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REVIEW

It Ain't Over 'Til It's Over: SARS CoV-2 and Post-infectious Gastrointestinal Dysmotility

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Abstract

The ongoing pandemic resulting from severe acute respiratory syndrome—caused by coronavirus 2 (SARS-CoV-2)—has posed a multitude of healthcare challenges of unprecedented proportions. Intestinal enterocytes have the highest expression of angiotensin-converting enzyme-2 (ACE2), which functions as the key receptor for SARS-CoV-2 entry into cells. As such, particular interest has been accorded to SARS-CoV-2 and how it manifests within the gastrointestinal system. The acute and chronic alimentary clinical implications of infection are yet to be fully elucidated, however, the gastrointestinal consequences from non-SARS-CoV-2 viral GI tract infections, coupled with the generalized nature of late sequelae following COVID-19 disease, would predict that motility disorders are likely to be seen in these patients. Determination of the chronic effects of COVID-19 disease, herein defined as GI disease which is persistent or recurrent more than 3 months following recovery from the acute respiratory illness, will require comprehensive investigations comprising combined endoscopic- and motility-based evaluation. It will be fascinating to ascertain whether the specific post-COVID-19 phenotype is hypotonic or hypertonic in nature and to identify the most vulnerable target portions of the gut. A specific biological hypothesis is that motility disorders may result from SARS-CoV-2-induced angiotensin-converting enzyme 2 (ACE2) depletion. Since SARS-CoV-2 is known to exhibit direct neuronal tropism, the potential also exists for the development of neurogenic motility disorders. This review aims to explore some of the potential pathophysiologic mechanisms underlying motility dysfunction as it relates to ACE2 and thereby aims to provide the foundation for mechanism-based potential therapeutic options.

Keywords Intestinal motility · Gastrointestinal microbiome · SARS-CoV-2 · ACE2

Introduction

SARS-COV-2 is the causative agent of the ongoing global coronavirus disease 2019 (COVID-19) pandemic. The adverse impact on human health and the consequence of the acute phase is already prodigious but unfortunately still accelerating in scope. Assuming herd immunity is achievable because of the cumulative effects of ongoing vaccination and unmitigated infection, the focus will turn toward the chronic health effects of SARS-COV-2, which are predicted to be as highly varied as the primary disease. The chronic secondary effects of SARS-COV-2 are yet to be revealed. Primary SARS-COV-2 infection most commonly affects the respiratory tract [1] which, in susceptible individuals, can result in lethal acute respiratory distress syndrome [2]. Beyond lung involvement, COVID-19 is now recognized to result in multi-organ dysfunction, rendering the scope of scientific inquiry to include the highly varied, concurrent extra-pulmonary manifestations. This review will focus on disorders of GI tract motility that persist or recur more than 3 months following recovery from acute COVID-19 disease and is considered a manifestation of so-called "long-COVID."

Gastrointestinal manifestations are common in COVID-19 disease with a recent study of 318 hospitalized patients reporting 61% of patients having at least one important GI tract symptom [3]. After convalescence from a SARS-CoV-2

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infection, the lasting physiologic implications within the gastrointestinal tract are yet to be elucidated. Post-infectious dysmotility disorders such as irritable bowel syndrome (PI-IBS) and gastroparesis have been demonstrated in several studies [4–6]. The gastrointestinal consequences from non-SARS-CoV-2 viral GI tract infections, coupled with the generalized nature of late sequelae following COVID-19 disease, would predict that motility disorders are likely to be seen in these patients and have chronic effects past the acute infection [7]. Dysregulation of gut motility has been associated with symptoms including but not limited to, diarrhea, nausea, vomiting, and abdominal pain [8]. It is noteworthy that persistence of SARS-CoV-2 RNA was found in fecal specimens in 23% of the patients after negative results were seen in respiratory samples, providing a potential explanation for persistent GI tract manifestations [9].

