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Neurochemical Dysregulation of Covid 19 Infection

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Introduction

Coronaviruses are so named because of the halo of spike (S) proteins that decorate their surfaces [1,2]. These S proteins interact with specific cellular receptors to bind host cells and the binding is followed by protease-mediated S protein cleavage, which exposes fusion-promoting domains that enable viral entry. SARS-CoV-2 infects cells through interactions between its S protein and the Angiotensin I Converting Enzyme 2 (ACE2) receptor on target cells. ACE2 plays a crucial modulatory role in the renin-angiotensin system, which regulates blood pressure, salt and water balance [3]. Infection requires S protein cleavage, likely by the host cell serine protease TMPRSS2 (Transmembrane protease, serine 2) although other proteases may also be involved. SARS-CoV-2 belongs (Severe acute respiratory syndrome-related coronavirus 2) to the coronavirus family, which includes the pandemic MERS-CoV (Middle East respiratory syndrome coronavirus) and SARS-CoV (SARS (Severe acute respiratory syndrome)-associated coronavirus) and the lesser known but more common endemic coronaviruses HCoV-OC43 (*Human coronavirus OC43)*, HCoV-HKU1, HCoV-229E, and HCoV-NL63. The endemic coronaviruses can infect the upper airway and frequently cause the common cold, which in turn is associated with both acute and chronic changes in smell and taste [4,5]. The main proposed mechanisms for acute viral-mediated changes in smell include conductive deficits caused by loss of patency due to swelling of the mucosa and increased mucus production, changes in mucus composition, and secondary changes in olfactory signaling caused by local release of inflammatory intermediates like cytokines While cold-causing viruses likely act through multiple mechanisms to influence smell, recovery from virus-associated olfactory deficits tend to resolve with a time course similar to that of other cold-related symptoms like nasal congestion With the exception of HCoV-NL63, the endemic coronaviruses do not use ACE2 as their primary cellular receptor [6], a molecular distinction that likely underlies key differences in pathophysiology. SARS-CoV also uses ACE2 as its main receptor, and in one case study SARS-CoV infection was associated with anosmia [7], although (unlike COVID-19) chemosensory disturbances are not a hallmark of SARS. Differences between SARS-CoV and SARS-CoV-2 in terms of their impacts on chemosensory systems may relate to biophysical differences, as the receptor-binding domain of the SARS-CoV-2 spike protein binds ACE2 with higher affinity and with a different binding mode than that of SARS-CoV [8]. Species variation in the protein sequence of ACE2 significantly affects its affinity for the SARS-CoV-2 S protein, which in turn renders distinct model organisms differentially susceptible to infection [9]. Given data suggesting that ACE2 is necessary for SARS-CoV-2 to infect host cells, researchers have used a variety of approaches to discern the pattern of expression of ACE2 and other viral entry proteins across the tissue landscape, with the goal of inferring possible target cells and disease mechanisms. For example, two studies have reported that cells in the nasal Respiratory Epithelium (RE) have higher expression of SARS-CoV-2 entry genes than cells in the RE that line the trachea or lungs [10]. Consistent with this finding, recent work in macaques, ferrets, and cats identifies the nasal epithelium as a major source of viral RNA after SARS-CoV-2 infection [11]. These data suggest that the nasal epithelium may act as a major reservoir for the virusandSARS-CoV-2 attacks the olfactory system through mechanisms distinct from those used by the more benign endemic coronaviruses. Many patients report anosmia as their first symptom, or in the absence of rhinorrhea or nasal congestion, suggesting that if inflammation is a key component of pathogenesis, it is local rather than generalized [12]; indeed, the sensitivity of anosmia as a predictor of COVID-19 increases in patients without other nasal symptoms [13]. The OE is a complex chemosensory tissue composed of multiple cell types, including immature and mature OSNs (Olfactory sensory neurons), non-neuronal cell types such as sustentacular, Bowman's gland, and microvillar cells, and stem cells including globose and horizontal basal cells. Sustentacular cells are particularly intimately associated with OSNs, and they "enwrap" the sensory dendritic cilia that project into the airspace and enable odor detection [14]. Four recently pub-

