reports

Perspective

Neuronal and Non-Neuronal GABA in COVID-19: Relevance for Psychiatry

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Abstract: Infection with SARS-CoV-2, the causative agent of the COVID-19 pandemic, originated in China and quickly spread across the globe. Despite tremendous economic and healthcare devastation, research on this virus has contributed to a better understanding of numerous molecular pathways, including those involving γ-aminobutyric acid (GABA), that will positively impact medical science, including neuropsychiatry, in the post-pandemic era. SARS-CoV-2 primarily enters the host cells through the renin–angiotensin system's component named angiotensin-converting enzyme-2 (ACE-2). Among its many functions, this protein upregulates GABA, protecting not only the central nervous system but also the endothelia, the pancreas, and the gut microbiota. SARS-CoV-2 binding to ACE-2 usurps the neuronal and non-neuronal GABAergic systems, contributing to the high comorbidity of neuropsychiatric illness with gut dysbiosis and endothelial and metabolic dysfunctions. In this perspective article, we take a closer look at the pathology emerging from the viral hijacking of non-neuronal GABA and summarize potential interventions for restoring these systems.

Keywords: GABA; SARS-CoV-2; renin–angiotensin system; microbiome; neuropsychiatric disorders

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1. Introduction

The infection with SARS-CoV-2 became a pandemic on 11 March 2020, ushering in immeasurable economic and healthcare catastrophes. Up until 14 May 2022, more than 517 million people had been afflicted by COVID-19, and more than 6 million had died (https://covid19.who.int/ (26 May 2022)). However, the extensive research conducted on this virus in a short period of time has broadened our understanding of its numerous pathogenetic mechanisms, leading to novel paradigms that will likely bear fruit in the post-pandemic era. For example, local renin–angiotensin systems (RAS) expressed in the brain and gastro-intestinal (GI) tract, although previously acknowledged, were poorly defined prior to the COVID-19 pandemic. Likewise, the crosstalk between host RAS and microbial γ-aminobutyric acid (mGABA) was seldom considered when explaining the high comorbidity of inflammatory bowel disease (IBD) and neuropsychiatric conditions, including anxiety, depression, psychosis, and seizure disorder [1–4]. By the same token, endothelial GABA (eGABA) and its role in blood pressure homeostasis and neuropsychiatric pathology began to be examined only after the appearance of COVID-19 [5].

Although neuronal GABA (nGABA) has been studied for several decades, also within the context of viral infections, its non-neurotransmitter functions were poorly understood

until very recently [6,7]. For example, the antiviral and anti-inflammatory properties of GABA were highlighted by recent preclinical studies showing that GABA supplementation decreased COVID-19 death rates [8–10]. Along this line, a novel study has demonstrated that *Limosilactobacillus fermentum*, a GABA-producing gut microbe, thwarts Norovirus infection, further attesting to the antiviral actions of this biomolecule [11]. In addition, mGABA was demonstrated to augment host autophagy, including that of pathogen-infected cells, indicating participation in antimicrobial defenses [12]. Interestingly, gut angiotensin-converting enzyme-2 (ACE-2), the SARS-CoV-2 entry portal, upregulates mGABA by increasing its release from the gut flora [13]. This is significant, as earlier studies have demonstrated that angiotensin receptor blockers (ARBs) possess antiepileptic, anti-depressant, and anti-anxiety properties, suggesting that the functions of RAS and GABA are highly intertwined [14–16]. Indeed, blood–brain barrier (BBB)-crossing ARBs were reported to lower CNS inflammation, highlighting the role of RAS in neuropsychiatric pathology and placing this system on an equal footing with serotonin (5-HT) and dopamine (DA) [17,18]. Furthermore, in the CNS and pancreas, ACE2–GABA crosstalk was reported to optimize glucose metabolism, probably accounting for the anti-diabetic properties of ARBs [19,20]. As many psychotropic drugs are associated with metabolic dysfunction, using centrally acting ARBs, such as candesartan, for hypertension may bring additional benefits to psychiatric patients [21].

SARS-CoV-2 depletes host GABA by several mechanisms:

1. The viral spike (S) protein contains a GABA-mimicking sequence or short linear motif that can directly usurp host GABAergic signaling [22,23].
2. The SARS-CoV-2 proteins nonstructural protein 6 (NSP6), open reading frame 8 (ORF8), and open reading frame 3 (ORF3a) interact directly with host mammalian target of rapamycin complex 1 (mTORC-1), interleukin 17 (IL-17), and transmembrane protein 16F (TMEM16F), inducing premature EC senescence, a phenotype characterized by low GABA [24–29] (Figure 1).
3. SARS-CoV-2/ACE-2 binding disrupts the function of the protective renin–angiotensin system (RAS) branch, including Mas receptor (MasR) signaling, lowering GABA [14,30].
4. The viral protein ORF3a interacts with toll-like receptor 4(TLR4), triggering EC senescence and lowering GABA [31].
5. The SARS-CoV-2 viral proteins nonstructural protein 4 (NSP4), nonstructural protein 8 (NSP8), and open reading frame 9c (ORF9c) decrease GABA by disrupting the mitochondria, triggering vascular senescence [32] (Figure 1).