Determination of the chronic effects of COVID-19 disease will require comprehensive investigations comprising combined endoscopic- and motility-based evaluations. It is uncertain as to whether the specific post-COVID-19 phenotype is hypotonic or hypertonic in nature, and the most vulnerable target portions of the gut require investigation. A specific biological hypothesis is that motility disorders may result from SARS-CoV-2-induced angiotensin-converting enzyme 2 (ACE2) depletion. Since SARS-CoV-2 is known to exhibit direct neuronal tropism, the potential also exists for the development of neurogenic motility disorders. Correlation of motility status and ACE2 expression determined by biopsy will be critical to help inform clinically important pathological pathways and the most appropriate treatment approaches.

ACE2 Dysregulation in COVID-19

ACE2 is a type I integral membrane protein with carboxypeptidase activity that cleaves the carboxyl-terminal amino acid phenylalanine from angiotensin II to produce the peptide angiotensin 1–7, which exhibits potent anti-inflammatory and vasodilator effects [10]. The interaction between the receptor-binding domain (RBD) of the viral spike protein with ACE2 initiates the host entry process, which requires proteolytic cleavage by the host receptor transmembrane protease serine 2 (TMPRSS2) [11]. Continuous infection of host target cells by SARS-CoV-2 facilitates ACE2 down-regulation and ultimately leads to chronic ACE2 deficiency [12] (Fig. 1). The pulmonary phase of the SARS-CoV-2 infection targets alveolar epithelial cells in both the upper and lower respiratory tracts composed of type 1 and 2 pneumocytes, which express high levels of ACE2.

The highest expression of ACE2 occurs in the small intestine particularly in the ileal enterochromaffin cells (ECs) with other locations being the upper esophagus, rectum ECs, as well as epithelial cells in the stomach and colonocytes [13]. In vitro laboratory analysis has shown that the enterocyte lineages are infectable when exposed to SARS-CoV-2 virus. Furthermore, a strong interferon expression from these infected cells has been observed consequent to infection [14]. ACE2 has also been shown to have a renin–angiotensin system (RAS)-independent function related to intestinal amino acid regulation, and in intestinal microbiome homeostasis [15].

Interestingly, ACE2 expression is increased in the terminal ileum and the colon in IBD patients compared to healthy individuals [16]. This is more evident in Crohn's disease (CD) compared to ulcerative colitis (UC). This was even true for the non-inflamed region of the colon pointing toward underlying pathophysiology at the genetic level. It is noteworthy that IBD features elevation in ACE2 and trypsin-like proteases, especially in the ileum and colon, which provides a facilitated point of entry for SARS-CoV-2 [17]. On the contrary, higher soluble ACE2 levels are found in IBD patients, which compete with the SARS-CoV-2 virus, thus providing plausible compensatory protection [18, 19]. Nevertheless, IBD is neither a statistically protective nor predisposing factor for SARS-CoV-2 infection [16, 20, 21].

ACE2 and Gastrointestinal Motility

Burgeoning evidence suggests that the renin–angiotensin–aldosterone system (RAS) modulates gastrointestinal function in both humans and animals [18, 22]. The RAS system was mechanistically thought to exhibits its effects solely through the endocrine systemic effects, but more recent data indicate that most organs, including the gastrointestinal tract, express all of the required components for local production and action of RAS, suggestive of additional paracrine/autocrine functions [22]. Several intermediate mediators in the RAS cascade exhibit a multitude of complex downstream effects. The ACE/Ang II/AT1R has literature-validated adverse physiologic effects including vasoconstriction, inflammation, and/or increased oxidative stress [23]. Increasing attention has been accorded to the RAS system as the understanding of its modulatory role within the gastrointestinal tract continues to evolve. ACE2 is an integral component of the RAS system and converts high-affinity angiotensin (Ang) II to Ang (1–7) [24] leading to Mas receptor activation which counters the effects of Ang II. The therapeutic benefit attributed to ACE inhibitors and AT1R blockers (ARBs) is theorized to be the shunting RAS substrates toward Ang (1–7) production and Mas receptor activation [25]. In the context of ACE2 deficiency, RAS substrate homeostasis is altered to increase Ang II production and reduce Ang (1–7)/mas receptor activation systemically [26]. The MAS1 oncogene [MAS receptor (MasR)] is a G