lished studies-using species ranging from mouseto human-have explored the cell types in the OE (olfactory epithelium) that express ACE2 and other viral entry genes [15], all four conclude that OSNs do not express ACE2. Instead, co-expression of ACE2 and TMPRSS2 was observed in key support cells (including sustentacular, Bowman's gland, and microvillar cells) and stem cells that repopulate the epithelium after damage. Although ACE2 mRNA was identified using single-cell RNA sequencing (scSeq) techniques in only a small subset of these cells, a high level expression of ACE2 protein in a large population of sustentacular cells concentrated in the dorso-medial aspect of the mouse OE, which corresponds to the dorsal "zone" traditionally identified via molecular markers [16]. Consistent with this observation, mouse and human sustentacular cells identified as ACE2 positive by scSeq largely derive from the dorsal zone [17]. The co-expression of ACE2 and TMPRSS2 suggests that OE support cells may be the initial targets of SARS-CoV-2 infection. These inference-based conclusions are increasingly being pressure-tested by experiments in which model organisms are directly subject to SARS-CoV-2 infection. One recent paper in the golden hamster reports that SARS-CoV-2 infects sustentacular cells but not OSNs [18]. Intriguingly, this phenotype is accompanied by damage to the OSN ciliary layer and an increase in the number of microglia present in the OE, both of which are partially reverted to normal at 14 days after infection. A similar study in the hamster identified a large number of cells in the OE that were infected by SARS-CoV-2, although OE cell types were not definitively identified; inspection of the photomicrographs in that paper reveals that most SARS-CoV-2-positive cells traverse the thickness of the OE, suggesting that sustentacular cells are primary targets for infection [19]. Human OE samples obtained from COVID-19 patients have similarly been queried for infection by SARS-CoV-2, which has revealed coronaviral antigens present in OE cells; the infected cell types were not unambiguously identified, but their shape and position is consistent with the virus targeting sustentacular cells rather than OSNs [20]. What mechanisms might link infection of support cells to the acute changes in smell reported in COVID-19. Localized inflammation in the epithelium might block the olfactory clefts, a pair of narrow passages located in the superior regions of the nasal epithelium through which air must flow to reach the OE, which comprises only 5% of the total nasal epithelium in humans [21]. Consistent with this possibility, a recent CT study of a COVID-19 patients who presented with anosmia revealed the blocked olfactory clefts [22]. Alternatively, infection of support cells and the attendant inflammation may cause local increases in inflammatory intermediates such as cytokines, which have been shown to influence OSN function in a non-cell-autonomous manner [23]. Indeed, a recent study demonstrates elevated levels of inflammatory cytokines in the OE of infected patients [24]. Inflammatory intermediates have been suggested to indirectly lower the expression of Odorant Receptor (OR) genes by OSNs, which could cause significant changes in odor perception and this work also shows that OR expression levels return to normal after cessation of the inflammatory insult [25]. Finally, SARS-CoV-2 infection of support cells might alter the OE microenvironment in a manner deleterious to function. Bowman's glands, for example, secrete mucus, which is essential to normal odor detection that bulb neurons, do not express detectable levels of ACE2. Consistent with this finding, targeted deep sequencing of dopaminergic juxtaglomerular cells, which receive direct inputs from nose OSNs, failed to reveal Ace2 mRNA in vascular pericytes in the OB (olfactory bulb) expressed high levels of ACE2 protein, consistent with the reported expression of ACE2 in perivascular cells in the brain and throughout the body [26]. Pericytes are critical for maintaining the blood-brain barrier, for defining local blood pressure, and for mediating neuroimmune responses [27] and the infection of these cells has the potential to alter perfusion or recruit inflammation, both of which can indirectly influence the function of neural circuits. SARS-CoV-2 can directly infect neurons or glia and it is important to recognize the key caveats in interpreting data suggesting SARS-CoV-2 does or does not infect neurons and glia directly. SARS-CoV-2 in principle has access to the brain through routes independent of the nasal epithelium, including via vasculature and nerves innervating infected tissues; type II and III TRCs (taste receptor cells) in mice reveal that ACE2 is expressed by sour-sensing type III TRCs, and to a lesser extent by bitter and sweet/umami-sensing type II TRCs [28]. While type II and type III TRCs express little to no TMPRSS2, Cathepsins (CTSB, CTSL) are abundant and may function as proteases to cleave SARS-CoV-2 spike protein at type II and III TRCs, type I cells degrade ATP, which is used as a neurotransmitter by type II cells to convey taste information to the brain via the gustatory nerves [29]. If type I cells are indeed ACE2 positive and targeted by SARS-CoV-2, the loss of support cells could lead to taste bud collapse via cell death and/or reduced efficacy of taste signals to gustatory nerves (unlike OSNs-TRCs are not neurons; thus, all of the cell types identified as ACE2 positive in the tongue to date are either stem or epithelial cells. Chemesthesic stimuli are detected by a variety of epithelial sensors and relayed to the brainstem via trigeminal ganglion sensory neurons, distinct branches of which innervate the nasal respiratory epithelium and the non-taste epithelium of the tongue, among other targets [30]. These trigeminal somatosensory afferents are enriched for TRP (transient receptor potential) channel receptors that detect chemical irritants. Chemical perception due to COVID-19 has only just begun, and much remains to be learned about the pathophysiology of SARS-CoV-2 and thecurrent evidence favors a model in which SARS-CoV-2 cell entry genes in the olfactory, gustatory, and chemesthetic systems are not expressed in primary or secondary neurons, but rather are expressed in epithelial, support, and stem cells responsible for maintaining perception. It also remains possible that SARS-CoV-2 directly infects OSNs or bulb neurons. The understanding of molecular mechanisms underlying the chemosensation and the neural pathways that convey information about chemical cues to the brain, still know little about the non-neuronal cells and structures that support sensory transduction. In this sense, SARS-CoV-2 provides an important opportunity to gain insight into how the complex peripheral tissues that support taste, smell, and chemesthesis enable meaningful interactions with the world. Although the evidence that ACE2 is obligate for SARS-CoV-2 entry is strong, it has been suggested that other molecules such as BSG, neuropilin-1, or PIKfyve may participate in SARS-CoV-2 entry [31]. Furthermore, it has recently been reported that low-level expression of ACE2 may be sufficient to support SARS-CoV-2 infection [32,33], suggesting that SARS-CoV-2 may infect apparently ACE2-negative cell types. ACE2 gene is regulated by inflammation in human cells, and other SARS-CoV-2 entry genes may be similarly modulated by primary infection and inflammation [34]. This observation raises the possibility that a broader spectrum of cells expresses ACE2 during SARS-CoV-2 infection than is currently appreciated. A key open question is how primary infection of non-neural cells alters chemical perception. Defining the pathophysiological mechanisms underlying anosmia and other SARS-CoV-2-associated disturbances in chemical sensation will require moving past inference based upon gene

or protein expression. In particular, brain chemistry, nociceptive processing, inflammation, and autonomic function are modulated by neurostimulation for different therapeutic purposes.

