ACE2 as Link between COVID-19 and Parkinson's Disease

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Coronavirus disease 2019 (COVID-19) is frequently accompanied by neurological manifestations such as headache, delirium, and epileptic seizures, whereas ageusia and anosmia may appear before respiratory symptoms. Among the various neurological COVID-19-related comorbidities, Parkinson's disease (PD) has gained increasing attention. Some cases of PD disease have been linked to COVID-19, and both motor and non-motor symptoms in Parkinson's disease patients frequently worsen following SARS-CoV-2 infection. Although it is unclear whether PD increases the susceptibility to SARS-CoV-2 infection or whether COVID-19 increases the risk of or unmasks future cases of PD, emerging evidence sheds more light on the molecular mechanisms underlying the relationship between these two diseases. Among them, angiotensin-converting enzyme 2 (ACE2), a significant component of the renin-angiotensin system (RAS), seems to play a pivotal role. ACE2 is required for the entry of SARS-CoV-2 to the human host cells, and ACE2 dysregulation is implicated in the severity of COVID-19-related acute respiratory distress syndrome (ARDS). ACE2 imbalance is implicated in core shared pathophysiological mechanisms between PD and COVID-19, including aberrant inflammatory responses, oxidative stress, mitochondrial dysfunction, and immune dysregulation. ACE2 may also be implicated in alpha-synuclein-induced dopaminergic degeneration, gut–brain axis dysregulation, blood–brain axis disruption, autonomic dysfunction, depression, anxiety, and hyposmia, which are key features of PD.

Keywords: neurodegeneration ; dopaminergic degeneration ; neuroinflammation

1. Introduction

Coronavirus disease 2019 (COVID-19) emerged in December 2019 as a global pandemic, causing a significant health threat worldwide [1]. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is well documented that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) in order to enter host cells [1]. ACE2 is a significant component of the renin-angiotensin system (RAS), which is critically involved in the cardiovascular system, but also plays a major role in the regulation of inflammatory responses in multiple tissues, including the brain [2].

More specifically, reduced ACE2 expression and activity have been shown in hypertension, heart failure, atherosclerosis, diabetic nephropathy, and other disease models. Local inhibition or total ablation of ACE2 in the brain reduces baroreflex sensitivity [3]. Furthermore, ACE2-null animals have been demonstrated to suffer either high blood pressure or cardiac dysfunction [3]. ACE2 overexpression, on the other hand, has protective effects on local tissues, including the brain. ACE2 is found throughout the brain, including nuclei involved in the central control of cardiovascular function, such as the brainstem's cardio-respiratory neurons, as well as non-cardiovascular regions, such as the motor cortex and raphe. The existence of ACE2 mRNA and protein in the mouse brainstem has also been verified. While these data indicate that ACE2 is a novel component of the brain RAS, they also reveal that ACE2's participation in the central nervous system extends beyond the control of cardiovascular function [3].

2. The Role of ACE2 in COVID-19: Mechanistic Insights

SARS-CoV-2 belongs to the betacoronaviruses group [4]. It is an enveloped single-stranded RNA virus, containing approximately 30,000 nucleotides [5]. The genetic content of SARS-CoV-2 encodes four proteins: spike glycoprotein (S), the nucleocapsid protein (N), a small envelope protein (E), and matrix protein (M) [6]. The spike glycoprotein (S) mediates the entry of the virus into the host cells, and it has two subunits, known as S1 and S2 [6].

ACE2 is required for the entry of SARS-CoV-2 into the host cell and, subsequently, the following viral replication [7]. In particular, the RBD of the spike (S) protein of SARS-CoV binds to ACE2, which acts as the functional cellular receptor [7] [8]. The serine protease transmembrane protease serine 2 (TMPRSS2) of the host cell is used for S protein priming [9].

Importantly, SARS-CoV could still infect cells expressing mutant forms of ACE2 with no catalytic activity [10]. The spike (S) protein of SARS-CoV could interact with the tip of subdomain I of the catalytic domain of ACE2 without affecting subdomain II or occluding the enzymatic active site [11].

Despite the significant genetic and structural similarities between SARS-CoV and SARS-CoV-2, SARS-CoV-2 displays greater infectivity and transmissibility, which has resulted in the massive and rapid increase in the number of COVID-19 patients [4]. The spike protein of SARS-CoV-2 also exhibits increased binding affinity to ACE2 compared to SARS-CoV [12]. The entry of SARS-CoV2 into the host cells has also been demonstrated to depend on ACE2 and S protein priming by TMPRSS2 [13], suggesting that ACE2 is a main determinant of SARS-CoV-2 entry into the target cells. Importantly, the peptidase activity of ACE2 is separated by the site of ACE2 that binds to the spike protein (S) of SARS-CoV-2, and the binding of S protein to ACE2 seems to not alter the catalytic activity of the virus [13].