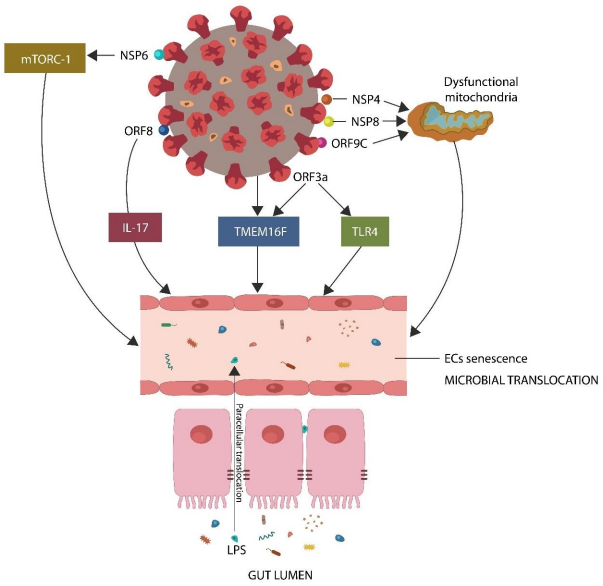

Figure 1. SARS-CoV-2 downregulates GABA by inducing endothelial senescence directly (by protein

–protein interactions) and indirectly (via mitochondrial dysfunction and ANG II upregulation). A dysfunctional endothelial barrier facilitates microbial translocation from the GI tract, where the flora is immunologically tolerated, into the systemic circulation, where it evokes inflammation and immunogenicity. Legend: NSP6, nonstructural protein 6, ORF8, open reading frame 8, IL-17, interleukin 17, TMEM16F, transmembrane protein 16F, TLR4, toll-like receptor 4, NSP4, nonstructural protein 4, NSP8, nonstructural protein 8, ORF9C, open reading frame 9C, ORF3a, open reading frame 3a, LPS, lipopolysaccharide.

SARS-CoV-2-mediated GABA depletion likely explains the neuropsychiatric manifestations of COVID-19, including anxiety, depression, posttraumatic stress disorder (PTSD), cognitive impairment, and seizure disorder [33–37].

In this perspective article, we take a closer look at the viral hijacking of endothelial, pancreatic, and gut GABA and the associated pathology. We also discuss potential interventions for GABAergic system restoration.

2. Two Senescence Mechanisms in SARS-CoV-2 Infection

SARS-CoV-2 is a single-stranded, enveloped RNA virus that contains four structural proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E). The S protein is composed of two subunits, S1 and S2. The former engages ACE-2, while the latter (FCS) interacts with furin, merging viral envelope and host plasma membrane as well as cells, thus forming syncytia [38]. The viral attachment to ACE-2 disrupts the physiological function of this protein, leading to the unchecked accumulation of angiotensin II (ANG II), a mitochondrial toxin linked to premature EC senescence [39,40].

2.1. S1/ACE-2 Attachment and ANG II-Induced Senescence

The SARS-CoV-2 envelope protein S1 binds ACE-2, contributing to the loss of this enzyme's biological function as well as to the shutting down of the anti-inflammatory/antioxidant (protective) RAS (Figure 2). The unchecked accumulation of ANG II enhances the proinflammatory/prooxidative RAS branch, which, under normal circumstances is counterbalanced by the protective axis. The imbalance between the two RAS arms results in ANG II-driven hyperinflammation or "cytokine storm" [41,42] (Figure 2). Depletion of ACE-2 and loss of anti-inflammatory/antioxidant RAS induce premature cellular senescence, lowering eGABA, which in return may trigger a neuropsychiatric pathology [43–46].

2.2. S2/Furin Attachment and Syncytia-Induced Senescence

Enveloped viruses are known for generating multinuclear giant cells by inducing cell–cell fusion or syncytia formation. Cell–cell fusion is a physiological or pathological process in which neighboring cells merge their plasma membranes, sharing intracellular organelles, including cytoplasm and nuclei [47,48].

SARS-CoV-2 entry into host cells requires furin cleavage of the S antigen at the S1/S2 site to initiate membrane fusion [49]. The insertion of the polybasic PRRAR motif at FCS is crucial for fusing viral envelopes with host plasma membrane, as well as the host cells with each other [50]. PRRAR is a triple-arginine motif that forms cell membrane pores via its guanidinium side chains, compelling the cells to fuse for protection [51,52].

Taken together, the SARS-CoV-2 virus induces cellular senescence via ANG II and/or syncytia formation, downregulating the antiviral amino acid GABA [53,54].

2.3. Molecular Mechanisms of Syncytia Formation

The subunit β3 of GABA-A receptors contains a triple-arginine motif (RRR) that interacts with the endocytic pathway (EP) protein AP2, likely disrupting SARS-CoV-2 endocytosis [55]. On the other hand, the triple arginine (PRRAR) in the S antigen of SARS-CoV-2 may counteract this GABA action, usurping the EP and opening it for viral ingress.