Coronavirus disease 2019 (COVID-19), which is clinically characterized by fever, myalgia, diarrhea, and respiratory illness, the presentation of patients with extremely low blood oxygenation, but no sensation of dyspnea. Patients admitted with COVID-19 can suffer sudden death after voluntary "breaks" from the oxygen supplementation. Recognizing "happy hypoxia" as a feature of COVID-19 pneumonia has led to better patient care [35], this phenomenon has given rise to the term "happy hypoxemia"has been associated with neurological syndromes such as meningoencephalitis, ischemic stroke, encephalopathy, Guillain-Barré syndrome (GBS), acute necrotizing encephalopathy, and Acute Disseminated Encephalomyelitis (ADEM). Possible mechanisms implicated in these neurological conditions are neuronal injury associated with direct virus infection, hyperinflammation syndrome associated with cytokine storm, a para- or post-infectious inflammatory disease, an immune-mediated disease, or a secondary process due to severe effects of a systemic disorder (sepsis, hyperpyrexia, hypoxia, hypercoagulability, critical illness). Expression of angiotensin converting enzyme 2 (ACE2), the cell entry receptor for SARS-CoV-2, is also distinct between human organs. ACE2 is highly expressed in airway epithelia, kidney cells, small intestine, and lung parenchyma [36], and not surprisingly, this correlates with high viral loads demonstrated in some of these tissues [37]. In the CNS, ACE2 is expressed in neurons, astrocytes, and oligodendrocytes, and it is concentrated in the substantia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex, and the olfactory bulb, although at lower levels than that in lungs [38]. These findings, in addition to the spontaneous recovery of neurological alterations described in most of cases of COVID-19 in the literature support the idea of transient and/or limited SARS-CoV-2 dissemination in the CNS rather than direct damage promoted by SARS-CoV-2 replication. Neurological injury is likely a result of misdirected immune responses either associated with autoimmunity or systemic inflammation in response to limited viral replication, the stimulation of host inflammatory responses involved in subsequent CNS injury, shown by increased levels of total Tau and NfL proteins. Several biomarkers of COVID-19 severity have been identified in blood, including C-reactive protein, D-dimer, lactate dehydrogenase, interleukin-6, and ferritin [39], but less evidence is available for Cerebrospinal Fluid (CSF) biomarkers. Viral antigens have been detected in the brainstem, where the infected regions included the nucleus of the solitary tract and nucleus ambiguous, suggesting that respiratory failure in infected animals or patients may be due to the dysfunction of the cardiorespiratory center in the brainstem. Recently Gordon *et al*. have identified 332 high confidence SARS-CoV-2-human Protein-Protein Interactions (PPIs) andthey performed host-virus protein interaction studies by expressing various Open Reading Frames (ORFs) of COVID-19 in HEK293 cells, including 16 nonstructural proteins (Nsp1-16) which form the Replicase/Transcriptase Complex (RTC), four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) 17, and nine putative accessory factors [40,41].

Two proteins, the spike protein (S) and main protease Nsp5 are potential molecules as a prominent number of interactions were related to lipid modifications and vesicle trafficking to S protein whereas Nsp5 showed high confidence interaction with the epigenetic regulator histone deacetylase 2 (HDAC2). Both these molecules are potential targets for therapeutic inhibition as on one hand lipid modulation can promote neuroinvasion and on the other hand, HDAC2 which is highly expressed in neuronal tissues plays a crucial role in CNS development and is a potential therapeutic target of neurodegenerative diseases.There is an urgent need to understand the neurotropic potential of the COVID-19 virus by understanding the possible mechanism of neuromodulation which will be significant for the prevention and treatment of the SARS-CoV-2-induced respiratory failure [42]. In the current scenario, various research strategies need to be employed to understand the mechanisms of neuromodulation resulting either directly in respiratory failure or causing neurological deficits. Host-virus interaction studies using either omics approach [43] (genomic/transcriptomic/proteomic/lipidomic/metabolomic) or cloning and expressing individual COVID-19 proteins in different neuronal cell lines followed by pull-down assays and mass spectrometry and analyzing the interacting protein network. Further proteomic/chemoinformatic analysis can help in identifying already available drugs and clinical molecules from the databases that might interfere with the viral-human interactome. SARS-CoV-1 has been reliably detected in brain tissue specimens of autopsy donors with SARS, specifically in the cytoplasm of neurons in the cortex and hypothalamus, sometimes associated with neuronal edema and nuclear degeneration [44]. Examination of autopsy tissue from a patient with encephalitis revealed neuronal necrosis, glial cell hyperplasia, and infiltration of monocytes and T cells. Additionally, virions were visualized in neurons on electron microscopy, and SARS-CoV-1 RNA was isolated from the specimen. In murine models, SARS-CoV-1 enters the CNS via the olfactory bulb and exhibits rapid transsynaptic spread. Viral neuroinvasion [45] could plausibly be achieved by several routes, including transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier (BBB). There is increasing evidence that human and nonhuman CoV invade peripheral nerve terminals, spread retrograde along nerve synapses, and gain access to the CNS [46]. Transsynaptic transfer of virus has been demonstrated for several CoV, including HCoV-OC43, hemagglutinating encephalomyelitis virus 67 (HEV67), and avian bronchitis virus. For example, HEV67 enters the oronasal cavity and infects the nasal mucosa, lung epithelium, and small intestine of suckling piglets and rats. It then infects the peripheral nerves and spreads retrograde to the dorsal root ganglion, ending in the medullary neurons. A membrane coating-mediated endocytotic or exocytotic pathway facilitates HEV67 transfer between motor cortex neurons [47]. A similar, vesicle-mediated secretory pathway allows HEV67 to spread between neurons and satellite cells. For intracellular spread within a neuron, fast axonal transport uses axonal microtubules to move molecules retrograde or anterograde [48]. Herpes simplex virus, HIV, and HCoV-OC43 have all been shown to use retrograde fast axonal transport to infect the cell body of neurons. The BBB (Blood Brain Barrier) is composed of vascular endothelium, astrocytes, pericytes, and extracellular matrix. Vascular endothelial cells are joined by tight junctions and regulate the permeability of the BBB. Endothelia throughout the body express ACE2 and are at risk for infection by SARS-CoV-2. Once the virus gains access to vascular and neuronal tissue, it could begin a cycle of viral budding and further damage vascular and neuronal tissue as the virus comes into contact with ACE2 on neurons, glia, and vessels [49]. The SARS-CoV-1 virus has been shown to infect lymphocytes, granulocytes, monocyte derivatives, and monocytes, which all express ACE2 [50]. It has been demonstrated that T lymphocytes allow SARS-CoV-2 infection

