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Does COVID-19 Affect Adult Neurogenesis? A Neurochemical Perspective

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Abstract

COVID-19 has been found to cause neuropsychiatric symptoms which indicate brain involvement. SARS-CoV-2 may enter the brain by damaging and penetrating olfactory mucosa and via other possible routes like damaged blood–brain barrier, and hematologic spread. With SARS-CoV-2 having a higher affinity to ACE2 receptors, brain regions that have higher ACE2 receptors like the hippocampus, are more vulnerable to the effect of the viral invasion. In addition, immune cell activation, an important feature of COVID-19, leads to cytokine storm which causes neurotoxicity, neuroinflammation, and neurodegeneration. Impaired adult neurogenesis is related to many psychiatric disorders including depression, bipolar disorder, anxiety disorder, schizophrenia, and PTSD. It is known to be related to the depletion of neurotransmitters, dopamine, serotonin, norepinephrine, GABA, and glutamate which play a major role in adult neurogenesis. A recent study reveals that SSRI which acts by increasing serotonin is proven beneficial in COVID-19 patients. Thus, the current chapter will discuss the impact of COVID-19 on adult neurogenesis with emphasis on the role of ACE2 and neurotransmitters.

Keywords: COVID-19, SARS-CoV-2, ACE2, adult neurogenesis, glutamate, monoaminergic neurotransmitters, GABA

1. Introduction

The last two decades have seen epidemic outbreaks by novel viruses including SARS, MERS, and influenza which shared certain commonalities such as a likely zoonotic origin, high mortality rates, and less available therapeutic methods to counteract them. The COVID-19 pandemic shows no signs of slowing down with affecting 223 countries, with 224,811,910 cases, and 4,633,797 death tolls till date [1]. With what history on earlier pandemics has made us understand and with the rapidly mutating nature of the SARS-CoV-2 virus, it is not unreasonable to say that the pandemic is here to stay, and the world must learn to co-exist with it. The first reported case of COVID-19 was found in Wuhan, China in December 2019. By March 2020, the disease had spread across the globe and had become a public health emergency. The WHO declared a pandemic state to the disease spread on March 11, 2020 [2]. With more than a year since the declaration of the pandemic, the scientific community has yet not developed a definitive anti-viral drug to combat the disease

spread. Even though the advent of vaccination has set the pace in favour of global health, we have a long way to go to eradicate if at all suppress the disease spread.

SARS-CoV-2 is highly virulent and highly contagious with the R_0 value of 3.77 [3]. Though it predominantly affects the respiratory system, other organ systems like the gastrointestinal system, heart, kidney, and central nervous system are also targeted by the virus. Fever, chills, cough, shortness of breath or breathing difficulty, sore throat, nasal congestion, diarrhoea, nausea, vomiting, generalised body aches are some of the common symptoms noted in patients infected with COVID-19 [4].

Neurological manifestations of COVID-19 include non-specific symptoms like headache, dizziness, fatigue, and myopathy and more specific symptoms like anosmia, ageusia, impaired consciousness, stroke, meningitis, acute transverse myelitis, and Guillian-Barre syndrome [5, 6]. More than one third of the individuals with COVID-19 were found to present with neurological symptoms [7, 8]. The presence of viral RNA in cerebrospinal fluid and the brain was observed in COVID-19 patients [9]. Preliminary *in vitro* studies have found that SARS-CoV-2 can replicate in neuronal cells [10]. A post-mortem study has found that 48% of the studied cases had human CoV RNA in the CNS that was detectable [11]. SARS-CoV-2 is found to exhibit organotropism for the nervous system and SARS-CoV and MERS-CoV which are closely related to SARS-CoV-2 have neuro-invasive potential. Hence, apart from the secondary impact on the brain as a result of systemic complications like coagulopathy and hypoxia, the direct effect of SARS-CoV-2 infection on the brain and spinal cord is plausible and is being thoroughly studied by researchers globally. The neuropsychiatric symptoms in COVID-19 could be attributed to a variety of factors apart from the direct effect of the virus on the brain like psychological distress due to social isolation, the novelty of the disease spread and pandemic, concerns about family and friends contracting the disease, social stigma, etc. [12]. This chapter will, however, focus on the direct effects of the SARS-CoV-2 virus on the brain which could be attributed to the pathophysiology of neuropsychiatric symptoms with a special focus on ACE2 and monoaminergic neurotransmitters.