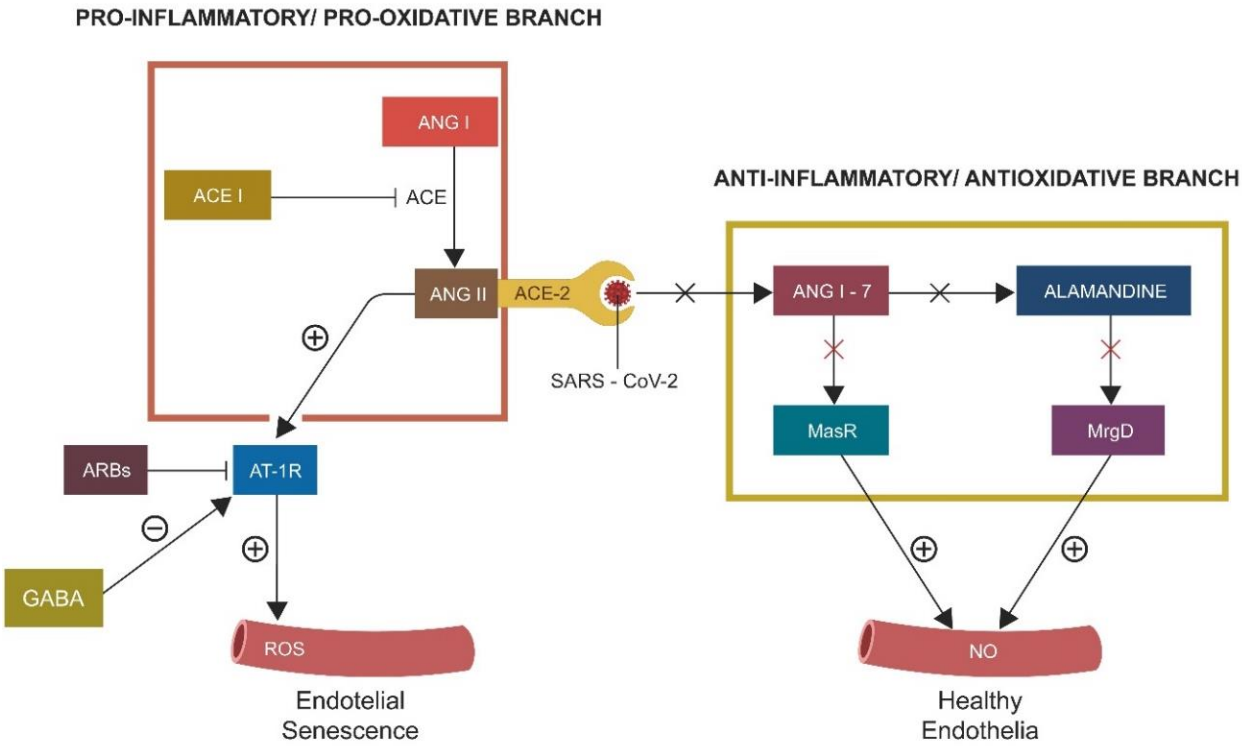

Figure 2. Human RAS consists of two opposing branches, the proinflammatory/prooxidative (driven by ANG II) branch and the anti-inflammatory/antioxidant (driven by ANG 1-7) one. ANG II, acting via AT-1Rs, induces EC senescence. ARBs and GABA negatively regulate AT-1Rs, opposing ANG II. The protective RAS branch, comprised of ANG 1-7, alamandine, and their respective receptors Mas and MrgD, inhibit inflammation and oxidative stress. SARS-CoV-2 engagement with ACE-2 disrupts the entire anti-inflammatory/antioxidant branch, leading to unchecked ANG II accumulation and premature EC senescence. Legend: ANG I, angiotensin I, ACEi, angiotensin-converting enzyme inhibitors, ANG II, angiotensin II, ARBs, angiotensin receptor blockers, AT-1r, angiotensin receptor type 1, ROS, reactive oxygen species, ANG1-7, angiotensin 1-7, MasR, Mas receptor, MrgD, MrgD receptor, NO, nitric oxide.

A human endogenous retrovirus W (HERV-W) was identified in the regulatory region of GABA-B receptor subunit 1 gene, suggesting that this ancestral retrovirus can be activated by exogenous viruses, including SARS-CoV-2 [56]. HERV-W activation and increased GABA-B expression likely depresses the antiviral GABA-A, facilitating SARS-CoV-2 replication [57]. We surmise that the triple-arginine FCS of SARS-CoV-2 has retrovirus-activating properties, switching on HERVs and human immunodeficiency virus-1 (HIV-1) [58,59] (please see section Ancient and modern viruses disrupt GABAergic signaling).

The SARS-CoV-2 proteins ORF3a and S activate TMEM16F, a calcium-dependent phospholipid scramblase that executes the fusion of both viral envelope with plasma membrane and host cells with each other [60]. In addition, SARS-CoV-2 can deplete GABA by disrupting the mitochondria, which in turn activate the cellular senescence program [24,61] (Figure 1). Furthermore, ORF3a stimulation of TLR4 can induce EC senescence and TMEM16F activation, forming syncytia [31,60,62].