but do not support viral replication. The systemic inflammation that characterizes COVID-19 likely increases the permeability of the BBB, thereby allowing infected immune cells, cytokines, and possibly virus to pass into the CNS. Severe COVID-19 disease is characterized by increased IL-2, IL-6, IL-7, granulocyte-colony-stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor α. and cytokine storm likely contributes significantly to toxic-metabolic encephalopathy in severe cases [51]. For neurochemical evidence of neuronal injury and glial activation in patients with moderate and severe COVID-19, the clinical utility of monitoring plasma NfL and GFAp are investigated. Severe COVID-19 had higher plasma concentrations of GFAp and NfL than controls, while GFAp was also increased in patients with moderate disease. In patients with severe disease, an early peak in plasma GFAp decreased on follow-up, while NfL showed a sustained increase from first to last follow-up, perhaps reflecting a sequence of early astrocytic response and more delayed axonal injury [52]. Plasma biomarkers of CNS injury by single molecule array, neurofilament light chain protein (NfL; a marker of intra-axonal neuronal injury) and glial fibrillary acidic protein (GFAp; a marker of astrocytic activation/injury), nature of COVID-19-related CNS damage and its relation to both clinically defined CNS events such as hypoxic and ischemic events and mechanisms more closely linked to systemic severe acute respiratory syndrome coronavirus 2 infection and consequent immune activation, Increased CSF levels of NfL, GFAp and total-tau protein were seen in 63%, 37%, and 16% of patients, respectively. Increased NfL correlated with disease severity, time in intensive care and level of consciousness. NfL in CSF was higher in patients with central neurological symptoms [53]. Neurological symptoms included altered mental status (42%), headache (42%), central (21%) and peripheral weakness (32%). Minor pleocytosis and increased immunoglobulin G levels in CSF are detected andthe neuronal autoantibody testing using commercial tests was negative. SARS-CoV-2 replication in CNS may trigger infiltration by immune cells. COVID-19 patients with neurological diseases present oligoclonal bands in the CSF [54]. Chloroquine and hydroxychloroquine, initially developed as antimalarial drugs, work by preventing the acidification of endosomes, which interrupts cellular functions and may prevent viral entry via ACE2 binding. Hydroxychloroquine inhibits SARS-CoV-2 in vitro, but in vivo studies are lacking [55]. Particularly, the two largest randomized controlled trials to date (RECOVERY and WHO SOLIDARITY), both confirmed that CQ/HCQ regimen does not provide any clinical benefit for COVID-19 patients [56].

Tocilizumab is a monoclonal antibody to the IL-6 receptor that may attenuate cytokine release in patients with severe inflammatory disease. There are limited retrospective data that suggest possible benefit and it has poor penetration into the CNS [57]. Remdesivir is a viral RNA-dependent RNA polymerase inhibitor and in vitro data have shown that it is a potent SARCoV-2 inhibitor [58-60].

Molecular docking technique is used to analyze the binding of non-structural proteins to porphyrin. The porphyrin in the human body is mainly iron porphyrin, namely heme and many hemes are not free but bound to hemoglobin. Viruses have a massive demand for porphyrins [61]. Therefore, the novel coronavirus may target hemoglobin, attack heme, and acquire porphyrin. In order to study the attack behavior of nsp16-nsp10 (orf1ab), ORF3a, and ORF10 proteins, used ZDOCK molecular docking technology to examine these three proteins and it can analyze protein interactions and find the approximate location of these three proteins on hemoglobin. For oxidized hemoglobin, nsp16-nsp10 acted on the middle bottom of the alpha and beta chain and closed to the alpha chain. ORF3a acted at the bottom of the beta chain and ORF10 acted below the alpha chain. The possible mechanism was that nsp16-nsp10 first attacked the alpha chain, and then, ORF3 and ORF10 successively attack the beta chain. For deoxyhemoglobin, nsp16-nsp10 acted on the top of the 1-beta. ORF3a acted at the bottom of the 1-beta. ORF10 acted on the top of 1-beta and ORF3 and ORF10 have embedded in deoxyhemoglobin and directly docked to the heme of the beta chain and it indicates that the viral protein can attack heme on hemoglobin. The possible mechanism was that nsp16-nsp10 first attacked the 1-beta chain, and then, ORF3 and ORF10 successively attack the 1-beta. It is challenging to perform molecular simulations. Due to the close distance of the attack postures of some proteins, so it is unclear the order of three proteins attacked. The nsp16-nsp10 molecule may be an essential protein, playing a vital role throughout the attack. It is worth noting that the above simulation shows that the deoxyhemoglobin is more vulnerable than oxidized hemoglobin. Attack of oxidized hemoglobin by viral proteins will lead to less and less hemoglobin that can carry oxygen, carbon dioxide and blood sugar. People with diabetes can have unstable blood sugar and body cells have extreme inflammation due to excess iron, carbon dioxide and oxygen [62]. Patients with respiratory distress will be made worse, organs and tissues of the whole body have different degrees of damage. Since the emergency epidemic, it is of high scientific significance to use bioinformatics to analyze the roles of novel coronavirus proteins. The study results show that some viral proteins could combine to the porphyrin to form a complex and at the same time, orf1ab, ORF3a, and ORF10 proteins could coordinate to attack the heme on hemoglobin. Lung cells are toxic and inflammatory derivatives produced by the attack, which eventually resulted in ground-glass-like lung damage [63]. Capillaries easily were broken due to inflammation. Proteins such as fibrinogen fill the capillaries' cracks through the coagulation reaction. Therefore, many fibrin accumulates in the alveolar tissue of the patient. As the porphyrin complexes of the virus produced in the human body, the mechanism also interfered with the normal heme anabolic pathway by a wide range of infection and disease. The virus may first infect cells with ACE2 receptors, including immune cells. Immune cells produced antibodies and viral proteins. Antibodies and red blood cells generated immune hemolysis, or red blood cells were infected by Spike-CD147 pathway [64]. The virus also captured porphyrin and inhibited heme metabolism andcytokine storm causes multiple organs failure. The protein, which acts as an ion channel, could be a target for new drugs against the SARS-CoV-2 virus [65].

The high expression of ACE2 in lateral ventricular choroid plexus further increases the possibility of SARS-CoV-2 invading the CNS [66]. Recently, the SARS-CoV-2 was also detected by genomic sequencing in CSF sample from a 24-year-old male COVID-19 patient in Japan [67]. The infection of SARS-CoV-2 in the CNS may produce unpredictable effect on neurodegenerative diseases. SARS-CoV-2 can activate glial cells, induce pro-inflammatory state, and even cause severe innate immune response and sustained increase in cytokine levels. In addition, persistent SARS-CoV-2 infection can also induce neuroimmune responses [68]. Retrospective studies have showed that corticosteroids were frequently used in the treatment of hospitalized COVID-19 patients [69], while it's worth noting that inappropri-

ate corticosteroid therapy produced adverse neuropsychiatric symptoms, affecting about 35% of COVID-19 patients, including cognitive and sleep disorders, delirium, hypomania, mania, depression, and psychosis [70]. Angiotensin-converting enzyme 2 is also highly expressed in dopaminergic neurons [71] and direct infection of SARS-CoV-2 upon neuronal cells, vast inflammatory agents induced by severe systemic inflammation flooding into brains leading to respiratory failure associated brain ischemia, thrombosis and stroke [72]. Nearly 30-60% of patients with COVID-19 suffer from CNS symptoms. Neuronal infection can be prevented by blocking ACE2 with antibodies or by administering cerebrospinal fluid from a COVID-19 patient [73]. In autopsies from patients who died of COVID-19, SARS-CoV-2 is detected in cortical neurons and pathological features associated with infection with minimal immune cell infiltrates [74].