2. SARS-CoV-2

Coronaviruses are the largest among RNA viruses. They have a crown-like spikes on their surface and hence the name. SARS-CoV-2 is the latest/seventh coronavirus to become pathogenic to humans. It belongs to the Coronaviridae family which includes four genera; α -, β -, γ -, and δ -CoV. Out of these human pathogens include HCoV- 229E, HCoV- NL63 [α – CoV] and OC43, and HKU1 [β – CoV] that in most cases cause mild self-limiting respiratory disease. γ – and δ -CoV strains mainly affect avian species [13]. SARS-CoV and MERS-CoV, causatives of SARS and MERS, are beta coronaviruses that caused up to 9.6% and 34.3% mortality rates which were responsible for earlier pandemics that resulted in a death toll of 812 and 866, respectively [14]. SARS-CoV-2 is more similar to SARS-CoV and MERS-CoV while being far more pathogenic and transmissible than the earlier known coronaviruses.

SARS-CoV-2 is a beta coronavirus that is positive-sense single-stranded RNA virus with 29–30 kb in size. It has four structural proteins and 16 non-structural proteins. Nucleocapsid protein [N], membrane protein [M], spike protein [S], and envelope protein [E] are the four structural proteins (**Figure 1**). The capsid of the genome is formed by N protein and the genome is further surrounded by an envelope that is made up of M, E, and S proteins. Like other coronaviruses, SARS-CoV-2 has enveloped with a crown-like spikes on its surface. It is the spike protein that is responsible for the variations in host specificity and tissue tropism of the different coronavirus. Spike protein is a type-I membrane glycoprotein and has two functional

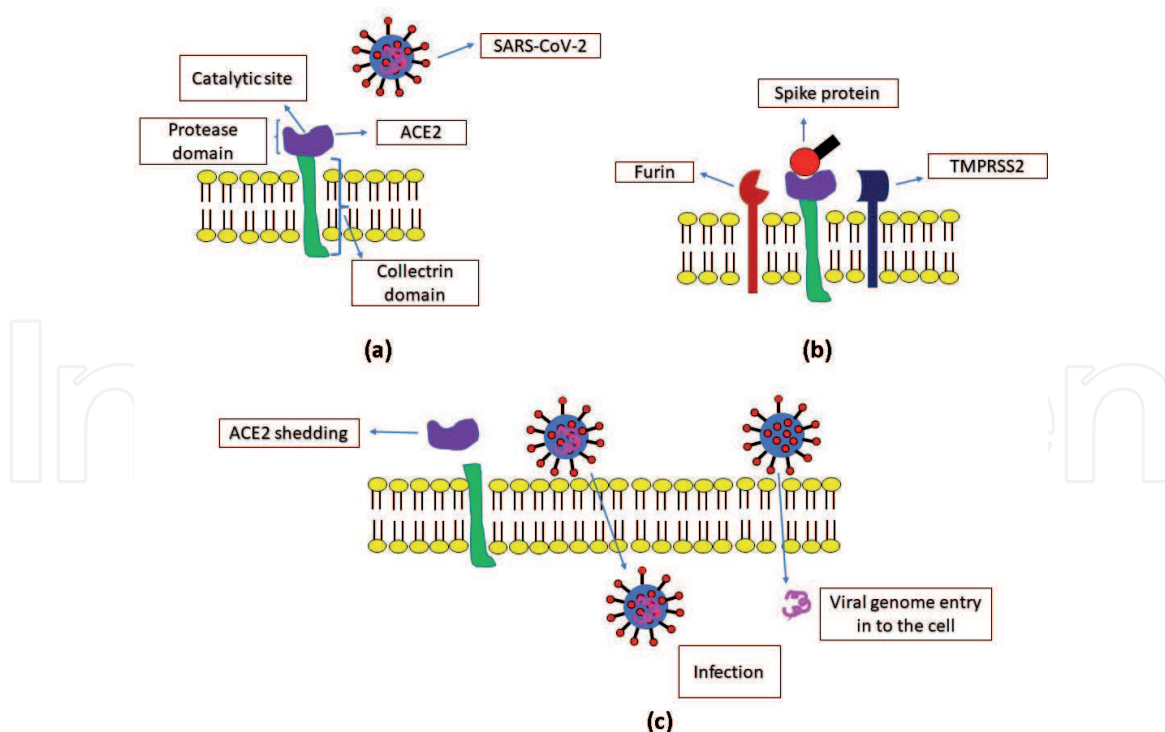


Figure 1.
 (a) Structure of ACE2 and SARS-CoV-2; (b) Interaction of spike protein and ACE2; (c) Shedding of ACE2 and entry of SARS-CoV-2 into the cell.