2.4. Biological Barrier Dysfunction

Senescent endothelia may disrupt the BBB and the gut barrier, facilitating the translocation of GI tract microbes and/or their molecules, including LPS, into the systemic circulation, as reported in COVID-19 critically ill patients [63,64] (Figure 1). In addition, the S protein of SARS-CoV-2 can bind directly to circulating LPS, triggering a hyperinflammatory pathology [65]. Interestingly, ANG II upregulates TLR4, the main LPS sensor, augmenting inflammation and neuropsychiatric pathology [43,66–68]. As GABA is a negative regulator

of TLR4, it likely inhibits both cell–cell fusion and premature senescence, counteracting not only the "cytokine storm" but also neuroinflammation [62,69]. Indeed, low GABA and elevated LPS were demonstrated in the brains of patients with Alzheimer's disease (AD), suggesting BBB dysfunction and poor LPS suppression [70,71]. Moreover, several studies have demonstrated that LPS can induce pathology by fusing cells into multinuclear structures [72]. For example, brain cells can merge, forming physiological or pathological syncytia that alter both neuronal networks and information processing [73,74] (Figure 3). For example, neuron–neuron fusion occurs during normal aging as well as in the presence of viral infections, multiple sclerosis (MS), AD, and following radiation exposure and chemotherapy [75].

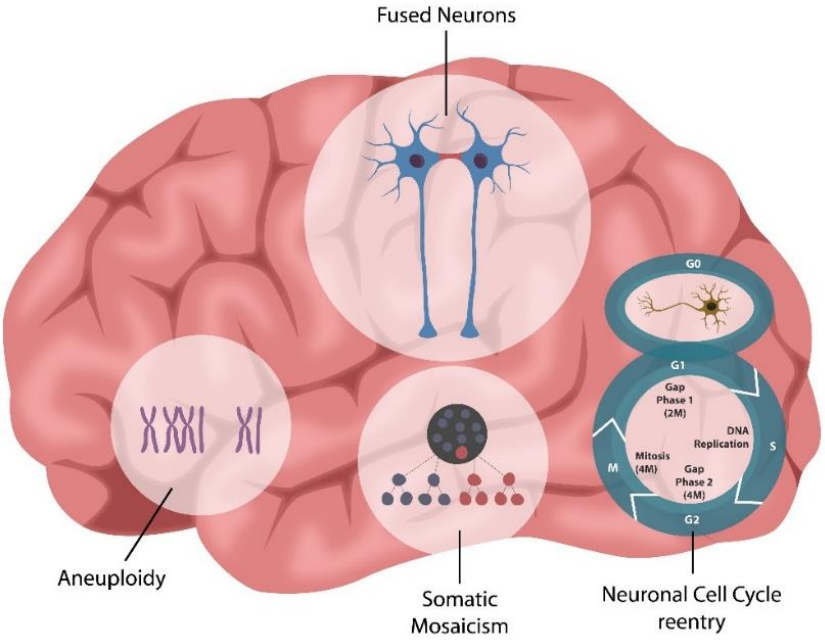

Figure 3. Neuronal cell–cell fusion occurs physiologically, in normal aging, or pathologically, in various conditions, including viral infections, Alzheimer's disease (AD), multiple sclerosis (MS), radiation exposure, or chemotherapy [76] Neuronal syncytia formation likely accounts for previously unexplained phenomena, such as aneuploidy, somatic mosaicism, and neuronal cell cycle reactivation, documented in various neuropsychiatric conditions.

Cell–cell fusion is a major cause of genome destabilization and generation of aneuploidy, somatic mosaicism, and reactivation of the cell cycle in postmitotic cells [61,75–78] (Figure 3).

Taken together, SARS-CoV-2 may precipitate premature vascular aging via ACE-2 depletion and syncytia formation. Senescent ECs downregulate eGABA, predisposing to neuropsychiatric disorders.

3. Cellular Senescence in Psychopathology

Psychiatric disorders have been associated with shorter-than-average patient lifespan and high comorbidity with age-related diseases, suggesting that premature cellular senescence plays a major role in the pathogenesis of these conditions [79,80]. SARS-CoV-2, like many other viruses, induces premature tissue aging, a phenomenon also demonstrated in depression, anxiety, schizophrenia, and seizure disorder, indicating that GABA depletion may be the common denominator of these pathologies [81–84]. On the other hand, GABA supplementation was associated with less inflammaging and improved sleep and mood, pointing to a potential therapeutic modality [85,86]. In addition, as GABA promotes autophagic elimination of damaged and virus-infected cells, GABA supplementation may benefit not only COVID-19-affected patients but also those with age-related diseases [5,12].