The hypermetabolic state is unique to the SARS-CoV-2-infected cells [75] and highlights the ability of SARS-CoV-2 to hijack the host neuron machinery to replicate. It is confirmed that infection by SARS-CoV-2 induced a locally hypoxic environment in neuronal regions by staining for HIF1α in mock-infected and SARS-CoV-2-infected organoids and it indicates the potential of SARS-CoV-2 in manipulating host metabolic programming, which may create a resource-restricted environment for the cells [76]. SARS-CoV2 infection have also developed a hyper inflammatory syndrome (also termed cytokine release syndrome), a dysfunction in autonomic tone to the cytokine release syndrome and related multiorgan damage in COVID-19 [77]. It is hypothesized that a cholinergic anti-inflammatory pathway could be targeted as a therapeutic avenue. This inflammatory response and the activated immune cells and inflammatory cytokines can spread through the bloodstream to cause multiorgan failure [78]. The cytokine release syndrome is likely an indirect effect of the virus and has been associated with rapid clinical deterioration leading to Acute Respiratory Distress Syndrome (ARDS) [79], multiorgan failure, and mortality. The COVID-19 syndrome results in the upregulation of inflammasomes, dysregulation of T cells with associated lymphopenia, and unfettered production of cytokines/chemokines, including IL6, TNFα, and CCL2. The virus alters the microenvironment of the immune system, especially as it pertains to macrophages [80]. Highly inflammatory FCN1+ macrophages predominate over fatty acid-binding protein 4 (FABP4+) macrophages in patients with a more severe COVID-19 clinical course. In contrast, in milder cases of COVID-19, the expansion of clonal CD8+ T cells in the lung microenvironment suggests a robust adaptive immune response connected to a better control of COVID-19.

HLH (Hemophagocytic lymphohistiocytosis) is characeterized by prolonged fever, cytopenia, and high serum ferritin, and is frequently associated with pulmonary disease [81]. Therefore, diagnosis and treatment of hyperinflammation have been suggested as a possible therapeutic approach. Consistent with this hypothesis, some experimental treatments (e.g., steroids, selective cytokine blockade with anakinra or tocilizumab) are currently being evaluated in clinical studies, despite their relative immunosuppressive effects. The pathological changes to various organ systems may be caused directly by the cytopathic effect mediated by SARS-CoV2 infecting cells expressing the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 counterbalances the function of ACE, which in return negatively regulates AngII production and may contribute to hyperinflammation [82,83]. ACE2 lowers blood pressure by catalyzing the hydrolysis of angiotensinII (vasoconstrictors) into angiotensin 1-9 and 1-7 respectively (vasodilators). Thus, a change in ACE2 function or level of expression can affect blood pressure and also neuronal regulation of inflammation and inhibition of the brain ACE2 function decreases the parasympathetic tone [84]. SARS-CoV infection has been associated with an impaired ACE2 expression and function. In mice, SARS-CoV infection considerably downregulates the ACE2 expression, including in the lungs [85,86]. The so-called ACE2 shedding process is tightly coupled with TNFα production. Notably, as part of a feedback loop, hyperactivation of the vagus nerve via the nicotinic acetylcholine receptor (nAChR) downregulates the expression or activity of ACE2 [87-89], which could prevent viral infection. Infections and danger-associated molecular patterns (DAMPs) can activate immune cells to produce inflammatory cytokines [90]. In turn, these inflammatory cytokines can activate the afferent sensory vagus nerve that transmits the information to the central nervous system where it is processed. If needed, the central nervous system can activate the efferent vagus nerve to control inflammation by inhibiting the production of inflammatory cytokines in macrophages [91]. Acetylcholine (ACh), the principal neurotransmitter of the vagus nerve, is well studied as a critical neurotransmitter but ACh also modulates immune cells. Acetylcholine is well conserved across evolution and is used by the nervous system to regulate organ function and physiological homeostasis including the immune system and inflammation. Indeed, it is reported that the vagus nerve, the longest nerve connecting the brain with most organs, controls immune cells by producing ACh [92]. This mechanism is so significant that some regulatory T lymphocytes replicate the nervous system through ACh synthesis in order to control cytokine production by macrophages. ACh can signal through either muscarinic or nicotinic receptors. The spleen is the target organ of the nicotinic-cholinergic system [93]. ACh inhibits the production of inflammatory cytokines in macrophages specifically via α7 nicotinic ACh receptors (α7nAChR) [94]. Specific inhibition of α7nAChR in human macrophages causes overzealous production of inflammatory cytokines and prevents the potential of either ACh or nicotine to inhibit its production in human macrophages. Electrical stimulation of the vagus nerve in rodent models induces the production of ACh and inhibits systemic inflammation for wild-type but not α7nAChR-KO mice with experimental sepsis induced by either endotoxemia or polymicrobial peritonitis [95-97]. Acute lung injury and ARDS are often derived from sepsis-induced pulmonary inflammation. Alveolar injury to the lungs as a result of mechanical ventilation (ventilator-induced lung injury) is enhanced by concomitant inflammation. Conversely, surgical vagotomy in animals undergoing mechanical ventilation increases the alveolar damage that is associated with robust production of inflammatory cytokines such as IL-6 [98]. Therefore, electrical or pharmacological vagal nerve activation attenuates lung injury by modulating the inflammatory response and subsequently cellular damage and organ injury and failure. Finally, Vagus Nerve Stimulation (VNS) also eases the downstream effects of cytokine activation on systemic coagulation in rodent models [99]. This supports the current prevailing concept that dysregulated endothelial inflammation upregulates thrombin generation in COVID-19-associated thrombus formation [100]. Patients with an increased vagal tone might be protected from a cytokine release syndrome [101]. The observation of lower rates of symptomatic COVID-19 infections in active smokers potentially suggests that active nicotine exposure activates the cholinergic anti-inflammatory pathway, previously shown to be protective in various infectious illnesses, despite the deleterious effects of tobaccos use. A milder COVID-19 disease course in children, who have a naturally higher vagal tone

[102], even in an infectious setting, could support the significance of the cholinergic anti-inflammatory pathway uniquely in COVID-19 patients.

