PERSPECTIVES | The Pathophysiology of COVID-19 and SARS-CoV-2 Infection

The potential role of the carotid body in COVID-19

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Porzionato A, Emmi A, Stocco E, Barbon S, Boscolo-Berto R, Macchi V, De Caro R. The potential role of the carotid body in COVID-19. Am J Physiol Lung Cell Mol Physiol 319: L620–L626, 2020. First published August 5, 2020; doi:10.1152/ajplung.00309.2020.—The carotid body (CB) plays a contributory role in the pathogenesis of various respiratory, cardiovascular, renal, and metabolic diseases through reflex changes in ventilation and sympathetic output. On the basis of available data about peripheral arterial chemoreception and severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), a potential involvement in the coronavirus disease 2019 (COVID-19) may be hypothesized through different mechanisms. The CB could be a site of SARS-CoV-2 invasion, due to local expression of its receptor [angiotensin-converting enzyme (ACE) 2] and an alternative route of nervous system invasion, through retrograde transport along the carotid sinus nerve. The CB function could be affected by COVID-19-induced inflammatory/immune reactions and/or ACE1/ACE2 imbalance, both at local or systemic level. Increased peripheral arterial chemosensitivity and reflex sympathetic activation may contribute to the increased morbidity and mortality in COVID-19 patients with respiratory, cardiovascular, renal, or metabolic comorbidities.

carotid body; chemosensitivity; COVID-19; nervous system; sympathetic nervous system

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak, with its devastating impact on health and economic systems, focused research attention on pathogenetic and clinical aspects, such as effects on the respiratory function, possible invasion of the nervous system, and mechanisms involved in the morbidity-induced increase in morbidity and mortality. A large number of articles have appeared in recent months on the above topics; conversely, the potential role of peripheral arterial chemoreceptors has not yet been considered, despite cardiorespiratory regulation is obviously mediated by a functional integration between central and peripheral nervous structures.

Peripheral arterial chemoreception is mainly mediated by the carotid body (CB), which is stimulated by hypoxia, hypercapnia, and pH reduction, although a large body of literature supports its additional roles in immune and metabolic sensing.

From a structural point of view, the CB is composed of lobules of type I and II cells. Type I cells are considered the true chemoreceptor elements, producing and releasing many neurotransmitters/neuromodulators. Type II cells are considered supportive cells enveloping type I cells, although they may also be stem cell precursors for type I cells and probably play a role in coordination of chemosensory transduction.

Neurotransmitters/neuromodulators released by type I cells act on the afferent nerve terminals of the carotid sinus nerve (CSN), a sensitive branch of the glossopharyngeal nerve with neurons in the petrosal ganglion. Centrally, the CSN projects to the solitary tract nucleus, which increases ventilation and sympathetic output through other brainstem nuclei.

In the present paper, the potential role of CB in COVID-19 will be addressed.

THE CB COULD BE A POTENTIAL SITE OF SARS-CoV-2 INFECTION AND AN ALTERNATIVE ROUTE OF CENTRAL NERVOUS SYSTEM INVASION

Central nervous system manifestations in COVID-19 have been reported in percentages up to 25% (e.g., 9, 28, 41, 80). They include headache, dizziness, confusion, impaired consciousness, and acute cerebrovascular events. In addition, neurological manifestations are more frequent in severe patients [88% in the series by Mao et al. (41)].

Some autopic and experimental data are present in the literature about neurotropism of other animal and human (H) coronaviruses (CoV). In particular, neuroinvasive capability has been demonstrated for most βCoV, such as SARS-CoV (22), Middle East respiratory syndrome-CoV (MERS-CoV) (34), HCoV-229E (66), HCoV-OC43 (17), mouse hepatitis virus (83), and porcine hemagglutinating encephalomyelitis coronavirus (HEV) (36, 37). SARS-CoV particles have been demonstrated in the brain, with specific reference to neurons (16, 77). As a consequence, in the last months, some articles specifically considered and discussed the neuroinvasive potential of the severe acute respiratory syndrome-CoV-2 (SARS-CoV-2), considering the possibility that neuroinvasion and damage to the central respiratory nuclei may be involved in SARS-CoV-2-induced respiratory failure (e.g., 4, 35).

In addition, the potential role of the peripheral nervous system as entry route has been considered. Peripheral neurological symptoms have been reported by Mao et al. (41) in 8.9% of cases, hypoguesia (5.6%), and hyposmia (5.1%) being the more frequent ones. Thus, the olfactory epithelium and nerves have been proposed as a way of brain entrance (e.g., 7). SARS-CoV (46) and MERS-CoV (34) also enter the brain when given intranasally, probably through the olfactory nerves.

