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# Silent hypoxia in COVID-19: a gut microbiota connection

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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has triggered the COVID-19 pandemic. Several factors induce hypoxia in COVID-19. Despite being hypoxic, some SARS-CoV-2-infected individuals do not experience any respiratory distress, a phenomenon termed 'silent (or happy) hypoxia'. Prolonged undetected hypoxia could be dangerous, sometimes leading to death. A few studies attempted to unravel what causes silent hypoxia, however, the exact mechanisms are still elusive. Here, we aim to understand how SARS-CoV-2 causes silent hypoxia.

## Addresses

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## Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has initiated the current COVID-19 pandemic. COVID-19 symptoms are diverse and extend from mild to severe manifestations of pneumonia, acquired respiratory distress syndrome (ARDS) and multi-organ failure [1]. A prevalent feature associated with COVID-19 is the onset of hypoxemia {low blood oxygen (O<sub>2</sub>) level}. SARS-CoV-2 replication within the lungs causes an uncontrolled inflammatory response, the 'cytokine storm', which impinges on the lung function or perfusion, leading to hypoxemia [2]. This causes a deficiency in tissue oxygenation leading to hypoxia. Compensatory mechanisms like increased ventilation and dyspnea, which are generally initiated in hypoxia, are surprisingly

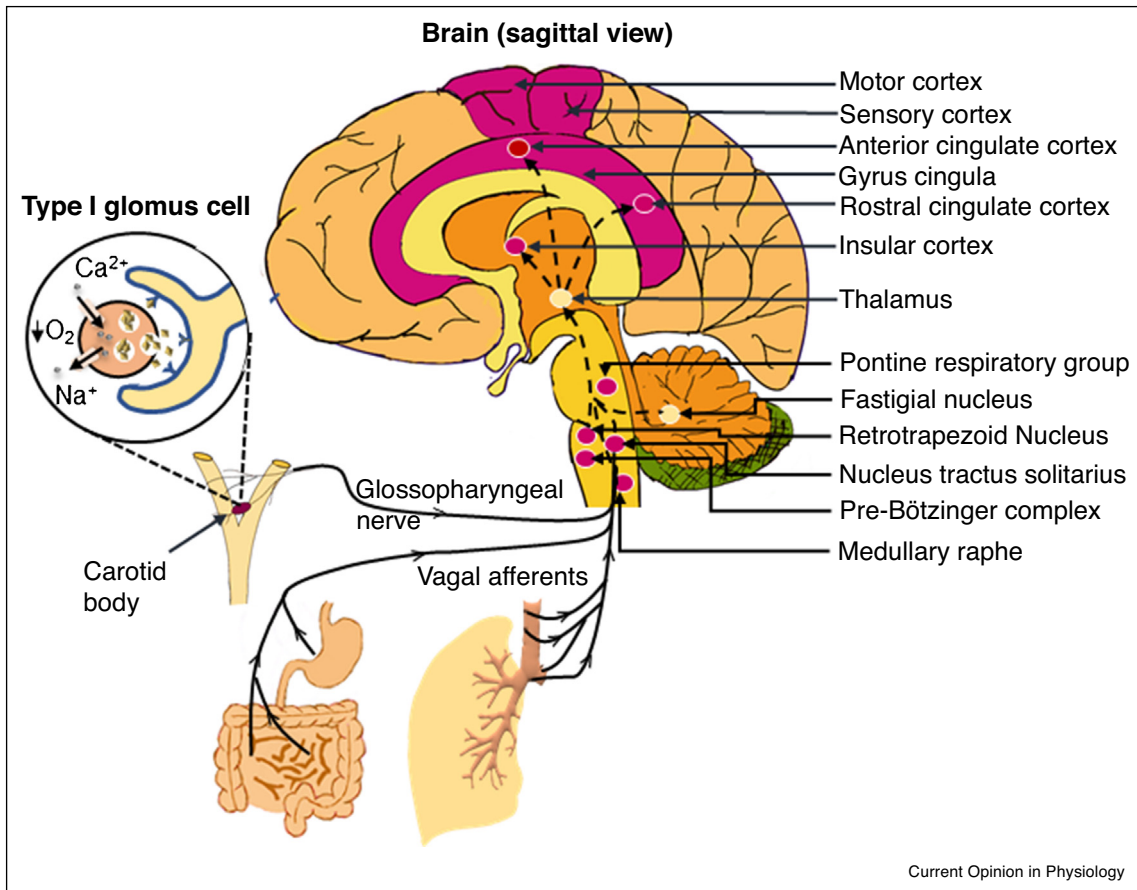
lacking in many COVID-19 patients. This phenomenon is known as 'silent/happy hypoxia' or non-dyspneic hypoxemia [3,4]. Since the patient remains unaware of the condition, undetected hypoxia could be dangerous. Studies indicate that gut dysbiosis (disruption of the gut microbial homeostasis) is an important manifestation in COVID-19 and can hamper respiratory control [5]. This article explores the potential role of gut microbiota-brain communication in causing silent hypoxia in COVID-19.