Targeting the cholinergic anti-inflammatory pathway via vagus nerve stimulation

Importantly, nAChR plays a role in the expression of ACE2 [103,104] which has been identified as the key target receptor of SARS-CoV2 [105]. Thus, vagal stimulation can potentially prevent SARS-CoV2 propagation by inhibiting ACE2 expression. Vagal stimulation reduced blood C-Reactive Protein (CRP), fecal calprotectin, and abdominal pain, and improved mood. Vagal stimulation also improved clinical symptoms and significantly lowered serum levels of inflammatory cytokines such as TNF-α and IL-6 in 18 patients after 3 months of treatment. Clinically, VNS can be achieved pharmacologically or electrically via invasive cervical vagal stimulation or non-invasively via the ear or by electro acupuncture. An additional target for neuromodulation is the splenic nerve, which contains sympathetic and distal vagal parasympathetic nerve fibers to the spleen. In the experimental setting, the anti-inflammatory properties of the vagus nerve depend on the splenic nerve [106]. The splenic nerve stimulation exhibits comparable immunosuppressive effects as VNS and can be attempted percutaneously in an invasive and non-invasive fashion (ultrasound waves) [107]. To target the cholinergic anti-inflammatory pathway as a treatment for COVID-19 and the associated cytokine release syndrome, ongoing and future efforts will determine the potential utility of autonomic nerve modulation in the prevention and treatment of COVID-19 as shown in (Table 1) [108].

Table 1: Efforts to target the cholinergic anti-inflammatory pathway.

Strategy	Agent/technology
Pharmacological	Nicotine, GTS-21, a nAchR agonist
	Implantable cuffbased VNS
Neuromodulation	Transcutaneous non-invasive VNS via neck or ear
	Electroacupuncture
	Splenic nerve stimulation

VNS: vagus nerve stimulation; nAChR: nicotinic acetylcholine receptor.

In patients with COVID-19 and neurologic symptoms, an unusual pattern of marked CSF inflammation occurs, in which soluble markers were increased but white cell response and other immunologic features typical of CNS viral infections were absent [109]. These features distinguish COVID-19 CSF from other viral CNS infections and raise fundamental questions about the CNS pathobiology of SARS-CoV-2 infection. CSF biomarkers of intrathecal inflammation (CSF white blood cell count, neopterin, β2-microglobulin, and immunoglobulin G index), blood-brain barrier integrity (albumin ratio), and axonal injury (CSF neurofilament light chain protein [NfL]) were assessed in 6 patients with moderate to severe coronavirus disease 2019 (COVID-19) and neurologic symptoms. CSF neopterin (median 43.0 nmol/L) and β2-microglobulin (median 3.1 mg/L) were increased in all. Median immunoglobulin G index (0.39), albumin ratio (5.35), and CSF white blood cell count (<3 cells/μL) were normall, while CSF NfL was elevated in 2 patients. The ratio of albumin in Cerebrospinal Fluid (CSF) to serum may serve as an index of the integrity of the blood-CSF barrier, with increases in this ratio indicating increased permeability. The ratio of immunoglobulin G (IgG) in CSF to serum (divided by the albumin ratio to correct for variance in blood-CSF permeability) represents an index of the endogenous production of IgG in the Central Nervous System (CNS), with increases reflecting a possible infectious and/or autoimmune process stimulating central IgG synthesis, CSF/serum albumin ratios or CSF/serum IgG indices [110].

Chemosensory Anatomy Defines the Potential Attack Surface for SARS-CoV-2. Chemosensation occurs in sensory epithelia in the nose and mouth. Multiple cranial nerves relay the senses of smell, taste, and chemesthesis to the brain. Airborne odors are detected by olfactory sensory neurons that reside in the olfactory epithelium; their axons pierce the bony cribriform plate to enter the olfactory bulb in the brain. Taste buds on the tongue are innervated by sensory afferents from the facial nerve (VII) and glossopharyngeal nerve (IX). The vagus nerve (X) also innervates taste buds residing in the pharynx. The detection of pungent chemicals, also known as chemesthesis, is mediated by both oral and nasal afferents of the trigeminal nerve (V). Although deficits in smell are most commonly reported in COVID-19, all three chemosensory modalities have been reported to be affected. Possible Mechanisms of Chemosensory Disturbances are [111].

(A) COVID-19 patients have reported olfactory loss in the absence of features common to upper respiratory infections like widespread nasal inflammation or obstruction. Such symptoms are consistent with recent CT imaging suggesting that SARS-CoV-2 infection may cause inflammation that is localized to the olfactory clefts [112].

(B) Sustentacular cells, Bowman's gland cells, and microvillar cells in the olfactory epithelium express both ACE2 and TMPRSS2 and may be directly infected by SARS-CoV-2. Support cell infection may cause changes in the olfactory mucus or ion imbalances that can inhibit olfactory signaling; such changes may be rapidly reversible. The loss of these support cells in animal models can also result in the death of olfactory sensory neurons.

(C) Inflammatory cytokines may also directly or indirectly inhibit olfactory sensory neuron function.

(D) Although current data suggest that sustentacular and other support cells are the primary targets of SARS-CoV-2, a remaining possibility is that SARS-CoV-2 directly infects OSNs.

(E) Immunostaining for ACE2 protein in the mouse olfactory bulb suggests that ACE2 expression is restricted to vascular pericytes [113], which may directly (via perfusion changes) or indirectly (via inflammation) affect chemosensory perception in the brain.

(F) Taste and chemesthetic disturbances may result from the direct infection of cells in the tongue, the secondary consequences of obstruction due to inflammation, or damage following the release of inflammatory cytokines.