It has also been proposed that SARS-CoV-2 may enter the brainstem via peripheral vagal afferents and trans-synaptic transfer (35). This hypothesis is consistent with previous findings from SARS-CoV and other CoV. There is evidence that the brainstem, and particularly the solitary tract nucleus, is invaded by various CoV, such as the avian bron-
chitis virus (43), MERS-CoV (34) and SARS-CoV (44, 46), so that an analog pattern of neuroinvasion for SARS-CoV-2 is probable (35).

There is evidence that other CoVs (e.g., HEV67, avian bronchitis virus) may enter peripheral nerve terminals and then invade the brain through retrograde transport and trans-synaptic transfer (e.g., 2, 8, 36, 37, 43, 45). HEV has been identified in the neurons of sensory (trigeminal, inferior vagal, dorsal root) and autonomic (superior cervical) ganglia (2, 36). Virus entrance into satellite cells of dorsal root ganglia has also been reported, through releasing from the sensory neurons and phagocytosis by adjacent satellite cells, although without signs of viral replication (36).

The cellular receptor for SARS-CoV and SARS-CoV-2 is the angiotensin-converting enzyme 2 (ACE2), usually a membrane-bound homolog of angiotensin-converting enzyme. SARS-CoV-2 has been reported to show about fourfold (72) or 10- to 20-fold (75) higher receptor affinity than SARS-CoV. ACE2 is widely expressed not only in lungs but also in other organs, such as heart, brain, kidney, and intestine, where it may permit virus invasion.

SARS-CoV-2 RNA has been identified in blood, plasma, serum, and cellular fraction of blood (67, 73, 74, 82). In an autopsy study, viremia correlated with viral load in the heart, liver, and kidney, strongly suggesting organ invasion through the bloodstream (74). Transplacental transmission has also been demonstrated with ascertainment of both maternal and neonatal viremia (71). Thus, the potential SARS-CoV-2 invasion of the CB may also be hypothesized, as the CB is one of the structures with highest blood flow (2,000 mL·100 g⁻¹·min⁻¹), and it expresses ACE2 (48). In fact, the CB has a locally expressed renin-angiotensin system, which plays a role in the modulation of chemoreceptive function. Retrograde transport in the afferent fibers of the CSN may also be possible (Fig. 1). Virus invasion of the CB and CSN could intrinsically affect peripheral chemoreception, as also proposed by Soliz et al. (65). Moreover, this route could represent an alternative entry way for the solitary tract nucleus, which also expresses ACE2 and is known to be invaded by other CoV.

ACE2 is also expressed by endothelial cells (19) and evidence was found of direct viral infection of endothelial cells, together with diffuse endothelial inflammation. In fact, viral inclusion structures were observed by electron microscopy in endothelial cells of the renal vasculature. Inflammatory cells associated with endothelium (endothelitis) were also found in vessels of lung, heart, kidney, liver, and small intestine submucosa (69). Local modifications in blood flow are involved in chemoreceptor discharge. Thus, viral infection also of the glomic microvasculature may be hypothesized, with possible contributory effects on chemoreception modifications. Analogously, it has been proposed that invasion of the cerebral vascular endothelium by the virus may reduce its functionality, contributing to the elevation of blood pressure and consequent blood vessel rupture (10, 63). The blood vessels of the CB are innervated by sympathetic and parasympathetic nerve terminals and retrograde transport through these nerves cannot be excluded.

**SARS-CoV-2 COULD AFFECT PERIPHERAL ARTERIAL CHEMORECEPTION THROUGH LOCAL OR SYSTEMIC INFLAMMATORY/IMMUNE STIMULI**

CB invasion by SARS-CoV-2 (at the level of chemoreceptive and/or endothelial structures) may induce local inflammatory reactions which could further contribute to derangement of chemoreception (Fig. 1). For instance, chronic carotid glomitis has been reported in aging and opiate-related deaths (55), and experimental studies have shown that the CB may show local inflammatory reactions also in response to systemic stimuli, with possible detrimental effects on ventilatory control.

Prenatal and postnatal lipopolysaccharide (LPS) administration affects peripheral chemoreception in different experimental animals (18, 42, 61). Maternal intraperitoneal LPS administration lowers baseline ventilation, increases apnea frequency, and produces hypersensitivity to hypoxia/hypercapnia.
in mouse newborns (61). In the rat, intraperitoneal postnatal LPS administration increases the frequency of desaturation episodes and reduces hypoxic chemosensitivity. Increases in glomic inflammatory cytokines (IL-1β and IL-6) and in the volume fraction occupied by type II cells have also been found, together with reduced dopamine content and ultrastructural changes in type I cells (42).