## Hypoxia and hypoxia-sensing

The cause of hypoxia in COVID-19 is multifactorial and includes thrombosis, pulmonary infiltration, viral invasion in pneumocytes, profuse cytokine release and inflammatory responses. Sepsis and pulmonary edema-mediated thickening of the alveolar-capillary barrier, viremia and dysregulated renin-angiotensin-aldosterone system (RAAS) also cause systemic hypoxia in COVID-19 [2,6].

The central chemoreceptors of the respiratory center (RC) (the medulla oblongata and pons in the brainstem) and the peripheral chemoreceptors of the carotid body (CB) sense O<sub>2</sub> and carbon dioxide (CO<sub>2</sub>) in the arterial blood [7,8]. RC is modulated by several metabolites including lactate and are more sensitive in detecting slight increases in CO<sub>2</sub>-tension (Pa<sub>CO2</sub>) or a drop in pH than Pa<sub>O2</sub>-decrease. CB evokes peripheral chemoreflex and ventilatory activity [9]. Although both RC and CB can detect hypoxia, the CB has the main role in O<sub>2</sub> homeostasis. Hypoxia depolarizes glomus cells (type I) in the CB, promoting the release of neurotransmitters that signal the nucleus tractus solitarius (NTS) via a small division of the glossopharyngeal nerve (carotid sinus nerve) [10]. These signals are integrated and relayed to the rostral ventrolateral ('pressor') region of the medulla and the hypothalamic paraventricular nucleus that initiate ventilatory output which regulate breathing. Central chemoreceptors communicate (glutamatergic) with the pre-Bötzing complex (PBC) of the medulla oblongata, the medullary raphe (serotonergic), the fastigial nucleus (glutamatergic) of the cerebellum and the astrocytes of the glial cells [11]. PBC and the retrotrapezoid nucleus/parafacial respiratory group of the brainstem neurons are considered the primary and secondary respiratory rhythm-regulators, respectively. The RC receives signals from these chemoreceptors, the cerebrum and the hypothalamus to determine the rate or depth of respiration as

Figure 1



Components of the neuronal system involved in  $\text{O}_2$  sensing. The sagittal view of the brain showing components of the neuronal system involved in sensing  $\text{O}_2$  level. Vagal afferents and afferent neurons of the glossopharyngeal nerve from the peripheral chemoreceptors reach the medulla and the hypothalamus. Retrotrapezoid nucleus of the medulla contains the central chemoreceptors which is connected to the pre-Bötzing complex in the medulla oblongata and the cerebellum. Afferent connections from these regions to the thalamus relay the signal to the corticolimbic network that ultimately control ventilatory responses. Areas which are possibly damaged in COVID-19 are colored in magenta. Inset: Decrease in partial pressure of  $\text{O}_2$  in the blood causes depolarization of the type I glomus cells of the CB and release neurotransmitters.

well as the sensation of dyspnea [12]. Figure 1 provides a schematic representation of the major neural components involved in  $\text{O}_2$ -sensing.

Respiratory-responses hugely vary among individuals and are further complicated by respiratory virus infections. SARS-CoV-2 reaches the central nervous system (CNS) by various routes. As discussed later, the neuroinvasive potential of SARS-CoV-2 might directly impair hypoxia-response by targeting the chemosensors [13–15]. In addition, SARS-CoV-2 can disturb the intricately balanced gut-brain axis [16] to ultimately impact the functioning of the RC.

### Gut dysbiosis in COVID-19

The symbiotic relationship of gut microbes with the host regulates metabolic pathways, immune and neuroendocrine crosstalk [17]. Gut microbes can interact with the

brain via the vagus nerve and produce many neuroactive substances such as metabolites, endocrine modulators and neurotransmitters.