S proteins of SARS-CoV-2 and SARS-CoV are highly similar, sharing a sequence identity of 77% [114]. In addition, we found that the SARS-CoV-2 S protein is slightly more positively charged than that of SARS-CoV since it contains four more positively charged residues and five less negatively charged residues which may lead to an increased affinity to bind to negatively charged regions of other molecules through nonspecific and specific interactions. Analysis the S protein binding to the host ACE2 receptor showed a 30% higher binding energy for SARS-

CoV-2 than for the SARS-CoV S protein [115]. These results might be useful for understanding the mechanism of cell entry, blood-brain barrier crossing, and clinical features related to the CNS infection by SARS-CoV-2.

Brain and lung crosstalk during COVID-19 infection [116] as SAR-CoV-2 employs ACE2 as the receptor for viral cell entry and induction of lung injury through increasing the immune system cytokines. It can downregulate the central ACE2 protein expression; inhibition of ACE2 activity reduces the sensitivity of the baroreceptor reflex control of the heart rate as well as increases sympathetic tone which eventually results in the blood pressure elevation and cardiac dysfunction. In addition, concerning the neuroprotective property of ACE2, its downregulation may disturb the balance of neurotoxicity/neuroprotection inside the brain. Increase of inflammatory cytokines during lung injury, hypoxemia, and elevation of sympathetic tone through ACE2 downregulation leads to CNS hyperactivation which might play a crucial role in the etiopathogenesis of neurogenic pulmonary edema which may play a role in COVID-19 pulmonary complications [117] in patients.

COVID-19 initiates the inflammatory cascade and, as a result, releases inflammatory cytokines [118] which is called cytokine storm syndrome [119]. Consecutively, these cytokines can drive neuronal hyperexcitability via activation of glutamate receptors and play a role in the development of acute seizures [120-122]. Elevation of sympathetic tone through ACE2 downregulation leads to CNS hyperactivation which might play a crucial role in the etiopathogenesis of Neurogenic Pulmonary Edema (NPE) [123], a life-threatening complication following a neurologic insult [124], and finally leading to deterioration with the respiratory and cardiovascular complications in these patients.

The crucial step in the viral infection is the process of viral entry into the host cells. The endocytic pathway including endosomes and lysosomes and the autophagy process in viral entry has attracted. The presence of the virus in the brain stem may affect chemosensing neural cells related to respiration as well as respiratory center neurons, thus damaging the lung ventilatory function [125]. Spike protein and ACE2 represent the key, but not the exclusive, site of entry of the virus into the cell; thus, non-ACE2 pathways for virus infection of neural cells cannot be excluded. Whether COVID-19 infects neurons and astroglial cells and enters astrocytes by endocytosis remains to be studied. The Spike protein dependent pathway is thought to be more important than clathrin-dependent endocytosis for cell entry and BBB crossing. Therefore, the Spike dependent pathway should be taken into account in therapeutic strategies for specific antibodies or vaccine production research.

Research suggests that the virus may gain access to the brain via the forebrain's olfactory bulb, which is important for the processing of smell. Loss of smell is a symptom in many patients with COVID-19. The olfactory bulb is rich in the chemical dopamine, which is important for pleasure, motivation and action. It may be that COVID-19 alters the levels of dopamine [126] and other chemicals, such as serotonin and acetylcholine, in the brain. All these chemicals are known to be involved in attention, learning, memory and mood. These changes in the brain are likely responsible for the mood, fatigue and cognitive changes that are commonly experienced by COVID-19 patients [127]. This in turn may underlie the reported symptoms of stress, anxiety and depression in patients who have contracted the virus. But it's not just people who have contracted the COVID-19 virus that have suffered from increased anxiety and depression during the pandemic. Excessive worry over contracting or spreading the virus to other family members, as well as isolation and loneliness, can also change our brain chemistry. Repeated stress is a major trigger for persistent inflammation in the body, which can also affect the brain and shrink the hippocampus and therefore affect the emotions. Stress can also affect levels of brain serotonin and cortisol, which can affect our mood. Eventually, these changes can cause symptoms of depression and anxiety [128]. The good thing about the brain, however, is that it is incredibly plastic, which means it is changeable and can compensate for damage. Memory loss and depression can be improved by doing things that alter the brain function and its chemistry [129].

Due to COVID-19 outbreak, few individuals were overwhelmed with pain & filled with great void because of being lonely and isolated at home. Aggression is a psychological construct in which the individual is not able to control mood impulses. It is closely linked to depression, suicidal tendencies, and substance abuse. In other words, such people show impulsive aggression towards oneself and others and become depressed under the stressful situations of life. Aggression & COVID-19 has emerged as a global public health crisis & threat. From the neurobiological point of view, there are structures, neuronal circuits that play a role [130]. To normalise the level of serotonin medical professionals can prescribe drugs against called as SSRs (Selective Serotonin Reuptake Inhibitors). Fluoxetine is most widely studied. β -adrenergic agonists are also one of the well-known drug used for dementia and brain injury. The neuronal center of aggression i.e. the Hypothalamus and the connections with the amygdala and hippocampus, located near the temporal lobe [131]. For the management of higher cognitive processes, frontal lobe plays an important role. i.e. regulations of emotions [132]. Centre for regulation of negative emotions, aggressive & violent behavior, impulsive acts, are situated in Prefrontal Cortex & the temporal regions of the brain. Experimentally induced anger in humans showed increased activation in the DLPFC (Dorsolateral Prefrontal Cortex) and OFC (Orbitofrontal Cortex). In non-human primates, OFC & DLPFC lesions reliably produce increased aggressive behavior. Studies also shows that Aggression in humans may be associated with decreased functioning in orbital and dorsolateral prefrontal cortical areas, and increased functioning in medial temporal (especially amygdala) brain regions. All neuronal pathways are complex and aggression in humans is due to decreased level of serotonin neurotransmitter. Sudden lockdown due to novel Corona virus (COVID-19) in rural area resulted in following consequences like lack of confidence, restlessness, lack of concentration, domestic violence- both verbal and non-verbal, nervousness, irritability, gender-based abuse, destructive thoughts, feeling to hit someone, frequent arguments at home, insecurity with spouse, violence at home and overthinking, suicidal cases & attempted suicide cases increased in lockdown period [133,134]. During quarantine period, counselling program is needed to prevent all these activities if people do not socialize, then the level of serotonin decreases leading to negative thoughts, depression, impulsive behavior, and arrogant nature. Even criminal tendency may develop in normal person for no reason. So, Serotonin plays a crucial role to maintain mood of person and it has been proved by genetic etiology. The polymorphic genetic variants of the serotoninergic system are deeply affected by genetic predisposition that alters serotonin levels in the central & peripheral nervous system i.e., rate of serotonin production, synaptic release & pathways.