Adult Neurogenesis and SARS-CoV-2 Infection

The COVID-19 pandemic has highlighted the role of RAS dysfunction, especially ANG II, in the pathogenesis of neuropsychiatric disorders [87]. On the other hand, ARBs and ACEi showed promising results in the treatment of these conditions, emphasizing the pathological role of dysregulated ANG II [88,89]. Moreover, recent epidemiological studies found that COVID-19 survivors may be at increased risk of several neuropsychiatric disorders, further emphasizing the role of RAS in this pathology [30,90,91].

COVID-19-induced premature cellular senescence may engender neuropathology by suppressing adult neurogenesis in the hippocampal subgranular zone (SGZ) and cerebral subventricular zone (SVZ) [92,93]. Unlike in the adult CNS, GABA is an excitatory neurotransmitter in immature neurons; therefore, the loss of GABAergic signaling may disrupt adult neurogenesis [92,94–96]. Interestingly, TLR4 was reported to play a key role in the conversion of immature into mature neuronal cells, linking viral exploitation of this protein to dysfunctional neurogenesis [97,98].

Taken together, virus-induced senescence lowers eGABA, contributing to neuropsychiatric pathology by precipitating premature vascular aging and disrupting neurogenesis.

4. GABA, Neuronal and Non-Neuronal Information Processing

GABA is a non-protein amino acid present in almost all life forms, including plants, bacteria, and gut microbes. In the central nervous system (CNS), GABA, signaling via inotropic (GABA-A) and metabotropic (GABA-B) receptors, functions as an inhibitory neurotransmitter and participates in numerous physiological processes, including cognition, wakefulness, and self-awareness [99–101].

Neuronal and non-neuronal GABA are synthesized from glutamate via glutamic acid decarboxylase (GAD), an enzyme located in all GABA-generating cells, including the gut microbes [102,103]. This is significant, as autoantibodies against GAD were documented in COVID-19 patients, suggesting molecular mimicry between this enzyme and SARS-CoV-2 proteins [104,105]. Dysfunctional GABAergic systems were associated with neuropsychiatric illness and disorders of consciousness [106–111]. For example, the GABAergic system was linked to gamma oscillations on electroencephalogram (EEG), a self-awareness pattern, disrupted in many neuropsychiatric disorders, including epilepsy, schizophrenia, autism, anxiety, and depression [112–114]. The EEG gamma-band (25–90 Hz) was positively correlated with resting GABA concentration as well as with the cerebral blood flow, emphasizing the potential of eGABA as a biomarker [115,116].

During development and early life, GABA is an excitatory neurotransmitter that matures gradually throughout childhood and early adolescence [117]. During this time, the partial or total loss of GABA causes circulatory abnormalities and inhibits the migration and placement of cortical interneurons [118]. In adolescence, GABA reaches sufficient levels to initiate microglia-mediated synapse elimination and axonal pruning, characteristic of mature cognition [119]. Indeed, recent studies have shown that GABA-sensing microglia are required for synapse remodeling in adolescence and the installment of adult information processing [120]. On the other hand, dysfunctional GABA signaling may contribute to the pathological reactivation of microglia known to eliminate healthy neurons and synapses, a phenomenon documented in both psychopathology and neurodegeneration [121]. These microglial functions can be hijacked by intracellular pathogens, especially those linked to mental illness [122–124].

4.1. Non-Neuronal Information Processing

Recent studies have shown that EC can form cellular networks and communicate via Ca2+ waves, suggesting that information processing may take place at the vascular level [125,126]. Likewise, astrocytes form physiological syncytia, a finding consistent with the Ca2+ wave hypothesis of information processing [127]. In addition, the dysfunctional eGABA association with altered cortical circuits and behavior likely highlights the role of ECs in cognition [118]. Indeed, ECs communicate with and shadow neurons throughout

the brain, likely participating in cognitive processes mediated by Ca2+. Moreover, as Ca2+ drives the rudimentary memory of plants and unicellular organisms, an ancient modality of non-neuronal information processing is emphasized [128–130]. Along this line, the antidepressant action of ketamine, based, at least in part, on its impact on calcium/calmodulin-dependent protein kinase II (CaMKII), likely implicates Ca2+ in emotional intelligence and cognition [131]. This is important, as virtual screening studies documented the existence of a CaMKII system in the S protein of SARS-CoV-2, linking this pathogen to affective disorders [132]. Moreover, non-neuronal information processing was reported in skeletal muscle, heart, and fascia, indicating that neuronal cells do not hold the exclusive monopoly on cognitive processes [133,134]. Along this line, the acquisition of donor personality characteristics following heart transplantation, documented by numerous studies, may reflect EC-mediated cognition [135–137]. This is in line with the hemo-neural hypothesis that connects information processing to endothelial blood flow [138].

In the following sections, we take a closer look at the COVID-19 influence on non-neuronal GABAergic systems, especially the endothelial, microbial, and pancreatic pathways, emphasizing their potential participation in neuropsychiatric pathology.