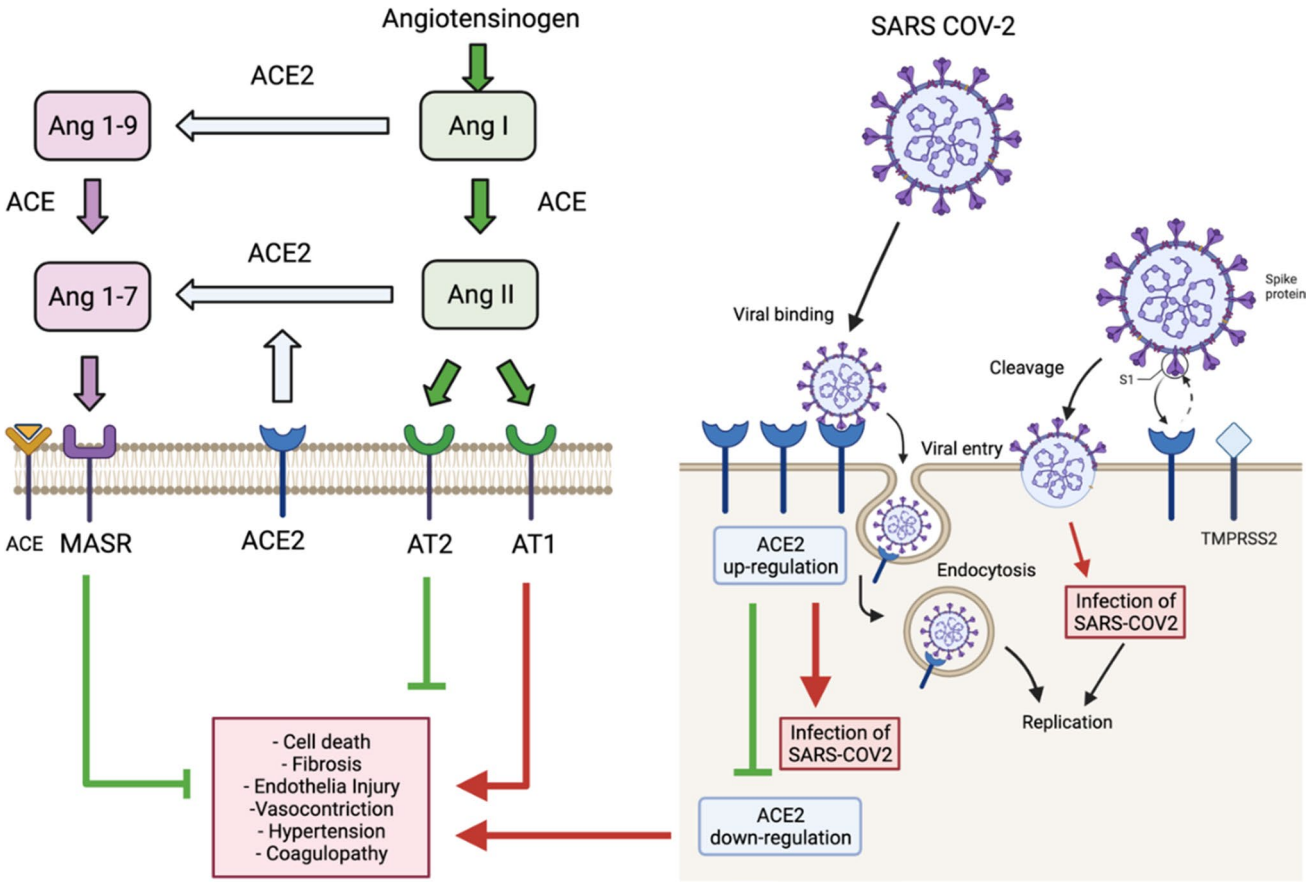

Fig. 1 The right side of the figure illustrates the SARS-CoV-2 host cell entry process and how it is mediated by binding of the receptor-binding domain (RBD) viral S1 spike protein to the cellular angiotensin-converting enzyme 2 (ACE2) functional receptor. This requires proteolytic cleavage by the host receptor transmembrane protease serine 2 (TMPRSS2). Then, the viral complex is endocytosed with subsequent viral replication that causes a multitude of effects (1b) including down-regulation of cell surface ACE2 and chronic ACE2 deficiency. The left side of the figure is a functional schematic of the renin-angiotensin system. Renin helps convert precursor angiotensinogen to angiotensin I (ANG I) that is subsequently converted to ANG II by angiotensin-converting enzyme (ACE). ANG II has two major receptor isoforms differential expressed throughout the body: AT_1R and AT_2R. AT_1R is the most studied and best understood angiotensin receptor. Through binding ANG II type 1 receptor (AT_1R), ANG II stimulates fibrosis, cell death, endothelial cell injury, coagulopathy, and vasoconstriction. Conversely, the ANG II type 2 receptor (AT_2R) appears to counterbalance effects of AT_1R and stimulates vasodilation, anti-fibrosis, and tissue repair. ANG I and ANG II can be metabolized via the carboxypeptidase ACE2 to form Ang-(1–9) and Ang-(1–7), respectively. Ang-(1–7) then binds to the Mas receptor (Mas-R) exerting protective antifibrotic, anti-inflammatory effects, along with stimulating nitric oxide release and vasodilation

protein-coupled receptor, which binds the angiotensin-II metabolite angiotensin (1–7) (Ang1–7). Activation of the MasR axis preserves the homeostatic milieu and is conducive to normal gastric motility. How SARS-CoV2 infection and subsequent pathway disequilibrium influence gastrointestinal motility may be dictated by several pathophysiologic mechanisms affecting RAS signaling.

Pawlik and colleagues determined Ang (1–7) to have a dose-dependent protective effect in the esophagi of rat models exposed to gastric refluxate through stimulation of MasR. MasR activation following Ang(1–7) administration in the rat esophageal reflux model induces protective circulatory and anti-inflammatory effects [27]. A similar study by Magierowski et al. concluded that Ang (1–7) provided gastric protection in rats exposed to water immersion and restraint stress (WRS)-induced ulcerogenesis through an increase in gastric blood flow (mediated by endogenous prostaglandins and sensory neuropeptides) and via inhibition of pro-inflammatory markers such as inducible Nitric Oxide Synthase (iNOS), interleukin- 1 β (IL-1β) and TNF-α [28]. Conversely, Ang II worsened WRS ulcerogenesis.