The Bacteroidetes (*Bacteroides*, *Alistipes*, *Prevotella*) and Firmicutes (*Eubacteria*, *Clostridium*, *Faecalibacterium*, *Roseburia*) are the most dominant phyla in the human gut, followed by the Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia [18<sup>•</sup>]. The loss of microbial diversity in COVID-19 correlates with increased inflammation [19<sup>•</sup>]. Firmicutes (*Ruminococcus torques* and *Ruminococcus gnavus*) and Bacteroidetes (*Bacteroides dorei*) get enriched while other Firmicutes (such as *Eubacterium rectale*, *Faecalibacterium prausnitzii*) and Actinobacteria (such as *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*) are depleted in COVID-19 [20<sup>•</sup>]. The GI tract and the respiratory epithelia express angiotensin-converting enzyme 2 (ACE2) which acts as the binding receptor of

SARS-CoV-2 and is involved in the maintenance of the gut microbiota [21]. Interestingly, Bacteroides downregulate ACE2 in the rodent gut and are depleted in COVID-19 patients [21]. An impaired ratio of Bacteroidetes to Firmicutes is reflective of the disease severity. Shotgun metagenomics of patients' fecal samples exhibit depletion of commensals and an upsurge in the population of opportunistic pathogens [20\*\*]. Opportunistic pathogens *Clostridium ramosum*, *C. hathewayi*, *Coprobacillus* sp., *Streptococcus* sp. and *Actinomyces* sp. increase with the disease severity [20\*\*,22]. The symbionts *F. prausnitzii*, *Ruminococcus obeum*, *E. rectale*, *Dorea formicigenerans*, *Lachnospiraceae* bacterium and *Alistipes onderdonkii* are depleted in COVID-19. Since systematic efforts to understand the contribution of SARS-CoV-2-mediated gut dysbiosis towards silent hypoxia have never been made, here we summarize the mechanisms that might be involved.

### Gut dysbiosis disrupts hypoxia-sensing in SARS-CoV-2 infection

SARS-CoV-2 directly infects enterocytes by binding with ACE2 and causes gut dysbiosis [21,23]. Like many other viruses, SARS-CoV-2 disrupts the intestinal barrier function, causes hematological dissemination of gut microbes and initiates systemic inflammation [23]. High levels of proinflammatory cytokines, interferon  $\gamma$  (IFN- $\gamma$ ), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin 6 (IL-6) are found in the blood of COVID-19 patients [24]. These cytokines travel via the systemic circulation and alter the blood-brain barrier (BBB) permeability [16]. Systemic inflammation increases the level of circulating reactive O<sub>2</sub> species (ROS) that may further affect the brainstem and the cerebrum [25,26]. The brain has a limited antioxidant capacity and, therefore, is known to be prone to oxidative stress [27]. Oxidative stress causes neuroinflammation and mitochondrial DNA damage in the NTS [28]. Studies involving germ-free mice also indicate that gut dysbiosis compromises the BBB integrity, consequently allowing the transmission of proinflammatory cytokines to the brain causing neuroinflammation [29].  $\alpha$ -synuclein is generated in the gut due to SARS-CoV-2-mediated cytokine storm, bacterial endotoxins {mainly, lipopolysaccharide (LPS)} and is subsequently transported to the brain by the vagus nerve causing neuronal damage [30]. LPS may also reach the brain, cause neuroinflammation and BBB disruption [31]. Another major mechanism behind SARS-CoV-2 entry into the brain is the reverse axonal transport from the peripheral nerves [32].

Neurons or glial cells, which express ACE2, get infected by the virus [4]. Studies on neurotropic flaviviruses indicate that astrocytes, by virtue of performing aerobic glycolysis, might provide the ideal replicative environment for SARS-CoV-2 [13]. The CNS damage can be triggered by neurotropic or neuroimmune effects of SARS-CoV-2 on the brainstem [33\*\*]. The PBC-infection might directly hamper hypoxia-sensing [34]. Ventilatory