subunits S1 and S2 with different functional domains in the amino and carboxy terminal. S1 subunit contains the receptor-binding domain [RBD] and binds with the receptor in the host cells. S2 subunit fuses the membranes of the host cells and the virus. The entry of the virus into the host cell involves binding of the S protein [S1 subunit] to a specific cell receptor followed by priming of the S protein by proteases in the host cell. This leads to the fusion of the spike protein to the cell membrane which is mediated by the S2 subunit [15]. The specific cell receptor through which SARS-CoV-2 enters the host cell is the ACE2 receptor and the protease in the host cell that processes the spike protein to reveal the fusion peptide between S1 and S2 subunits facilitating its entry, is a TMPRSS2 serine protease, member of the hepsin/TMPRSS subfamily [16]. Another protein named furin or paired basic amino acid cleaving enzyme [PACE], a member of the subtilisin-like proprotein convertase family, mediates proteolytic cut of the S protein at S1-S2 boundary, is required for TMPRSS2 processing of S protein. Both TMPRSS2 and furin are essential for the entry of SARS-CoV-2 into the cell. The furin cleavage site in the S protein of SARS-CoV-2 is not found in SARS-CoV and other beta coronaviruses [17].

3. ACE2

ACE2 is a cell surface protein, a metalloproteinase and an ectoenzyme which is an obligatory receptor for SARS-CoV and SARS-CoV-2. The affinity of SARS-CoV-2 to ACE2 is ten times higher than that of SARS-CoV which partly explains its higher pathogenicity [18]. It was discovered in 2000 by two independent groups of researchers while searching for human ACE homologues [19, 20]. The gene for ACE2 in humans is located in Xp22 and has 18 exons, a majority of which are similar to the exons of the ACE gene [21]. Despite ACE2 exhibiting 42% sequence identify and 61% sequence similarity with ACE, the two enzymes show enormous variations (**Table 1**) [27].

	ACE	ACE2
Forms	Exists as a 2-domain somatic form and a one domain testicular form	Exists as a single form
Structure	Transmembrane ectoenzyme with two active sites	Transmembrane ectoenzyme with one active site
Enzymatic action	Removes C-terminal dipeptide – peptidyl-dipeptidase	Removes single amino acid from C-terminus – carboxypeptidase
Substrate specificity	Converts Ang I to Ang II	Converts Ang I to Ang (1-9)
	Does not cleave Ang II	Converts Ang II to Ang (1-7)
	Converts Ang (1-9) to Ang (1-7)	Does not cleave Ang (1-9)
	Converts Ang (1-7) to Ang (1-5)	Does not cleave Ang (1-7)
	Does not cleave Ang A	Converts Ang A to Alamandine
	Hydrolyses bradykinin	Does not cleave bradykinin
	Does not cleave des-Arg9-bradykinin	Hydrolyses des-Arg9-bradykinin
Action on amyloid protein	Hydrolyses A β -43 to A β 41	Hydrolyses A β 43 to A β 42
	Hydrolyses A β -42 to A β 40	Does not cleave A β -42
Localisation within cells	Equal distribution between apical and basolateral membranes	Localised on the apical membrane
Transports intestinal amino acids	No	Transports intestinal neutral amino acids
Shedding into plasma	Unidentified. May involve metalloproteinase and A Disintegrin	By A Disintegrin and Metalloprotease 17 (ADAM 17)
Response to ACE inhibitor	Inhibited	Resistant, gets upregulated
Acts as a receptor to virus	No	Receptor for SARS-CoV and SARS-CoV-2

Table 1.
The comparison between ACE and ACE2 is given in Table 1 [22–26].