In the lung tissue, ACE2 is highly expressed in the alveolar epithelial cell types I and II, where it can facilitate SARS-CoV-2 invasion [14]. However, ACE2 is also expressed in vascular endothelial cells, as well as lung progenitor/epithelial stem cells [15]. This observation might at least partially explain the ability of SARS-CoV to continuously destroy the lung tissue, which is associated with limited repair capacity. The fact that ACE2 is also expressed in the heart, renal, and intestinal tissues [16] may also at least partially explain the multi-organ injury of SARS-CoV2-infected patients [17][18][19][20].

ARDS is a severe complication of SARS coronaviruses infection, characterized by high mortality [21][22][23]. ACE2 has been shown to act in a protective manner against ARDS. ACE2 knockout has been associated with more severe ARDS pathology in mice, accompanied by increased inflammation and lung tissue damage, increased pulmonary edema, and worse respiratory function compared with the wild type [24]. Delivery of recombinant ACE2 protein could also improve the respiratory function in ARDS animal models [25].

The SARS-CoV-2-mediated ACE2 downregulation and subsequent RAS upregulation may also be involved in other cellular pathophysiological mechanisms. Apart from the enhanced inflammatory responses and tissue injury, overactivation of RAS may also result in oxidative stress, mitochondrial impairment, and autophagy dysregulation. In this regard, SARS-CoV-2 infection of the renal tubular epithelium is associated with mitochondrial dysfunction in an ACE2-dependent manner [26]. Inhibition of ACE2 SUMOylation has also been shown to protect against SARS-CoV-2 infection via TOLLIP-mediated autophagy [27]. SARS-CoV-2-induced increases in ROS cause oxidative stress and mitochondrial electron imbalance. As a result, procaspases, cytochrome C, and pro-apoptotic mechanisms are upregulated, leading to cellular damage and apoptosis [28]. This evidence suggests that ACE2 may be involved in additional pathogenic mechanisms underlying COVID-19 that are not directly associated with inflammation.

Interestingly, serum levels of AT1R and ACE2 autoantibodies are associated with COVID-19, and correlate with the severity of the disease [29][30]. AT1R autoantibodies act as AT1R agonists and aggravate the RAS-mediated pro-inflammatory pathway, while ACE2 autoantibodies act as ACE2 antagonists, thereby functioning as pro-inflammatory factors too [31]. Hence, it has been hypothesized that these autoantibodies may aggravate the inflammatory cascade mediated by RAS in COVID-19 patients, resulting in worse clinical outcomes. Importantly, the plasma of patients with a history of COVID-19 and ACE2 autoantibodies displays reduced activity of the endogenous soluble ACE2 and inhibits the activity of exogenous ACE2. Based on this evidence, it has been hypothesized that the development of ACE2 autoantibodies in COVID-19 patients may upregulate RAS and result in a pro-inflammatory state [31]. This process may underlie the association between COVID-19 and other inflammatory chronic conditions, including neurodegenerative diseases.

3. The Relationship between ACE2 and PD: Exploring the Underlying Mechanisms

PD is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the deposition of Lewy bodies and Lewy neurites containing alpha-synuclein [32]. According to Braak staging, at prodromal stages of PD, Lewy pathology initially appears in the olfactory bulbs and the dorsal motor nucleus of the vagal nerve, possibly associated with hyposmia and constipation, respectively. Then, Lewy pathology may spread throughout various brain regions in a stereotypical manner, while it affects dopaminergic neuronal cells in the substantia nigra several years later [33]. Although the pathogenesis of PD remains elusive, several pathophysiological mechanisms, including oxidative stress, neuroinflammation, mitochondrial dysfunction, abnormal protein aggregation and spreading, autophagy dysregulation, impaired apoptotic mechanisms, and gut microbiome imbalance, are implicated in its development [34][35][36][37]. Increased levels of tumor necrosis factor alpha (TNF) and interleukin 1β (IL-1-β) have been related to increased PD risk [38]. Caspases upregulation, NF-κB upregulation, ROS production, and mitochondrial electron imbalance are

implicated in PD [28][39]. Inflammasomes, and especially the NLR family pyrin domain containing 3 (NLRP3) inflammasome, are majorly implicated in the elimination of damaged cells and pathogens by microglia. Alpha-synuclein can activate NLRP3, and its upregulation is implicated in PD pathogenesis [39].