4.2. eGABA

ECs line the inner layer of the circulatory system and regulate the vascular function via membrane-bound receptors that interact with various neurotransmitters, hormones, and metabolites. While previously conceptualized as passive components of membranes and biological barriers, ECs are now known to play an essential role in vascular homeostasis and the pathogenesis of thrombosis and inflammation [139]. Under normal circumstances, ECs synthesize and secrete eGABA, a molecule depleted in the virus-induced cellular senescence phenotype [118,140,141]. Aside from viral infections, EC senescence and low eGABA were associated with PTSD, anxiety, depression, autism, schizophrenia, and epilepsy, suggesting that the viral manipulation of this neurotransmitter may initiate or exacerbate neuropsychiatric pathology [35,142–146]. Moreover, as human ECs express abundant ACE-2, a positive regulator of eGABA, SARS-CoV-2 could disrupt the GABAergic signaling directly [20]. Indeed, ACE-2 variants with depleted GABA were linked to major depressive disorder, schizophrenia, bipolar disorder, and epilepsy, emphasizing the importance of RAS/GABA crosstalk for central nervous system (CNS) homeostasis [14,87,91,147].

4.3. pGABA

Recent studies have identified another GABA pool in pancreatic β cells that may be altered by SARS-CoV-2 infection, promoting metabolic dysfunction [148,149]. On the other hand, the administration of exogenous GABA was demonstrated to improve glucose tolerance in rodents, indicating that this biomolecule may play a key role in β cell homeostasis [150,151].

Excessive ANG II was associated with diabetes mellitus type 2 (DMT2), indicating that SARS-CoV-2 can trigger dysmetabolism by disrupting RAS [152]. In addition, the S and ORF3a antigens of SARS-CoV-2 were shown to activate TMEM16F, promoting cell–cell fusion, a phenotype associated with premature cellular senescence and low GABA [53,54,153]. Moreover, premature senescence of β cells and depleted pGABA may drive DMT2 and the neuropsychiatric pathology-linked dysmetabolism [154,155]. So far, several neuropsychiatric disorders and psychotropic drugs have been associated with impaired metabolism, suggesting that exogenous GABA may benefit individuals with these conditions [82]. Indeed, in a previous article, we discussed the relationship between obesity and impulsivity in psychiatric patients, emphasizing that attaining optimal results requires the concomitant treatment of both conditions [156].

4.4. mGABA

SARS-CoV-2 affinity for ACE-2 suggests that tissues with high expression of this protein, such as intestinal epithelial cells (IECs), are more vulnerable to infection [157]. As

ACE-2 protects the beneficial GI tract microbes, many of which generate mGABA, the viral exploitation of this protein may trigger intestinal dysbiosis [158,159]. Interestingly, gut ACE-2 is co-expressed with L-dopa decarboxylase (DDC), an enzyme required for microbial DA generation; thus, the viral exploitation of ACE-2 likely affects the brain dopaminergic system (DAS) [160]. As elevated DDC was demonstrated in patients with schizophrenia, the importance of RAS and DAS crosstalk is further emphasized [161].

In the GI tract, ACE-2 heterodimerizes with broad neutral amino acid transporter 1 (B0AT1) that participates in tryptophan (Trp) absorption, indicating that SARS-CoV-2 infection may deplete this amino acid [162] (Figure 4). For example, ACE2-deficient mice display low Trp blood levels, emphasizing the role of this protein in Trp homeostasis [163,164]. As Trp is crucial for serotonin biosynthesis, the viral exploitation of this essential amino acid may trigger neuropsychiatric symptoms, including depression [165]. Moreover, the gut microbes involved in tryptophan (Trp) metabolism are also implicated in adult neurogenesis via aryl hydrocarbon receptor (Ahr), a protein usurped by COVID-19 [166,167]. Ahr is a cytoplasmic ligand and xenobiotic sensor that regulates the microbiota population and the host–microbe crosstalk [168,169]. In our earlier work, we discussed the role of Ahr in psychotropic drugs-induced metabolic dysfunction and suggested that various microbial products, including indole-3-propionic acid, could ameliorate glucose tolerance [170]. As recent studies have linked Ahr to cellular senescence, it is likely that impaired Trp absorption may predispose to this low mGABA phenotype [171,172]. Moreover, mGABA enhances the expression of T helper 17 cells (Th17) characterized by the release of IL-17, an mTORC1-activating antiviral biomolecule [173–175]. Interestingly, SARS-CoV-2 exploits mTORC-1 and IL-17, disrupting both host antiviral defenses and the gut barrier [176,177] (Figure 1).