Metabolic pathways may also be affected by SARS-CoV-2-induced ACE2 deficiency. MasR knockout (MasR-KO) c57BL/6 mice evince changes characteristic of metabolic syndrome [29]. Specifically, MasR-KO showed variations in body morphology, a lower glucose tolerance, impaired insulin sensitivity, and increases in their fasting blood glucose [29]. Symptoms of gastric dysmotility are often described

in patients with diabetes mellitus [30]. Approximately 75% of diabetic patients report nausea, bloating, diarrhea, or constipation contingent on the duration of abnormal glucose homeostasis [31].

Ang II also has a direct relationship with electrolyte and fluid dynamics within the duodenum. Bicarbonate secretion is stimulated via Ang II acting on AT1 and AT2 in the duodenum [32] and is responsible for intestinal pH homeostasis required for pancreatic enzyme activation, micelle formation, and fat absorption [33]. Additionally, secreted bicarbonate is required for normal expansion and solubility of intestinal mucus [34]. During SARS-CoV-2 infection, ACE2 is down-regulated, effectively increasing Ang II production [35]. This could potentiate bicarbonate secretion, decrease mucosal viscosity, and accelerate gastrointestinal transit times within the small bowel and may explain the diarrheal phenotype commonly seen with acute infections [35]. Further, SARS-CoV-2 binding to ACE2 likely leads to the dysregulation of nutrient transport. ACE2 regulates sodium-dependent amino acid and glucose transporters in the brush border of enterocytes which regulates the absorption of nutrients and maintains osmotic and electrolyte balance [35, 36]. ACE2 mediated dysregulation of sodium-dependent glucose transporter (SGLT1 or SLC5A1) at the intestinal epithelium known to play a pathogenetic role in diabetes mellitus (DM) will prompt studies of gylcemic control during SARS-CoV-2 infection in patients with DM [36]. Prior inflammatory conditions which disrupt the multilayered intestinal mucosal system may allow for GI entry of the SARS-Co-2 using ACE2 and its resultant replication plausible [35], and this remains an urgent question in the field.