ACE2 is expressed in several brain regions, mainly in the thalamus, inferior olivary nuclei, and cerebellum [40], but also in the hippocampus, amygdala, visual cortex, and striatum [41]. Excessive RAS activation in the brain has been associated with oxidative stress, inflammation, immune dysregulation, and abnormal cell growth and proliferation [42][43]. AT1R overactivation upregulates NADPH-oxidase complex 2 (Nox2), resulting in the production of reactive oxygen species (ROS) [44]. Angiotensin II/AT1R/Nox4 pathway-induced oxidative stress is associated with dopaminergic degeneration [45]. In mouse models of age-dependent cardiomyopathy, ACE2 deficiency can increase angiotensin II-induced oxidative stress, inflammation, and neutrophilic infiltration via the AT1R [46]. Exosome-mediated transfer of ACE2 can increase endothelial cell survival [47], and ACE2 modulates mitochondrial function in mice [48]. Given the fact that dysregulation of cell survival, mitochondrial function, inflammation, and excessive oxidative stress are implicated in the pathogenesis of PD, it has been proposed that ACE2 may play a role in this case too.

Accumulating evidence suggests the potential implication of autoimmunity in the development and progression of PD, and autoantibodies targeting the extracellular region of glial or neuronal proteins receive increasing interest [49]. In this regard, a recent study demonstrated that ACE2 and AT1R autoantibodies were increased in the serum of PD patients compared to controls. The levels of AT1R autoantibodies were also associated with various cytokines, including tumor necrosis factor ligand superfamily member 14 (TNFSF14) and 27-hydroxycholesterol. In addition, the levels of both autoantibodies were increased in the serum and cerebrospinal fluid of 6-OHDA-induced rat models of PD. The levels of TNFSF14 and the activity of transglutaminase were also elevated in the substantia nigra of the rat models of PD. Delivery of AT1R autoantibodies in cell cultures could promote dopaminergic neuronal cell death and increase pro-inflammatory cytokine levels. This effect was suppressed by the use of candesartan, an AT1R antagonist [31].

4. ACE2 in PD and COVID-19: Connecting the Dots

Various factors, including environmental toxins, pathogens, tissue injury, and protein aggregation in the brain, may trigger the upregulation of innate immunity, primarily via the activation of microglia. Excessive neuroinflammation, blood–brain barrier dysfunction, alpha-synuclein aggregation, mitochondrial dysfunction, hypoxia, and microvascular damage have been postulated to contribute to post-viral parkinsonism [50]. The sustained activation of this inflammatory response may drive a pro-inflammatory milieu, which could contribute to neurodegeneration [39].

ACE2 is highly expressed in many brain regions, including the striatum, and SARS-CoV-2 has been shown to infect neuronal cells. Lesions in the basal ganglia have also been reported in COVID-19 thromboembolic encephalopathy [51]. As a result, it has been proposed that the virus could enter the brain hematogenously or via axonal transport via the olfactory or vagus nerves [52], which are also the initial sites of Parkinson's disease-related Lewy pathology according to Braak staging [33]. Previous studies in mice showed that the influenza A virus could be transmitted from the respiratory tract to the basal ganglia via the vagus nerve [53]. SARS-CoV-2 is also present in neuronal cells of the myenteric plexus [54]. Hence, it is possible that SARS-CoV-2 may also follow this route through ACE2. Hyposmia and constipation are well known symptoms of prodromal PD; ACE-2 is expressed in nasal goblet and ciliated cells, as well as in the intestinal epithelium [55], further strengthening this hypothesis. SARS-CoV-2 could enter the nasal cavity, then the olfactory bulb and the piriform cortex, and finally the brainstem, where the substantia nigra pars compacta is located [55]. Because the blood–brain barrier is absent in the olfactory bulb, viral entry is made easier [56]. A recent study revealed that COVID-19 infection was associated with reduced gray matter thickness in the parahippocampal gyrus and orbitofrontal cortex, as well as changes in brain areas with a functional connection to the primary olfactory cortex [57]. These alterations suggest tissue injury, and it could be speculated that the spreading of inflammatory and degenerative processes via the olfactory bulb to other PD-related brain regions might be possible [56].

The COVID-19 pandemic offers an important opportunity to examine how viral infections might aggravate PD-related neurodegeneration [53]. **Table 1** summarizes the mechanisms underlying the aggravation of PD-related neurodegenerations due to SARS-CoV-2 [58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90][91][92][93].

Table 1. Mechanisms underlying the aggravation of PD-related neurodegeneration due to SARS-CoV-2.