Since the 20 years of its discovery, ACE2 was found to have a multitude of physiological and pathological functions based on its three fundamental actions viz. negative regulation of renin-angiotensin system [RAS], facilitation of amino acid transport in the intestine, and surface receptor for SARS-CoV and SARS-CoV-2. ACE2 is mainly expressed in the lungs, intestine, liver, heart, kidneys, testes, and brain. In the brain, it is expressed in neurons, astrocytes and oligodendrocytes, and in ventricles, substantia nigra, hypothalamus, hippocampus, middle temporal gyrus, posterior cingulate cortex, nuclei in pons—the nucleus of tractus solitarius and pre-Bötzinger complex and olfactory bulb [21, 28]. ACE2 expression is higher in astrocytes, astrocytic foot processes, pericytes, and endothelial cells which form the key components of the blood–brain barrier [29]. In the olfactory epithelium, its expression is higher in the supporting sustentacular cells than in olfactory sensory neurons [30]. The sites of ACE2 expression are given in Table 2 [31].

3.1 Structure

ACE2 is a type 1 integral membrane protein that includes a short cytoplasmic C-terminus, a transmembrane region, collectrin, and N-terminal ectodomain. Zinc-binding motifs, HEMGH forms the active site of the enzyme. N-terminal domain

Vascular system	Endothelial cells, vascular smooth muscle cells, and migratory angiogenic cells
Heart	Cardiomyocytes, endothelial cells, pericytes, and epicardial adipose cells, and cardiofibroblasts
Skin	sebaceous gland cells and basal epidermal layer
Kidneys	glomerular endothelial cells, proximal tubule epithelial cells, bladder urothelial cells, luminal surface of tubular epithelial cells, and podocytes
Reproductive system	Ovary, oocyte, uterus, vagina, and placenta of the female reproductive system Adult Leydig cells and cells in the seminiferous ducts in the testis of the male reproductive system
Liver	Perinuclear hepatocytes, cholangiocytes, epithelial cells of the bile duct
Gut	Stratified epithelial cells of oesophagus, stomach, Intestinal epithelial cells, enterocytes of small intestine, absorptive enterocytes from the ileum, colon and rectum, and endothelial cells
Pancreas	Acinar cells and duct cells of the exocrine gland and alpha, beta, delta, and PP cells of islets of Langerhans
Thyroid	Glandular cells
Oral cavity	Tongue, buccal mucosa, gingiva, leucocytes within the oral mucosa, non-keratinising squamous epithelium of the oral cavity – basal layer
Upper airway	Ciliated epithelial cells, goblet cells
Lungs	Pulmonary vasculature, type I and II alveolar epithelial cells, bronchiolar epithelial cells
Eyes	Pigmented epithelial cells, photoreceptor cells, Müller glial cells
Central nervous system	Neurons, astrocytes, and oligodendrocytes, and in ventricles, substantia nigra, hypothalamus, hippocampus, middle temporal gyrus, posterior cingulate cortex, nuclei in pons – nucleus of tractus solitarius and pre-Bötzinger complex and olfactory bulb and cerebral vasculature and components of blood–brain barrier (astrocytes, astrocytic foot processes, pericytes, and endothelial cells)

Table 2.
Sites of ACE2 expression.

has a claw-shaped protease domain which is the binding site of receptor-binding domain [RBD] of SARS-CoV and SARS-CoV-2. N terminus is homologous to ACE and is a carboxypeptidase that metabolises peptides like angiotensin II, kinins, apelin-13, apelin-36, neurotensin 1–13, kinetensin, and morphins, and C terminus is homologous to collectrin which is involved in the trafficking of neutral amino acid transporter [B[o]AT1] in the intestinal epithelium [32].

4. Role of ACE2 in renin-angiotensin system [RAS]

Both ACE and ACE2 play a major role in maintaining renin-angiotensin system [RAS] homeostasis. ACE2 acts like a negative regulator of ACE in RAS. RAS involves a variety of proteins and enzymes. Angiotensinogen is an inactive precursor that gets cleaved by renin to form angiotensin I. ACE acts on angiotensin I to convert into angiotensin II [Ang II] while ACE2 converts Ang II to Ang [1-7]. Ang [1-7] then binds to Mas receptors and causes attenuation of the signal cascade that was activated by Ang II (**Figure 2**). Thus, ACE2 not only inactivates Ang II but also generates the antagonistic peptide Ang [1-7] [33]. Ang [1-7] can also be formed from Ang I by neutral endopeptidases and neprilysin, but the most effective pathway of Ang [1-7] generation is through ACE2 [34]. The conversion of Ang II