In patients with severe COVID-19, the occurrence of a “cytokine storm” (IL-6, IL-10, and TNF-α) has been reported (e.g., 52). The CB also recognizes blood immunogens and cytokines (53), showing immunosensing properties, so that potential effects of SARS-CoV-2 cytokine storm on carotid chemoreception cannot be excluded, even in the absence of local invasion of the CB.

SARS-CoV-2 COULD AFFECT PERIPHERAL ARTERIAL CHEMORECEPTION THROUGH LOCAL OR SYSTEMIC ACE1/ACE2 IMBALANCE

ACE1 and ACE2 show different enzymatic actions: ACE1 converts ANG I in ANG II, whereas ACE2 converts ANG I in ANG(1–9), then further converted in ANG(1–7), and may also convert ANG II in ANG(1–7). ACE2 decreases the production of ANG II in favor of ANG(1–7). ANG II mediates vasoconstriction, fibrosis, inflammation, hypertrophy, and sympatho-excitation through AT1R binding; ANG(1–7) mediates vasodilation, anti-fibrosis, anti-inflammation, antigrowth, and sympatho-inhibition through MasR binding (e.g., 48). As a consequence, a balance is present in the different tissues between the two pathways (ACE1/ANG II/AT1R and ACE2/ANG(1–7)/MasR), and this balance can be affected in various clinical conditions.

As it regards COVID-19, internalization of SARS-CoV-2 causes inhibition of ACE2 activity and progressive depletion of membrane-bound ACE2 (23, 26, 27, 31, 81), with potential increase in ANG II, which has been proposed to contribute to lung damage through stimulation of fibrosis and inflammatory reaction (26).

The local renin-angiotensin system of the CB plays a pivotal role in the modulation of chemoreceptive function and in plastic changes of CB structure and function in response to hypoxia, heart failure, and inflammatory conditions (reviewed in Refs. 20, 26, 30, 33, 48, and 56). In fact, ANG II enhances the hypoxic sensitivity of type I cells, through interaction with oxygen-sensitive potassium channels and decreased voltage-gated currents (I_KV) (38), whereas ANG(1–7) enhances I_KV, through activation of neuronal nitric oxide synthase and nitric oxide production (62).

With it regards local effects of SARS-CoV-2 in the CB, it is possible that virus-induced depletion of membrane-bound ACE2 could contribute to imbalance of the two signaling pathways, in favor of the ACE1/ANG II/AT1R one, with increased hypoxic sensitivity, afferent discharge, and sympatho-activation (Fig. 1). ANG II may also activate macrophages and other immune cells to produce inflammatory cytokines, such as IL-6, TNF-α, and others (32, 58, 79).

Apart from locally produced ANG II, the CB is also stimulated from circulating ANG II (e.g., 20) and in COVID-19, circulating levels of ANG II are increased, even proportionally with viral loads (40). Thus, we may hypothesize that in COVID-19 the systemic production of ANG II may additionally invest the CB.

In conclusion, we hypothesize that CB and its innervation could represent another way through which SARS-CoV-2-induced ACE1/ACE2 imbalance (local and/or systemic) may exert noxious actions on respiratory regulation and cardiovascular function, through increased peripheral hypoxic chemosensitivity and sympathetic output.

INCREASED PERIPHERAL ARTERIAL CHEMORESISTIVITY AND SYMPATHETIC OUTFLOW MAY CONTRIBUTE TO INCREASED MORBIDITY AND MORTALITY IN COVID-19 WITH COMORBIDITIES

In COVID-19, higher morbidity and mortality are associated with comorbidities, such as chronic lung disease, cardiovascular pathologies, hypertension, diabetes mellitus, and obesity (e.g., 76 and 83). The US Centers for Disease Control and Prevention reported that 89.3% of COVID-19 patients who were hospitalized in March “had one or more underlying conditions; the most common were hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (28.3%), and cardiovascular disease (27.8%)” (21). In COVID-19 patients, diabetes mellitus is associated with mortality, severe COVID-19, acute respiratory distress syndrome (ARDS), and disease progression (29). All of the above pathologies are also known to affect peripheral arterial chemoreception, with modifications which may be in turn detrimental for pulmonary, cardiac, circulatory, renal, and metabolic functions. On the other hand, COVID-19 deaths are frequently caused by a final homeostasis dysregulation caused not only by pulmonary damage but also by cardiac, circulatory, renal, and/mor metabolic effects. Thus, a potential role of CB should be considered and discussed (Fig. 2).