Study	Mechanisms
Angelopoulou et al. [36]	The peripheral SARS-CoV-2-induced release of pro-inflammatory cytokines might activate resident glial cells in the brain or stimulate the entry of peripheral immune cells such as T cells into the brain via specific or non-specific antigens.
Tulisiak et al. [33]	Viral infections may cause synucleinopathy in the brain, according to epidemiological and experimental evidence.
Lodygin et al. [58]	β-synuclein-reactive T cells can cause autoimmune neuronal degeneration in the brains of rats.
Matschke et al. [59]	COVID-19 patients display microglial activation and brain penetration of cytotoxic T-lymphocytes, especially in the brainstem.
Philippens et al. [60]	Lewy body pathology has been identified in macaques infected by SARS-CoV-2.
Kaufer et al. [61]	Alpha-synuclein accumulation has been detected in hamsters after SARS-CoV-2 infection.
Cui et al. [41]	Alpha-synuclein can enhance the SARS-CoV-2-mediated activation of microglia and the NLRP3 inflammasome via the ACE2/NF-kB pathway.
Pavel et al. [51]	SARS-CoV-2 infection causes increased levels of bioenergetic cellular stress. The vulnerable dopaminergic neurons may not be able to address the additional cellular COVID-19-induced stress, which could possibly overcome the degeneration threshold.
Wan et al. [62]	Next-generation sequencing analysis has identified ACE2 expression in the substantia nigra.
Wang et al. [63]	The respiratory and gastrointestinal epithelial cells are key hosts of both microbiota and SARS-CoV-2 targets, where ACE2 and TMPRSS2 are highly expressed.
Zuo et al. [64]	A lower number of beneficial microbes and higher levels of opportunistic pathogenic microbes have been found in COVID-19 patients in their fecal microbiomes compared to healthy controls.
Jaworska et al. [65]	Gut bacteria can regulate local gastrointestinal and systemic RAS, while an RAS imbalance in the intestinal wall may affect microbiota composition and activity.
Rodriguez-Perez et al. [30]	COVID-19 may trigger the development of ACE2 and AT1R autoantibodies.
Lamarca et al. [66] Dhillion et al. [67] Herro et al. [68] Jiang et al. [69] Perlin et al. [70]	Increase of the levels of AT1R and ACE2 autoantibodies due to IL-6, IL-17, and TNF-α and TNFSF14 upregulation.
Fleegal et al. [71] Wu et al. [72] Drelich et al. [73]	ACE2 autoantibodies may result in reduced levels of angiotensin 1–7, which play a protective role in the integrity of the blood–brain barrier. ACE2 is also located in the endothelial cells of the blood–brain barrier.
Albornoz et al. [39]	SARS-CoV-2 can impair the blood–cerebrospinal fluid barrier in human brain organoids, and it is also associated with disruption of the blood–brain barrier in hamster models, suggesting that the virus may be able to penetrate the blood–brain barrier.
Angelopoulou et al. [74] Ebrille et al. [75] Vitale-Cross et al. [76]	Given the presence of ACE2 in vagus nerves and the early involvement of the vagus nerve in PD-related Lewy body pathology, it could be speculated that ACE2 may be implicated in the autonomic dysfunction observed in both PD and COVID-19 infection.
Zhao et al. [77] Rocha et al. [78] Okechukwu et al. [79]	Depression and anxiety are common non-motor manifestations of PD. Serum levels of angiotensin I, angiotensin II, and angiotensin (1–7) negatively correlate with the severity of depressive and anxiety symptoms in PD patients, whereas serum ACE and ACE2 levels do not. ACE2 downregulation has also been associated with anxiety and depression in patients with SARS-CoV-2.
AlGhatrif et al. [80] Angeli et al. [81] Chen et al. [82] Lee et al. [83]	Older age is associated with reduced serum ACE2 levels in humans and animal models. A bioinformatics study indicated that ACE2 levels become lower with age in several tissues, including the nervous system and the blood. It is proposed that age-related ACE2 reduction is at least partially associated with the increased morbidity and mortality of COVID-19 elderly patients.
Lee et al. [83]	Given the fact that the gene encoding ACE2 is on the X chromosome, the higher mortality in men among COVID-19 patients could be at least partially explained by the lower expression of the ACE2 gene in males. Male gender is also linked to a higher risk for PD.

Study	Mechanisms
Liu et al. [84] Suzuki et al. [85] Lallai et al. [86] Li et al. [87] Angelopoulou et al. [88] Mappin-Kasirer et al. [89] Chen et al. [90] Lu et al. [91] Tong et al. [92]	**Smoking might possibly protect against COVID-19 contraction due to increased expression of ACE2, but it may be associated with worse morbidity and mortality in COVID-19 individuals. Smoking has been associated with a reduced risk of PD in several studies. It would be hypothesized that ACE2 may be implicated in the protective effects of smoking in PD.**
Verdecchia et al. [93]	**Pre-existing comorbidities characterized by chronic inflammation, including diabetes, hypertension, cancer, and obesity, upregulate the RAS pathway.**

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