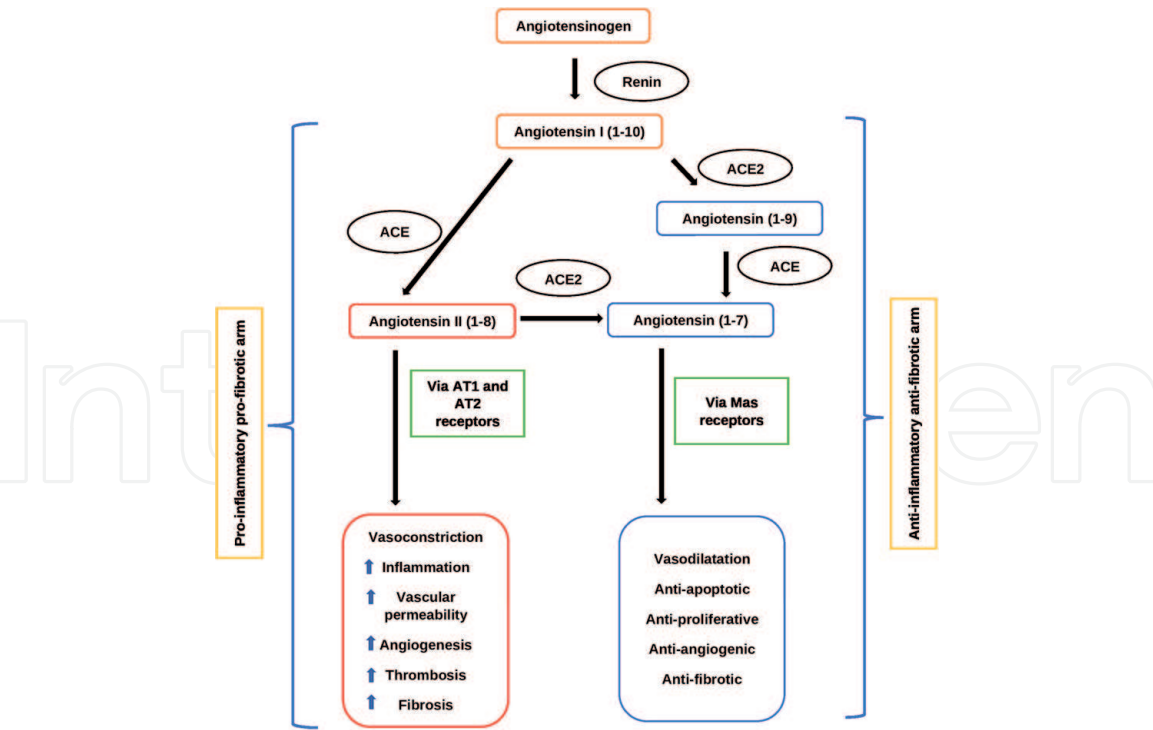


Figure 2.
Renin-Angiotensin System.

to Ang [1-7] by ACE2 is 70 folds more efficient than the conversion of Ang I to Ang [1-9] by ACE2. Thus, under physiological conditions, ACE2 mainly forms Ang [1-7] than Ang [1-9] [34].

While Ang II, which acts via angiotensin 1/AT1 [primary mediator] and angiotensin 2/AT2 receptors is a potent vasoconstrictor, a pro-fibrotic, and a pro-inflammatory agent, Ang [1-7] acts via Mas receptors and has vasodilator, anti-apoptotic and anti-proliferative effect. Mas receptors are G protein-coupled receptors and in the brain, they are highly expressed in the dentate gyrus of the hippocampus, a site-specific for adult neurogenesis and in blood vessels [35]. The ACE2/Ang [1-7]/Mas receptor axis of the RAS is considered to be the protective arm of the renin-angiotensin system. A balance in ACE/ACE2 is critical which implies a balance between the pro-inflammatory pro-oxidative arm and the anti-inflammatory and anti-oxidative arm of RAS. An increase in ACE/ACE2 ratio was observed in many pathological conditions including cardiovascular pathology, renal dysfunction, pulmonary hypertension, in cigarette smokers, and Alzheimer's disease [36–39]. SARS-CoV-2 which enters the host cells via ACE2 also causes downregulation of ACE2 and the major targets of SARS-CoV-2 are those which express higher levels of ACE2 [26]. The fibrotic and inflammatory processes observed in various organs in COVID-19 patients could be attributed to the dysregulation of ACE2 and subsequently, RAS which is observed in endocrine, paracrine, and intracrine levels in several organs [40]. Dysregulation of RAS in the brain is associated with neuroinflammation and neurodegeneration [41].

