioxide (OTD), both of which contain various administration options (e.g., intravenous, oral, cutaneous) and are well-tolerated. Previously, taurine has been shown to be effective as treatment for diseases such as diabetes and hypertension (Ito et al. 2012; Maleki et al. 2020a; Sun et al. 2016). For example, a clinical trial on 120 prehypertensive individuals reported that taurine supplementation of 1.6 g/day resulted in significant reductions in systolic and diastolic blood pressures (Sun et al. 2016). Furthermore, in a double-blind placebo-controlled study on patients with type 2 diabetes mellitus, taurine supplementation of 3 g/day for 8 weeks improved glycemic control (by reducing fasting blood sugar and insulin levels) and lipid profiles (through decreased total cholesterol and low-density lipoprotein cholesterol levels) (Maleki et al. 2020a). High doses have also been studied, including in a clinical trial in patients with stroke-like episodes of MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) in which doses of 9 g/day and 12 g/day were used (Ohsawa et al. 2019). The European Food Safety Agency (EFSA) considers up to 1 gram of taurine per kg of bodyweight per day to be safe (European Food Safety Authority (EFSA), 2009). Moreover, a study on the pharmacokinetics of taurine on healthy volunteers after oral administration of 4 g taurine demonstrated an absorption phase of 1−2.5 h (Ghandforoush-Sattari et al. 2010). In this study, the maximum plasma taurine concentration was 86.1 ± 19.0 mg/L (0.69 ± 0.15 mmol), which returned to normal 6−8 h following digestion. Taurine supplementation may be used in COVID-19 considering its low cost, wide availability, and high safety profile with minimal side effects, all of which contribute to the feasibility of conducting randomized controlled trials to test its clinical effects. Since taurine is hypothesized to reduce SARS-CoV-2 infection, taurine may be recommended in every subject with COVID-19, although the greatest benefit is expected in high-risk groups for severe COVID-19 considering their higher baseline levels of inflammation, oxidative stress, and vascular dysfunction. Based on studies in other disease states, beneficial effects may be expected to occur at dosages of 3 g/day for 8 weeks, although its high safety profile legitimizes its use throughout the entire COVID-19 disease course (Maleki et al. 2020a, b; Rosa et al. 2014). Future studies should be conducted to examine the involvement and applicability of taurine supplementation in COVID-19.

7 Conclusion

The amino sulfonic acid taurine has extensive regulatory versatility and is hypothesized to play a modulatory role in COVID-19. Existing evidence

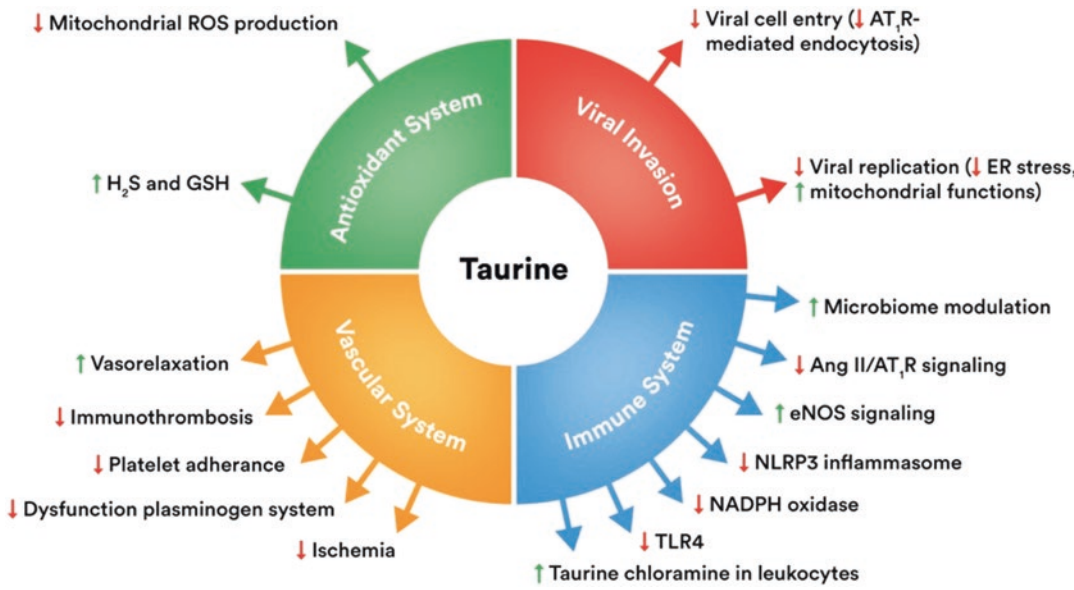

Fig. 3 Overview of stimulatory and inhibitory effects of taurine in coronavirus disease 2019 (COVID-19)

supports antiviral, antioxidant, anti-inflammatory, and vascular modulatory effects of taurine, which could target the multifaceted nature of COVID-19 pathophysiology (Fig. 3). These possible effects are diverse and range from inhibiting viral invasion on account of involvement in (AT_1R-mediated) SARS-CoV-2/ACE2 endocytosis to reducing immunopathology and vascular injury because of its complex involvement in both inflammatory and coagulation pathways. As with other infections, SARS-CoV-2 is associated with decreased levels of taurine, thereby limiting its protective properties normally occurring under physiologic circumstances. Next to its endogenous production, taurine can easily and safely be supplemented to improve body functions. Altogether, taurine should be regarded as a promising supplementary therapeutic option in COVID-19, although future clinical studies are warranted to explore its definite suitability in this disease.

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