responses and dyspnea are tightly regulated by Pa<sub>CO2</sub>. Prevailing hypotheses explaining the COVID-19-associated silent hypoxia are associated with existing hypocapnia (low Pa<sub>CO2</sub> in the blood) that prevents brainstem-involvement [35]. During SARS-CoV-2 infection-induced hypoxia, the brain raises the metabolic rate and produces lactate but the cerebral blood flow, which is well-maintained, carries away the excess CO<sub>2</sub> generated during the process [36]. This hypocapnic hypoxia may hamper the function of central chemoreceptors and cause dyspnea. A study involving a small group of COVID-19 patients show that Pa<sub>CO2</sub> lower than 39 mm Hg blunts the CNS-response to hypoxia [37]. In contrast, CB detects changes in Pa<sub>O2</sub> in the arterial blood but it cannot sense O<sub>2</sub>-saturation. In pyrexia, prevalent in COVID-19 patients, the O<sub>2</sub>-dissociation curve shifts to the right (i. e. causes hemoglobin-desaturation) rendering CB-chemoreceptors unstimulated and contributes to silent hypoxia. Poor respiratory control and BBB integrity in the elderly and diabetic COVID-19 patients may explain the prevalence of silent hypoxia in these populations.

The vagus nerve forms a major neural route connecting the gut to the brain and has innervations in the respiratory tract and the NTS [38]. As dysbiosis modulates the vagal tone, it can perturb the input signaling to the NTS [38,39], thereby affecting respiration. Damage to the lung vagal receptors and respiratory muscle mechanoreceptors further explains the absence of dyspnea in COVID-19 [40]. Microbe-released metabolites alter immune-inflammatory responses in the CNS [41]. As inflammatory mediators cause CNS neurodegeneration [16,42], gut dysbiosis-induced neuroinflammation damages the RC and might be a potential mechanism behind silent hypoxia [16,41]. These studies highlight gut-dysbiosis as a critical deregulator of neuronal function.

### Gut microbiota-derived circulating metabolites blunt hypoxia-sensing in COVID-19

The gut microbiota generates several neurotropic metabolites, neurotransmitters, peptides and gaseous substances, many of which show altered levels in COVID-19 (Table 1). Fermentation of undigested starch and dietary fibers by the colonic bacteria generates short chain fatty acids (SCFA) such as butyrate, propionate and acetate as the major metabolites [43\*]. Bacteroidetes mainly produce acetate and propionate, but butyrate is largely produced by Firmicutes which modulate rate/depth of breathing [44,45]. SCFA-producing commensal Firmicutes, for example, *Roseburia*, *Eubacterium* and *F. prausnitzii* are depleted in COVID-19 [20\*\*]. Butyrate and propionate regulate serotonin, dopamine, adrenaline or noradrenaline which alter the brain-neurochemistry [46]. SCFA, especially butyrate, maintain the intestinal tight junctions, BBB integrity, show neuroprotective effects [47] and even are capable of ACE2 downregulation in the

Table 1

## Altered gut microbiota leads to the dysregulation of neurotropic metabolites in COVID-19 patients altering neuronal responses

Bacterial phylum/genus (and status in COVID-19)	Microbial metabolite/ neurotransmitter	Impacts of the microbial metabolites/ neurotransmitters	References
<i>E. rectale</i> , <i>F. prausnitzii</i> (decreased)	Butyrate	Neuroprotective, anti-inflammatory, antioxidant	[20**,44,47]
<i>Roseburia</i> sp., <i>Akkermansia muciniphila</i> , <i>Ruminococcus</i> (decreased)	Propionate	Neuroprotective, anti-inflammatory, antioxidant	[20**,44,47]
<i>Bifidobacterium</i> sp. (decreased)	Acetate	Neuroprotective, anti-inflammatory	[5,20**,47]
<i>B. dorei</i> , <i>B. ovatus</i> , <i>B. caccae</i> , <i>B. vulgatus</i> (increased)	$\gamma$ -aminobutyric acid (GABA)	Neuroinhibitor	[19**,59,60]
<i>Enterococcus</i> sp., <i>Clostridium</i> sp. (increased)	Dopamine	Neuroinhibitor, blunts ventilation under normocapnic hypoxia	[9,20**,57,61–63]
<i>Corynebacterium</i> sp., <i>Brevibacterium</i> sp., <i>Ruminococcus</i> sp. (decreased)	Glutamate	Neurostimulator	[20**,59,64]

colonic organoids of rats [48]. Murine RC and CB are responsive to SCFA by the mediation of Olfr78, a Gs-coupled receptor involved in mild-moderate hypoxia-sensing [49]. All the evidence implicate that SARS-CoV-2-mediated depletion of SCFA can impair hypoxia-sensing.

Inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn's disease (CD), show striking-similarities with COVID-19 in their pathophysiological mechanisms. IBD are associated with immune dysregulation, damaged intestinal barrier and gut dysbiosis [50]. Eventually, inflammatory processes spread extra-intestinally and affect other organs including the respiratory organs and the brain. IBD patients display "pathological hypoxia" frequently but some patients remain nondyspneic [51] and asymptomatic unless assessed by lung function test [52]. The gut microbiome of IBD patients, has fewer SCFA producers such as *Roseburia* and *F. prausnitzii* accompanied by depletion of beneficial *Faecalibacterium* sp., *Ruminococcus* and increased *Clostridium* sp. abundance [50]. As in COVID-19, SCFA, specifically butyrate, is consistently low in the gut of individuals with IBD. Interestingly, ACE2 receptors are induced in IBD [53] and possibly correlates with the SCFA downregulation. These reports signify the need for future studies to unravel the relationship of gut metabolites with respiratory controls dependent and independent of SARS-CoV-2 infection.

The molecular mechanism of hypoxia-sensing is still elusive; however, the role of hypoxia-adaptive hypoxia-inducible factor-1 (HIF-1) and HIF-2 are well-known. Hypoxia stabilizes the  $\alpha$ -subunit of HIF. HIF-1 $\alpha$  deficiency and HIF-2 $\alpha$  accumulation contributes towards a blunted hypoxic response by the CB [54]. Moreover, direct invasion by SARS-CoV-2 induces inflammatory responses in the CB [15]. In contrast to SARS-CoV-2, other viruses attacking the respiratory system such as the influenza virus and respiratory syncytial virus, which do

not have any association with silent hypoxia, increase SCFA or valerate [55]. SCFA increase HIF-1 $\alpha$  stability in enterocytes which contributes in improving the intestinal barrier function [56]. It will be interesting to know whether SCFA downregulation in COVID-19 contributes towards HIF-1 $\alpha$  downregulation in CB and blunting of hypoxia-response.