5. Neurogenesis

The old dogma that the production of functional neurons does not occur in adult life was refuted when Altman and Das published evidence to support the

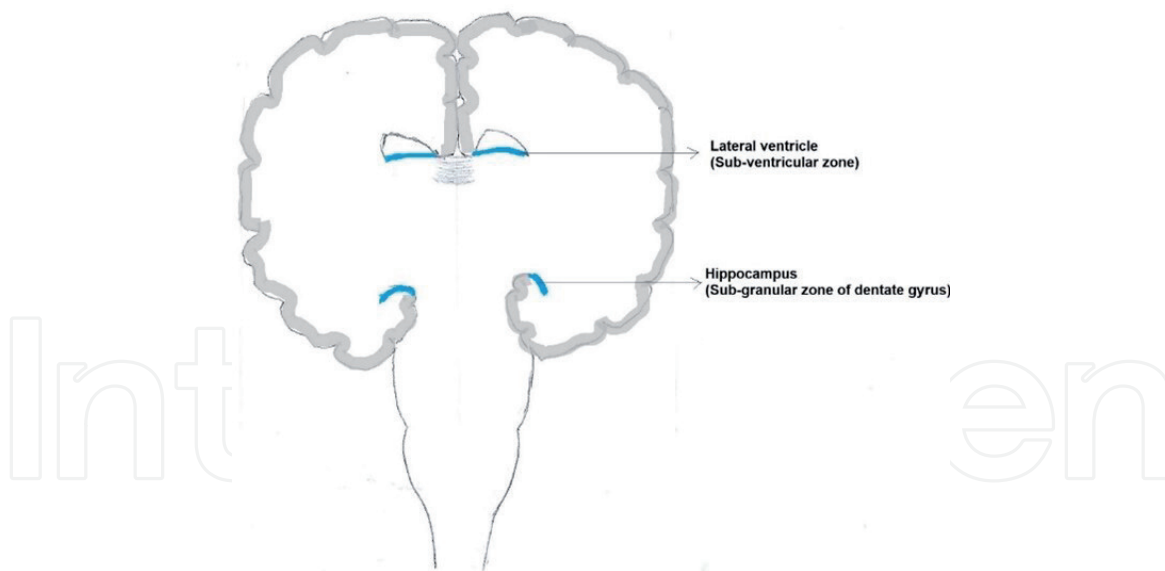


Figure 3.
 Coronal section of the brain showing the sites of adult neurogenesis.

continuation of neurogenesis in adult life in rodents [42]. Neurogenesis refers to the process of the generation of new neurons from neural stem cells. This process which plays a major role in brain development in embryonic life ceases to exist shortly after birth in the majority of brain areas except two. The subgranular zone [SGZ] of the dentate gyrus of the hippocampus and subventricular zone [SVZ], lining the lateral wall of the lateral ventricles are the two areas where neurogenesis persists well into adult life albeit declining slightly with ageing (**Figure 3**) [43, 44]. There is a complex microenvironment that nourishes and supports the neural progenitor cells and their progeny which is called the ‘neurogenic niche’. There are various trophic factors, blood vessels, supporting glial cells, and hormones in the neurogenic niche that help to control and enhance neurogenesis [45]. The newborn neurons mature and get integrated into neural circuits and are involved in a variety of functions including learning and memory like temporal and pattern separation, high-resolution memory, synaptic plasticity, fear conditioning and emotions, and olfaction [46]. Incidentally altered neurogenesis is implicated in several neuropsychiatric diseases like Alzheimer’s disease, Parkinson’s disease, depression, Huntington’s disease, and stroke, epilepsy, and demyelinating disease [46, 47].