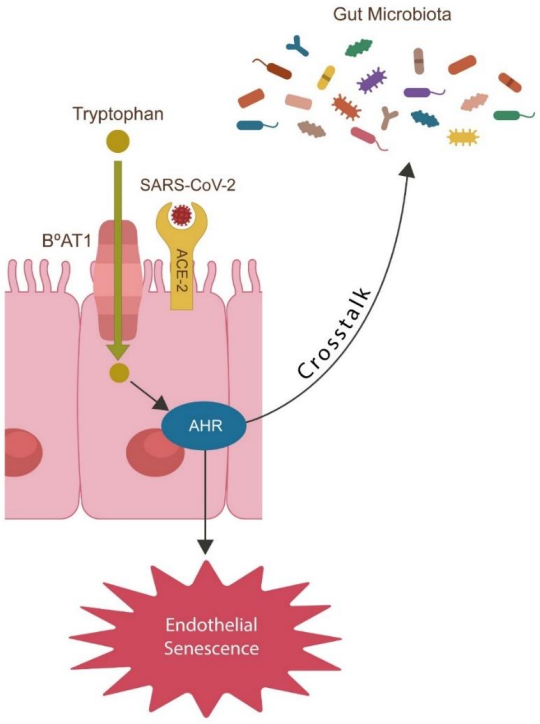

Figure 4. In the GI tract, ACE-2 dimerizes with the neutral amino acid transporter B0AT1 involved in Trp absorption. Trp, an Ahr ligand, coordinates host–microbiota interaction and local metabolism. Dysfunctional Trp absorption and defective Ahr may contribute to barrier disruption and microbial translocation into the systemic circulation. Legend: Trp, tryptophan, B0AT1, neutral amino acid transporter, AHR, aryl hydrocarbon receptor.

5. Ancient and Modern Viruses Disrupt GABAergic Signaling

The syncytia-forming S2 protein of SARS-CoV-2 is crucial for infectivity, as highlighted by its presence in several highly contagious viruses [178,179]. Indeed, FCS, absent in other SARS-linked coronaviruses, usurps host furin, enhancing COVID-19 transmissibility [180]. On the other hand, loss of FCS was shown to attenuate SARS-CoV-2 virulence and pathogenicity, emphasizing the utmost importance of S2 for the pandemic spread of this viral infection [181].

Aside from SARS-CoV-2, arginine-rich FCSs were identified in HIV-1 protein GP160 ENV, as well as in syncytin-1, a physiological placental fusogen encoded by HERV-W, suggesting that COVID-19 can activate dormant viral fossils [58,182,183]. This is significant, as it connects COVID-19 to retroviruses as well as to the reproductive pathology [184,185].

HERVs are ancient viruses, comprising about 8% of the human DNA, that under normal circumstances are not transcribed. However, various pathologies, including exogenous viral infections, can reactivate HERVs, and translate their DNA into proteins, such as syncytin-1, a molecule that generates trophoblast syncytia during placentation [186]. Pathologically, syncytin-1 promotes cell–cell fusion, hyperinflammation, and autoimmunity, as well as the psychopathology linked to defective GABA [187].

Posttranslational cleavage of syncytin-1 is executed by furin, a host protein usurped by viral FCS, disrupting both CNS and placental GABA [188]. Indeed, a recent meta-analysis connected SARS-CoV-2 infection during pregnancy to preeclampsia, linking this condition to usurped syncytin-1 [189]. Dysregulated GABA was previously reported in patients with preeclampsia, implicating the furin–syncytin-1 axis in reproductive pathologies [190,191]. Moreover, in the first trimester of pregnancy, GABA upregulates human chorionic gonadotropin (hCG), a key hormone for prenatal brain development, suggesting that the viral exploitation of GABA may trigger a developmental pathology [192,193].

5.1. Syncytia Inhibitors

Over the past decade, a considerable effort was devoted to the development of syncytia-blocking agents, including furin inhibitors [194]. The finding that arginine repeats play a major role in virus-induced cell–cell fusion, contributed to the development of FCS-attached arginine mimetics, including phenylacetyl-Arg-Val-Arg-4-amidinobenzylamide, to inhibit the formation of syncytia [195,196]. As furin is highly expressed in ECs and involved in vascular aging and dysmetabolism, furin inhibitors may be capable of averting premature EC senescence and disrupt viral replication [197,198] (Table 1).

Aside from inhibiting furin, syncytia formation can be blocked by lowering the expression of TMEM16F. TMEM16F is a Ca2+-driven phospholipid scramblase that maintains phosphatidylserine (PS) in the inner leaflet of the cell membrane, allowing its externalization only when the cell is ready for apoptosis or fusion [199,200]. Since externalized PS (ePS) is indispensable for syncytia formation, TMEM16F inhibitors may block pathological cell–cell fusion [201]. For example, niclosamide, a TMEM16F-targeting drug, was reported to inhibit both SARS-CoV-2 syncytia and viral transmissibility [202]. Niclosamide is an anthelmintic compound with demonstrated antiviral properties that is currently being evaluated for the treatment of COVID-19 [203]. Several recent studies show that TMEM16F interacts with inositol 1,4,5-triphosphate receptor 1 (IP3R1) in many cell types, including the GABAergic interneurons, implicating this protein in cell–cell fusion [204,205]. Interestingly, IP3R1 was associated with psychopathology, including schizophrenia, neurodegenerative disorders, and epilepsy, suggesting that niclosamide may have a therapeutic value in the treatment of these conditions [206–208]. Indeed, lithium and valproic acid, drugs routinely utilized in the treatment of bipolar disorder, alter IP3R1 expression, indicating that TMEM16F inhibitors could have a place in neuropsychiatry [209]. As lithium, valproate, and niclosamide alter the Wnt/β-catenin signaling, the latter may possess mood-stabilizing properties. Interestingly, a valproic acid/niclosamide combination was found therapeutic in some cancers, emphasizing the pleotropic role of the Wnt/β-catenin pathway [210,211]. Furthermore, dysfunctional TMEM16F–IP3R1–GABA signaling was found to pathologi-

cally activate the microglia, probably leading to aberrant phagocytosis of healthy neurons and synapses, documented in neuropsychiatric pathologies [212].