Ang II, in conjunction with the enteric sympathetic nervous symptom, acts to modulate sodium and water absorption within the jejunum and ileum [37–39]. In rat studies, low doses of Ang II administration to the jejunum resulted in sodium and water absorption via AT2R stimulation. Conversely, at higher doses, sodium and water absorption was inhibited through AT1R [40]. The increased endoluminal sodium and water concentration potentially portend an ATR1-mediated hypermotile phenotype. Conversely, other studies have demonstrated that Ang II and Ang III potentially increase sodium and water absorption through stimulation of sympathetic neurons acting on adrenergic receptors located on intestinal epithelial cells [22], suggesting that the net effect on sodium and water consequent to COVID disease may be context-dependent and tuned by the equilibrium of Ang II/ATR1/ATR2/Ang (1–7) signaling.

Separate lines of investigation suggest alimentary dysbiosis as a mechanism of gastrointestinal dysmotility. Here again, ACE2 plays a vital role in gut microbiota regulation [41]. Studies have demonstrated that ACE2 associates with a neutral amino acid transporter B0AT1 on the small intestine brush border membrane [42, 43]. ACE2-knockout mice exhibited decreased levels of serum amino acids, impaired uptake of amino acids, namely tryptophan, decreased expression of antimicrobial peptides, and alteration of the intestinal microbiota which was recovered by tryptophan administration [15]. The KO mice also had an increased susceptibility to developing severe colitis when challenged with intestinal irritants dextran sodium sulfate and trinitrobenzene sulfonic acid [15].

Determining the potential chronicity of a post-infectious dysmotility disorder is another important and evolving topic of consideration. The emergence of a novel lifelong disorder is not only distressing at the patient level but would further challenge the allocation of health care resources. Interestingly, studies have demonstrated that patients who have tested positive for SARS-CoV-2 may continue to shed viral RNA in stool samples [44]. Furthermore, Xiao et al. noted the presence of both fecal viral RNA and virus positive stool despite negative respiratory specimens [9]. Evidence also exists of active viral replication within the gastrointestinal tract [45] potentially leading to continued gastrointestinal infection beyond the respiratory phase. Gastrointestinal viral persistence may predispose to chronic down-regulation of ACE2 and ongoing symptoms. A recent study by Al-Aly et al. performed a cohort analysis investigating the 6-month outcomes of incident diagnosis between non-hospitalized SARS-CoV-2 patients and those unaffected by the virus. Multiple disorders affecting almost every organ system, including the gastrointestinal tract, was revealed by elevated hazard ratios (HR) greater than 1 per 1000 SARS-CoV-2 patients at 6 months, as follows: esophageal disorders (6.90 (4.58, 9.07)), gastrointestinal disorders (3.58 (2.15, 4.88)), dysphagia (HR 2.83 (1.79, 3.76)), and abdominal pain (5.73 (3.7, 7.62)). Moreover, there was noted to be increased use of laxatives (9.22 (6.99, 11.31)), antiemetics (9.22 (6.99, 11.31)), histamine antagonists (4.83 (3.63, 5.91)), other antacids (1.07 (0.62, 1.42)), and antidiarrheal agents (2.87 (1.70, 3.91)) [46]. Further longitudinal studies are required to characterize the post-COVID-19 GI tract disease burden.

SARS-CoV-2 Neurotropism

Documented neuronal tropism of the SARS-CoV-2 virus may account for the varied central neurogenic disorders observed in COVID-19 infection [47]. This also raises the possibility that direct enteric neuron invasion of the SARS-CoV-2 virus and suggests a neurogenic basis for COVID-19 related GI tract dysmotility although the data on this point is very fragmentary at present.