5.1 Stages of adult neurogenesis

The process of adult neurogenesis occurs in stages viz. maintenance of neural stem/progenitor cells [NPC] and proliferation of NPC, fate specification/commitment, differentiation, maturation, survival of immature neurons, and integration into neural circuitry. The defining abilities of NPC are self-replication and multipotency, that is, the ability to differentiate into multiple lineages of cells and in this case neurons, astrocytes, and oligodendrocytes [48]. There are different types of neural progenitor cells in SGZ and SVZ. Type-1 cells in SGZ, B-cells in SVZ, and radial glia-like cells in SGZ and SVZ are largely quiescent cells, which are similar to radial glia cells found during embryonic development and have a morphology similar to mature astrocytes. Type-2 cells in SGZ and C-cells in SVZ are small roundish cells that are highly proliferative, and they give rise to type-3 cells in SGZ and A-cells in SVZ which represent committed neuroblasts. The type-1/B-cells

are multipotent and have unlimited self-renewal capacity which get activated by various factors and multiply to form highly proliferative transient intermediate progenitor cells [TIP] in the SGZ. In SVZ, the transit-amplifying cells [TAC] [type-2/C-cells] has the ability to differentiate into neurons. These divide to form neuroblasts or immature neurons [type-3/A-cells] which proceed to neuronal differentiation and forms newborn neurons that mature and get integrated into neural circuitry in the brain. It is pertinent to know that many of the newborn neurons perish and only 15–30% of immature neurons survive the maturation process. There are various factors that regulate this step and thereby the process of adult neurogenesis [49–51].

In SGZ, the NPCs form granule cells which are the principal excitatory cells of the dentate gyrus. Their axons form the mossy fibres extending to the CA3 region and their dendrites are in the molecular layer which receives connections from the entorhinal cortex. Immature neurons that are less than a week-old start to have neurite outgrowth and by one- or two-weeks axons can be observed in the hilus, and dendrites start to extend to the molecular layer without spines which being developed by around the 16th day. By 17 days, functional connections are formed by the axons [mossy fibres] with the CA3 pyramidal neurons [52]. They release glutamate as the neurotransmitter. After around 1 week of birth, the newborn granule cells receive GABAergic inputs and after 2 weeks receive glutamatergic inputs [53]. These immature neurons exhibit enhanced excitability by virtue of high input resistance and subthreshold calcium ion conductance which enables them to develop action potential with less excitatory currents. They also have a low threshold for induction of LTP [long-term potentiation] [54, 55]. Between 3 weeks and 2 months, there occurs a gradual increase in spine formation, dendritic arborisation and connection, boutons on CA3 neurons, and maturation of mossy fibres. By less than 2 months, the newborn neurons become functionally indistinguishable from fully mature granule cells [52].

Intrinsic factors	Examples
Neurotrophic factors	brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), nerve growth factor (NGF), glia-derived nerve factor (GDNF), fibroblast growth factor 2 (FGF-2), epidermal growth factor (EGF)
Morphogens	Notch, sonic hedgehog (Shh), wingless ligands (Wnts), and bone morphogenic proteins (BMPs).
Inflammatory cytokines	tissue necrosis factors α (TNF α), interleukin-6 (IL-6) and IL-1 β IL-4 and IL-10
Neurotransmitters	gamma-aminobutyric acid (GABA), glutamate, dopamine, serotonin, norepinephrine, acetylcholine
Hormones	Glucocorticoids, sex hormones, leptin, incretin
Epigenetic factors	methyl-CpG-binding domain protein 1 (Mbd1), MYST family histone acetyltransferase Querkopf (Qkf), mixed-lineage leukaemia 1 (Mll1), polycomb complex protein (Bmi-1), histone deacetylase 2 (HDAC2), and microRNAs (miR124, 137, 184, 185, and 491-3p)
Transcriptional factors	sex-determining region Y-box 2 (Sox2), Orphan nuclear receptor TLX, forkhead box O proteins (FoxOs), prospero homeobox 1 (Prox1), neurogenic differentiation1 (NeuroD1), Kruppel-like factor 9, cyclic AMP response element-binding protein (CREB), paired box protein (Pax6), and neurogenin 2 (Neurog2)

Table 3.
List of intrinsic factors that affect adult neurogenesis.

In SVZ, restricted neural progenitor cells migrate along scaffolds maintained by specialised astrocytes via the rostral migratory stream [RMS] to reach the olfactory bulb. By 15–30 days, they differentiate into two types of interneurons, GABAergic granule neurons [95%] and GABA or dopaminergic periglomerular neurons [5%]. The newborn GABAergic granule neurons can become cells with dendrites that do not cross beyond the mitral cell layer and those with non-spiny dendrites that extend till the external plexiform layer. These interneurons mature and get integrated into olfactory network and start responding to olfactory signals [52].