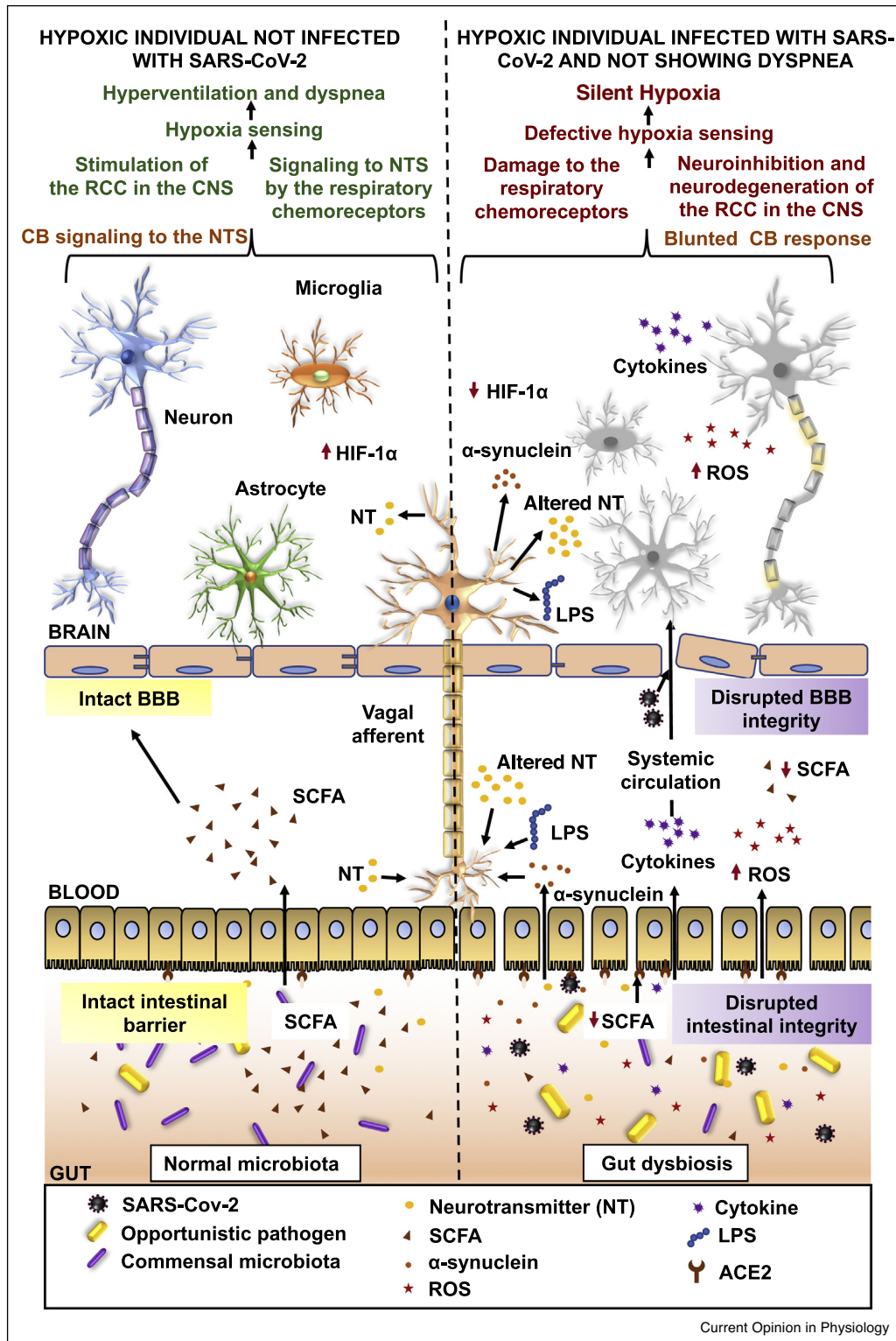
Gut microbiota produces various neuromodulators [43\*,57]. Among the neuronal compounds detected in the rat glomus cells are NO, enkephalins, neurotensins, neuropeptide Y, substance P, dopamine, GABA, vasoactive intestinal peptide and tyrosine hydroxylase [58]. The major catecholamine functional in the CB is dopamine which exerts inhibitory signals to both hypoxia-sensing and ventilatory efforts [9]. Pathogenic *Clostridium* sp., positively correlated with COVID-19 in elderly people, can synthesize dopamine and thus, possibly impairs hypoxia-sensing. The chemoreceptors present at the cardio-respiratory center of the NTS, the medulla oblongata and the cerebellum are glutaminergic and inhibited by GABA [59]. Enrichment of GABA synthesizing *Bacteroides* population in COVID-19 might inhibit these neurons impacting O<sub>2</sub>-sensing [20\*\*,60].

In summary, we theorize that SARS-CoV-2 modulates gut microbes which fine-tune gut-derived metabolites, potentially altering hypoxia-sensing (Figure 2).

### Conclusions and future remarks

COVID-19-research is still in its nascent stage. The problem associated with silent hypoxia in COVID-19 is the lack of dyspnea which also deters the opportunity to study the gut microbiota-brain axis during this stage. Increased testing can help in identifying infected individuals even if they do not show any respiratory distress and bring them under medical surveillance. Early detection of circulating metabolites in asymptomatic individuals would help in the prediction of silent hypoxia. The focus should be on exploring the reversal of gut dysbiosis

Figure 2



Summary figure comparing the gut-brain communication during hypoxia in the uninfected and SARS-CoV-2-infected non-dyspneic hypoxic individuals. The gut microbiota is involved in maintaining the intestinal barrier, the BBB integrity as well as overall homeostasis in the host. In COVID-19, SARS-CoV-2-mediated altered inflammatory and metabolic responses damage the intestinal barrier and the BBB. As a result, in the infected individuals, viral particles, increased inflammatory mediators, ROS, neurotropic gut microbial metabolites and depleted SCFA can cause damage to the central and peripheral neurons involved in hypoxia-sensing.

in COVID-19 through microbiota-modification therapy (food, prebiotic/probiotic and fecal material transplant) [65] which look promising in reversing gut dysbiosis in several diseases.

### Author contribution

Akshita, Soumyadeep and Asima prepared the original draft; reviewing and editing were done by Alok, Pratyush, Pragyesh, Debashish, Supriya, Indrajit, Arup and Asima; artworks were done by Soumyadeep, Pratyush and Alok. The entire work was planned and supervised by Asima. All authors approved this version of the manuscript to be published.

### Conflict of interest statement

Nothing declared.

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