There exist a variety of potential mechanisms of potential SARS-CoV-2 entry routes into the human brain based on ACE2 and cell entry protease expression in the olfactory epithelium, myelin-forming cells, enteric inhibitory

neurons, and vascular endothelium [48]. The presence of the viral entry receptors on the cells of the olfactory epithelium and central and enteric nervous system provides a possible viral entry mechanism for neural invasion by SARS-CoV-2 through the olfactory and transvagal routes [48]. Specifically, synaptic junctions of ACE2- and protease-rich inhibitory enteric neurons may allow retrograde spread of the virus in the central nervous system. It has also been proposed that SARS-CoV-2 ingress and transneuronal spread may occur through the olfactory nerves or via a hematogenous route after breaching the blood brain barrier (BBB) [48]. Thus, there are several alternative potential pathways which permit SARS-CoV-2 entry into the central nervous system, although the specific anatomical regions involved remain to be clarified (Fig. 2). It will be translationally important to determine if direct neurogenic invasion in the gut during SARS-CoV-2 infection results in motility disorders independently from the adverse effects of ACE2-mediated alterations in metabolism and inflammatory signaling.

Summary of Mechanisms of SARS-CoV-2-Induced Motility Phenotype

Collectively, these studies provide several putative pathophysiological mechanisms through which SARS-CoV-2 may affect GI tract tonus, apart from direct viral cytopathy, including RAS dysfunction, intestinal dysbiosis, and possible secondary enteric neuronal virus invasion. The central role of ACE2 seems compelling but remains speculative at this point pending careful motility-based investigations in post-COVID-19 patient cohorts. Many fascinating and clinical crucial questions remain unanswered such as whether ACE2 deficiency is reversible, and if chronic ACE2 deficiency is a pathogenetic driver of so-called "long-COVID-19" multi-organ disorders.