Chemical transmission between neurosecretory cells is

a central biological phenomenon. Detecting neurotransmitter molecules released in the brain or in cell cultures is key to understanding how, when, and where chemical transmission occurs. Carbon fiber microelectrodes provide a common basis for detecting not only dopamine but also a wide variety of neurotransmitters ranging from biogenic amines, purines, and amino acids to free radicals and peptides [135]. The neuroimmune pathway functions bidirectionally, where afferent neurons respond to immune signals at the periphery, and the efferent neurons promote the interaction between the brain and the periphery. This inflammatory reflex has been discussed viral invasion reaching the CNS through the olfactory bulb modulates brain cytokines in the brainstem, which could be related to elevation in the body temperature as well as disease progression [136]. The evidence of an exacerbated inflammatory response in severe cases of COVID-19 suggests that patients with olfactory and gustatory dysfunctions have less severe lung function impairments [137]. Viral genes involved in mechanisms such as biogenesis, entrance, replication, and infection are possible targets for host-cellular miRNAs and microRNAs (miRNAs) as possible therapeutic agents against SARS-CoV-2 [138]. The spike (S) protein of coronavirus, one of the surface glycoproteins, is divided into two functional units, S1 and S2. S1 facilitates virus infection by binding to host receptors, and S2 regulates the membranes fusion to enable viral RNA entering into host cells for further replication. Therefore, the S protein determines the host cell of the virus, regulates the viral attachment and fusion with the host cell membrane, and promotes cellular invasion. As such, the S protein is essential for viral infection, abnormal humoral metabolism is mainly manifested as imbalances of water and electrolytes [139]. Water and sodium disturbances along with the unusual serum potassium levels are most common. It has been shown that the incidence and severity of COVID-19 are closely related to abnormal metabolism of inorganic salts. Serum sodium shows a decrease trend in CODIV-19 development. Hyponatremia (low blood sodium concentration) as well as low concentrations of potassium and calcium in the blood serum are also associated with COVID-19 [140]. Patients in Intensive Care Units (ICU) have higher plasma levels of IL2, IL7, IL10, MCP1, MIP1A, GSCF, IP10, and TNFα [141]. In these patients, white blood cells count, neutrophil count and D-dimer level keep rising while lymphocyte count keeps decreasing as the disease progresses [142]. Therefore, the infection along with the rapid replication of SARS-CoV-2 causes a large amount of body fluid permeating through pulmonary alveoli, leading to ADRS and lower expression of alveolar Na-K-ATPase promotes pulmonary edema [143].

Bradykinin (BK) is an important cellular mediator that causes vasodilatation and leaky blood vessels, leading to vascular leakage and edema. BK is generated by cleavage of High-Molecular-Weight Kininogen (HMWK) from plasma-kallikrein and binds to the BKB2 receptor, and thus results vascular hemorrhage. Inhibition of ACE2 by SARS-CoV-2 impairs the hydrolysis of des-arg9-bradykinin [144]. Therefore, the excessive release and decreased hydrolysis of BK through activating BKB1 and BKB2 receptors result in extra vascular leakage and pulmonary edema, Inflammatory cytokines and inflammatory storm in COVID-19 patients can strongly induce the expression of HA-Synthase-2 (HAS2), while hyaluronidase level decreases, resulting in the accumulation of HA and inducing ARDS and pulmonary edema. The decreased expression of alveolar Na-K-ATPase, misregulation of sodium, potassium, AQP, and RAS channels and abnormal metabolism of BK and HA can all lead to lung liquid clearance failure and pulmonary edema, resulting in severe lung damage and ARDS in COVID-19 patients [145].

Immune-modulatory agents for COVID-19 include tocilizumab, human immunoglobulin and the convalescent plasma. IL6 monoclonal antibody or tocilizumab was thought to work by interrupting inflammatory storm after the infection, but the latest clinical study published in NEJM showed that Tocilizumab was not effective in preventing intubation or death in mild hospitalized COVID-19 patients. Convalescent plasma have been initially shown to be beneficial for COVID-19 patients with severe infection stabilizing the immune system, but the subsequent randomized controlled trial did not show significant improvement within 28 days [146].

Targeting sodium channels and pumps

Since the inhibition of ENaC induces pulmonary edema formation, targeting ENaC is rational in order to enhance fluid clearance from the alveoli. Studies showed that ENaC activators or stimulatorscan regulate ENaC-dependent fluid absorption in alveolar and pulmonary edema [147]. Activation of β-adrenergic receptor, especially β2, was found to stimulate Na+ and fluid reabsorption. It was observed that the expression of ENaC and Na+/K+-ATPase in primary alveolar type II cells from rat lungs increased responding toterbutaline. Inhalation or infusion of salbutamol, a β2-adrenergic agonist, reduced the incidences of pulmonary edema and was found to be beneficial in ARDS patients [148]. Amiloride, a prototypic inhibitor of ENaC, might also have a potential in treating COVID-19 patients. Amiloride was shown to induce the reduction of ACE2 expression in bronchial and alveolar epithelial cells and can counteract the low cytosolic pH which has been observed in COVID-19 patients by acting on Na+/H+ exchanger [149]. Glucocorticoids can reduce pulmonary edema by regulating fluid absorption in alveoli and can be used as anti-inflammatory drugs in ARDS and pulmonary edema as well as in COVID-19 patients [150].

CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) and NKCC (Na-K-2Cl cotransporter) inhibitors show promise in treating pulmonary edema. Furosemide, a NKCC inhibitor, has been acknowledged as first-line therapeutic drug for pulmonary edema in all the time [151]. CFTR inhibitors, like glibenclamide and CFTRinh-172 inhibitor, distinctly reduced absorptive alveolar fluid transport [152,153].

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