It has been known for several decades that diazepam displays anti-syncytial properties, as it inhibits the fusion of myoblasts during musculoskeletal system development [213]. In contrast, as arginine enhances myoblast fusion and abolishes the anxiolytic effects of diazepam, benzodiazepines may be able to counteract FCS-mediated cell–cell fusion [214,215]. Interestingly, ivermectin binds GABA-A receptors at the diazepam site, highlighting this drug's anti-syncytial mechanism of action [216].

Taken together, the TMEM16F–IP3R1–GABA axis comprises a signaling hub involved in viral infections, cancer, and neuropsychiatric illness. GABA upregulation may inhibit TMEM16F and the formation of pathological syncytia.

5.2. GABA, Autophagy, and Blood Pressure

The antiviral properties of GABA—the elimination of virus-infected cells—highlight the autophagy-activating role of this amino acid [217,218]. Indeed, GABA interferes with host EP that many viruses, including SARS-CoV-2, exploit to enter host cells [12,219]. Viral FCS usurps GABA-mediated autophagy by inhibiting subunit β3 interaction with the clathrin endocytosis AP2 protein [55].

Autophagy modulation may account for the other beneficial properties of GABA, including anti-hypertension, anti-diabetes, antioxidant, and anti-inflammatory actions, suggesting that supplementation with this amino acid may be salutary for patients with these disorders [220,221]. Exogenous GABA may or may not cross the BBB, as conflicting results were reported by different studies. However, CNS-reaching GABA ligands are routinely utilized for the treatment of neuropsychiatric diseases [222,223]. For example, GABA-enhancing anticonvulsants, including tiagabine, gabapentin, and topiramate not only increase neuronal GABA but also augment the non-neuronal GABAergic pathways [224]. For example, gabapentin and tiagabine lower blood pressure in patients with hypertension, while topiramate decreases intracranial pressure, connecting eGABA to the homeostasis of extracellular compartments [225,226]. Interestingly, diazepam displays both antihypertensive and antiretroviral properties (against HIV-1), further emphasizing the beneficial effects of GABA signaling [227,228]. Furthermore, due to their antiretroviral function, benzodiazepines may suppress HERV activation by exogenous viral infections, including SARS-CoV-2 [228,229].

Table 1. Potential syncytia-inhibiting drugs and mechanisms of action.

Drug	Mechanism	References
Arginine mimetics	Furin inhibition	[195,196]
Niclosamide	TMEM16F inhibition	[202]
Ivermectin	GABA upregulation	[36,37]
ARBs/ACEi	GABA upregulation	[14–16]
Benzodiazepines	GABA upregulation	[213]

Taken together, the syncytia-inducing FCS of SARS-CoV-2 activates HERV-W and lowers retrovirus-inhibiting GABA. GABA and its agonists likely inhibit S2-mediated HERV activation.

6. Conclusions

The COVID-19 pandemic has stimulated research highlighting numerous molecular pathways that were poorly defined prior to the arrival of this virus. The viral predilection for ACE-2 has shed light on RAS and the importance of balancing its two branches to prevent pathology, including neuropsychiatric diseases. As SARS-CoV-2 has been extensively studied in a relatively short period of time, several cellular mechanisms relevant for psychiatry have been highlighted, including:

1. ACE-2 is protective for the GABAergic signaling in both neuronal and non-neuronal pathways.

2. Inhibition of protective RAS promotes cellular senescence, lowering neuronal and non-neuronal GABA.
3. Virus-induced syncytia formation is a major trigger of premature cellular senescence and related pathology.
4. Aside from functioning as a neurotransmitter, GABA displays anti-hypertension, anti-senescence, anti-diabetes, antioxidant, and anti-inflammatory properties.
5. ARBs and ACEi upregulate GABA, promoting adult neurogenesis that prevents senescence-mediated psychopathologies.
6. The S2 protein of SARS-CoV-2 contains a triple-arginine insert that activates HERVs, promoting hyperinflammatory pathologies.
7. SARS-CoV-2 alters Trp catabolism and the GABA-producing gut flora, facilitating microbial translocation from the GI tract into various tissues and organs, including the brain.
8. Furin and TMEM16F inhibitors suppress syncytia formation, while ARBs and ACEi upregulate GABA, lowering ANG II-induced senescence.

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Abbreviations

eGABA	endothelial GABA
mGABA	microbial GABA
pGABA	pancreatic GABA
nGABA	neuronal GABA
TLR4	toll-like receptor 4
ANG II	angiotensin converting enzyme 2

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