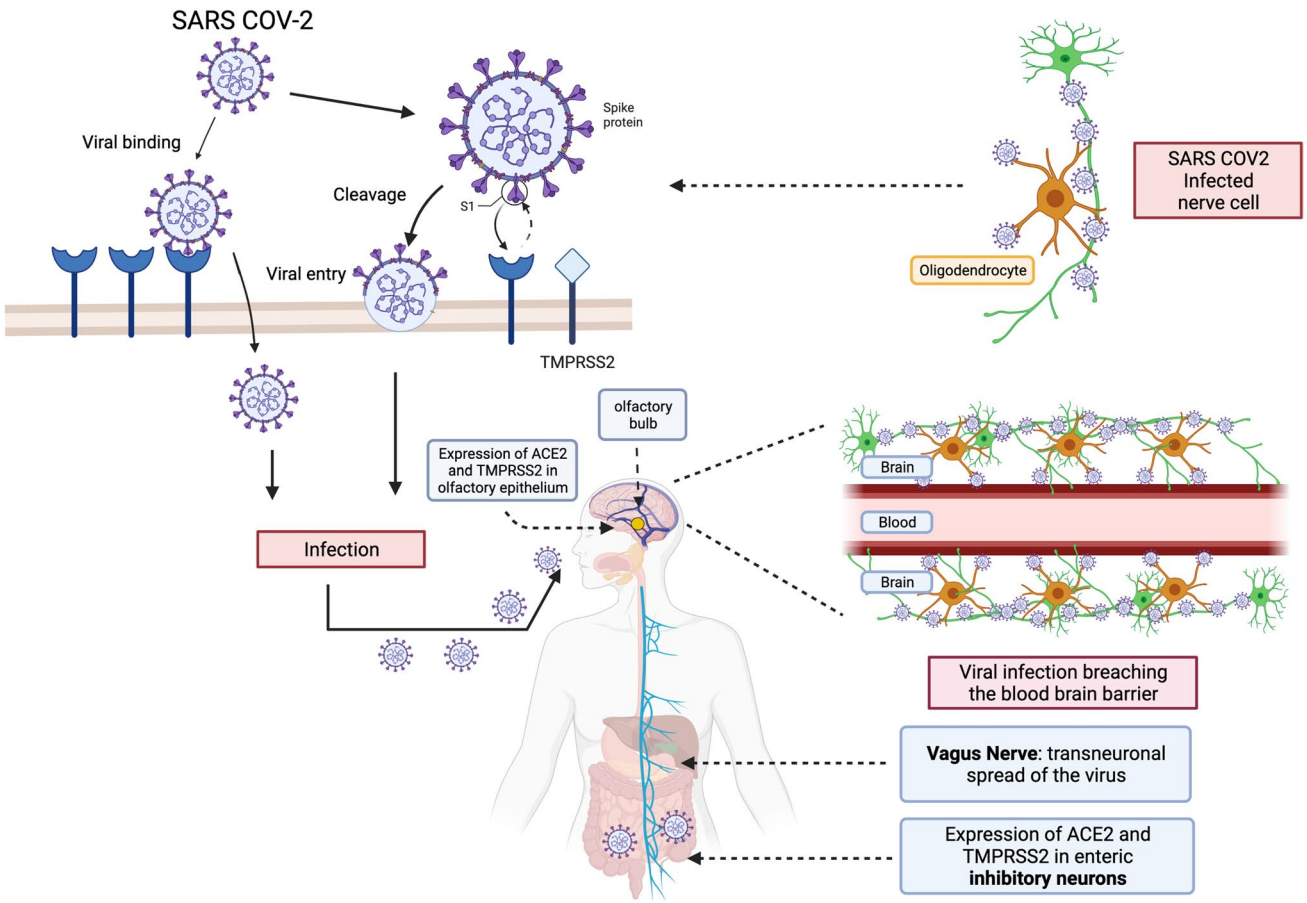

Fig. 2 Neural invasion of SARS-CoV-2 can occur via olfactory epithelium, enteric inhibitory neurons, or hematogenous spread after breaching the blood brain barrier. Both ACE2 and cell entry protease (TMPRSS2) aid in viral entry and are expressed in cells including olfactory epithelium, myelin-forming cells, enteric inhibitory neurons, and vascular endothelium. Therefore, enteric neural synaptic junctions containing ACE2 and related proteases may support retrograde spread of SARS-CoV-2 in the central nervous system and contribute to central neurogenic disorders observed in COVID-19 infection

Treatment Overview

This review invokes the rationale for mechanism-based treatments for post-COVID-19 motility disorders, specifically focused on restoring protective levels of ACE2. Additional treatments address the neurogenic component of post-COVID-19 motility disorders with innovative but mainly unproven therapeutics ranging from probiotics, autonomic modulators to neurostimulation.

Therapeutics Directed to ACE2

The administration of recombinant human ACE2 (rhACE2) in various animal disease models has been shown to have favorable results [49]. In conditions with an imbalance in the renin–angiotensin–aldosterone system, treatment with exogenous ACE2 in mice led to the prevention of deleterious effects associated with Ang 1–8 such as hypertension, oxidative stress, and tubulointerstitial fibrosis [50, 51]. Intravenous injections of rhACE2 in healthy human subjects suppressed Ang 1–8 levels for at least 24 h and multiple injections were well-tolerated without significant adverse effects or toxicity [52]. Similarly, increasing effective levels of ACE2 through exogenous rhACE2 may represent a possible therapeutic intervention in patients with post-COVID-19 motility disorders that result from chronic ACE2 depletion. There are several clinical trials involving rhACE2 that are currently underway. One study by Apeiron Biologics is investigating rhACE2 as a treatment for patients with the acute phase of COVID-19 to block viral entry and decrease replication (ClinicalTrials.Gov; NCT04335136). Another trial by GlaxoSmithKline is exploring the effects of rhACE2 on patients with acute lung injury (ClinicalTrials.Gov; NCT01597635). Recombinant ACE2 is also being studied as a potential treatment for pulmonary arterial hypertension (ClinicalTrials.Gov; NCT01884051).

ACE2 Activators

Several compounds have been discovered which enhance the activation of endogenous ACE2, namely 1-[[2-(dimethylamino) ethyl] amino]-4-(hydroxymethyl)-7-[[(4-methyl phenyl) sulfonyl] oxy]-9H–xanthone9 (XNT), diminazene (DMZ), and resorcinolnaphthalein [53, 54]. These compounds have mainly been studied for their cardiopulmonary protective effects in rodents. For instance, DMZ prevented the development of pulmonary arterial hypertension (PAH) in hypoxia, monocrotaline, and bleomycin models [55]. XNT was shown to reduce blood pressure and reverse cardiorenal fibrosis in spontaneously hypertensive rats [53, 56]. In the monocrotaline-induced PAH rat model, resorcinolnaphthalein prevented hemodynamics by improving vasorelaxation and attenuating anti-inflammatory cytokines [57, 58]. There have not been any studies evaluating the role of ACE2 activators in patients with post-COVID-19 motility disorders. While some of these compounds have undesired side effects, such as renal, hepatic, and cerebral toxicity with chronic use of DMZ, these molecules could serve as a starting point for the development of safer, more tolerable drugs [59].