Consistent and reliable evidence is available about the fact that the CB is a metabolic sensor contributing to the regulation of whole body insulin sensitivity and that its dysfunction may be involved in metabolic and cardiovascular disturbances (e.g., 11, 12). Insulin can stimulate the CB by binding to its receptors on type I cells, inducing a rise in intracellular Ca^{2+}, and eliciting the release of neurotransmitters, which act on the CSN terminals. The functional effect of insulin-induced stimulation of the CB and CSN produces an increase in ventilation and an augmented sympathetic output. In metabolic conditions characterized by insulin resistance and hyperinsulinemia, the CB is overstimulated. In fact, in rats, hypercaloric diets produce CB overactivation and stimulation of the sympathetic nervous system (60). The insulin-mediated increase in sympathetic output is prevented by surgical section of the CSN (60) or hyperoxic silencing of peripheral chemoreception (39). It is important to stress that sympathetic overactivation in turn increases insulin resistance (detected by insulin tolerance test), producing a vicious circle, which can be experimentally prevented by CB denervation (60). Various respiratory diseases, such as obstructive sleep apnea syndrome, are characterized by chronic intermittent hypoxia, which is another condition increasing the peripheral chemosensory response to hypoxia and consequently inducing a sympathetic overactivation that can be prevented by CB denervation (e.g., 57, 59). It is widely shared that sympathetic overactivity is associated with obstructive sleep apnea syndrome, cardiovascular diseases, renal patholo-
gies, and metabolic disturbances (diabetes, obesity, metabolic syndrome). Thus, increased chemosensitivity is strongly suggested to play a role in sympatho-activation of hypertension, heart failure, diabetes, obesity, obstructive sleep apnea syndrome, and chronic kidney disorders (e.g., 11–13, 51, 54). In the above conditions, the increased sympathetic outflow (at least partially induced by increased CSN discharge) may contribute to increased morbidity/mortality in COVID-19 through homeostasis derangement. Moreover, the increased sympathetic activity through stimulation of the chemoreceptive discharge may have specific detrimental respiratory effects by increasing pulmonary capillary leakage and favoring ARDS (1, 5, 14, 15).

Moreover, COVID-19-induced ACE1/ACE2 imbalance may acquire higher relevance in the presence of the above comorbidities, which share a relative prevalence of the ACE1/ANG II/AT1R pathway (70), with additional stimulatory effects on the CB. ACE2 deficiency may play a role in hypertension (49, 50) and seems to enhance susceptibility to heart failure (49). Diabetes mellitus is associated with reduced ACE2 expression, maybe due to glycosylation (47, 68, 78). Expression of ACE2 is reduced in the adipose tissue of obese animals (24). Fatty diet decreases ACE2 activity and increases ANG II and blood pressure in male rats (but not in female ones) (25). In these conditions, the ACE2 downregulation induced by SARS-CoV-2 could further imbalance the already critical ACE1/ACE2 equilibrium with homeostasis derangement. Conversely, because of the intrinsic high affinity of SARS-CoV-2 to ACE2 receptors (72, 75), in these pathologies the ACE2 deficiencies would not have a protective role from viral invasion (70).

In chronic heart failure, a reduced expression of ACE2 (62) and increased ACE1/ANG II/AT1R signaling have been reported in the CB. This imbalance enhances the hypoxic sensitivity and afferent discharge of the CB, with consequent increased sympathetic outflow (48).

On the basis of the above considerations about ANG II effects on the CB, it may be hypothesized that the systemic ACE1/ACE2 imbalance may exert its detrimental effect also through the CB, being widely shared that circulating ANG II increases hypoxic sensitivity and chemoreceptor discharge of the CB (e.g., 20). In COVID-19, the chemoreceptor-induced increase in sympathetic activity could obviously have negative effects also on pulmonary, cardiovascular, renal, and metabolic homeostasis.

On the contrary, it is also intriguing that high-altitude inhabitants seem to be less susceptible to severe COVID-19 (3), as they also show adaptative changes in peripheral arterial chemoreception and lower sympathetic reactivity (e.g., 6, 64).

CONCLUSIONS

In the present article, we highlighted some potential mechanisms of carotid body involvement. In the presence of respiratory, cardiovascular, renal, or metabolic comorbidities, increased carotid body chemosensitivity and reflex sympathetic outflow would contribute to the detrimental effects in COVID-19, which in turn would further increase hypoxic chemosensitivity and sympatho-activation in a vicious circle. ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; CSN, carotid sinus nerve; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.P., A.E., E.S., and S.B. prepared figures; A.P., A.E., and R.D.C. drafted manuscript; A.P., A.E., E.S., S.B., R.B.-B., V.M., and R.D.C. edited and revised manuscript; A.P., A.E., E.S., S.B., R.B.-B., V.M., and R.D.C. approved final version of manuscript.
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