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

As SARS-CoV-2 utilizes the ACE2 receptor for entry into human cells, the role of angiotensin-converting enzyme inhibitors (ACEI's) and angiotensin receptor blockers (ARB's) in COVID-19 has been posited. ACEI's upregulate the ACE2 receptor which could theoretically enhance viral entry into human cells [60]. ARB's, on the other hand, could theoretically exert a protective effect through the blockade of the ACE2 receptor [60]. ACEI's and ARB's have also been shown to have a protective effect on acute lung injury induced by oleic acid in animal models [61]. Several studies have concluded that ACEI's and ARB exposure was not associated with a higher risk of COVID-19 infection and, in fact, led to lower mortality when compared to patients on non-ACEI's/ARB's antihypertensive drugs [62–65]. The current guidelines recommend against the discontinuation of ACEI's and ARB's in COVID-19 patients.

Probiotics

Intestinal dysbiosis has been implicated in many common diseases such as obesity, type 2 diabetes, hypertension, and congenital heart disease [66, 67]. In hospitalized COVID-19 patients, intestinal dysbiosis was noted with decreased probiotics such as Lactobacillus and Bifidobacterium [68]. Several studies have demonstrated the communication between intestinal bacteria and the nervous system known as the microbiome-gut-brain axis [69–73]. Neufeld et. al investigated the mechanism by which intestinal bacteria alters the nervous system and found that communication occurred via afferent sensory neurons [74]. Probiotics have been shown to have antioxidant properties, reduce blood pressure, favorably modify cholesterol concentrations and release ACE-inhibiting peptides [75–77]. Probiotics may in part exert their effects by modulating the autonomic nervous system. One study showed that intraduodenal injection of Lactobacillus *johnsonii* resulted in reduced renal sympathetic nerve activity and increased gastric vagal nerve activity [78].

A study managing COVID-19 with oral bacteriotherapy in addition to standard treatment showed remission of gastrointestinal symptoms for nearly all patients compared to less than half of the control [79]. In addition, it decreased the risk of respiratory failure and ICU admission. Additionally, research has been done in an effort to block residual ACE2 receptor proteins by various probiotics [80]. The binding energies or certain probiotics were shown to be high enough to block the protease residues on the catalytic site on spike proteins, making them therapeutic for COVID-19 [80].

Thus, the beneficial effects of probiotics in post-COVID-19 motility disorders may accrue from restoration of the gut microbiosis and/or through potentiation of vagal nerve activity, although evidence in support of probiotic therapy is so far limited.

Neurostimulation

Vagal nerve stimulation may represent a possible therapeutic intervention in modulating the immune system. In patients who have evidence of autonomic dysfunction as a sequela of SARS-CoV-2 infection, vagal nerve stimulation assists in the downregulation of secreted pro-inflammatory chemokines such as interleukin-1ß, TNF, and IL-8 [81]. The attenuation of these chemokines may result in downstream alleviation in autonomic dysfunction and symptoms. Clinical trials involving noninvasive vagal nerve stimulation in COVID-19 patients are currently ongoing [82–85].

Future Perspectives

There are currently hundreds of clinical trials underway to evaluate the therapeutic efficacy of novel, mechanism-based approaches to address the protean sequelae of SARS-CoV-2 infection, several of which have been highlighted in this review. Only a limited number, however, have been designed to specifically address acute and chronic disorders caused by SARS-CoV-2 affecting the GI tract. A review of evolving data suggests that the role of ACE2 depletion can serve as mechanistic model to help inform more comprehensive investigations and therapies, both systemically and with specific focus directed to the GI tract. Addressing this challenging imperative will be required to control the devastating global burden of COVID-19.

Declarations

Conflict of interest None of the authors have conflicts of interest to declare, financial or otherwise. Authors confirm that the manuscript is original and that no aspect has been published elsewhere. Authors also have read and approved the final version of the manuscript prior to submission. The manuscript was drafted in accordance with each institution's IRB ethical publication policies.

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