There are various factors that regulate neurogenesis. These include intrinsic niche-derived intrinsic mechanisms and extrinsic systemic factors. The intrinsic factors that regulate adult neurogenesis are given in **Table 3**. There are extrinsic environmental cues and systemic factors that can positively and negatively affect adult neurogenesis like physical exercise, dietary intake, olfactory/hippocampal-dependent learning, environmental enrichment, ageing, stress, alcohol abuse, and certain inflammatory conditions [46, 56–59].

6. Entry of SARS-CoV-2 into the brain

There are different ways that are the possible pathway for the entry of SARS-CoV-2 into the brain. Some of the ways include olfactory transmucosal invasion, hematogenous dissemination, and neuronal retrograde dissemination [5]. The olfactory sensory neurons of the olfactory mucosa are bipolar neurons. The axons of the olfactory sensory neurons along the apical side project into the nasal cavity while that on the basal side merge into filia and protrudes into the olfactory bulb through the cribriform plate. Thus, the olfactory sensory neurons are in direct contact with the cerebrospinal fluid [60]. In the olfactory mucosa, ACE2 receptors are mainly found in the non-neuronal cells, sustentacular cells while their expression in the olfactory sensory neurons is less [30]. The blood vessels lining the olfactory mucosa express both ACE2 and TMPRSS2 protease receptors which help in the invasion of the SARS-CoV-2 virus and facilitate binding, replication, and accumulation of the virus [61, 62]. Studies have found that SARS-CoV-2 enters CNS through this neural-mucosal interface by infection of the olfactory neurons or by diffusion through channels formed by olfactory ensheathing cells in the olfactory mucosa [60, 63]. Following the olfactory transmucosal invasion, the virus passes along the olfactory tract via axonal transport, trans-synaptic transport, or microfusion to different areas of the brain linked with the olfactory tract [60, 64].

Recent studies have observed that SARS-CoV-2 RNA was found in brain regions that are not directly connected to olfactory mucosa like the cerebellum which shows that other forms/routes of viral entry into the brain are at play. Neuronal retrograde dissemination is the one where the virus may breach peripheral nerve terminals and take a trans-synaptic route to reach CNS. For instance, SARS-CoV-2 may invade peripheral chemoreceptors and may reach the cardiorespiratory centre in the brain stem [65] or through the gut-brain axis where the virus may enter the brain through enteric nerves [66]. In case of hematogenous dissemination, the virus after infecting the airways may breach the epithelial barrier and enter the bloodstream. Through systemic circulation, the virus may reach the cerebral circulation and could infect endothelial cells of blood–brain barrier or epithelial cells of the blood CSF barrier to reach the brain or via circumventricular organs which lack the blood–brain barrier [5]. Trojan horse mechanism is another way by which SARS-CoV-2 could reach the brain parenchyma. It is the process in which the virus infects leucocytes which get activated and disseminate to other tissues and cross blood–brain barrier [67].

Once SARS-CoV-2 enters the brain, it enters and infects the neurons, glial cells, and endothelial cells through ACE2 and replicates which leads to cell death. It causes damage to the blood–brain barrier which will increase its permeability and cause oedema, intracerebral bleeding, and neuronal death. The infected neurons can release inflammatory mediators that can activate other immune cells like mast cells, neurons, microglia, astrocytes, endothelial cells, and pericytes [68, 69].

7. Adult neurogenesis in COVID-19

Earlier studies show that survivors of critical illness have higher risk of developing neuropsychiatric consequences after discharge from the hospital. The prevalence of symptoms of depression, anxiety, and post-traumatic stress was found to be 29% [28–34], 34% [30–42], and 34% [27–50] in survivors of critical illness, respectively [70–72]. Impairment in memory, attention, and concentration was observed in SARS survivors 1 year after recovery [73]. Based on the knowledge from earlier infections by coronaviruses, SARS, and MERS, an increased risk of neuropsychiatric disorders like depression, anxiety, post-traumatic stress disorder, are possible in a long-term follow-up of patients recovered from COVID-19 [12].

Neuropsychiatric disorders that display impaired adult neurogenesis include major depressive disorder, Alzheimer's disease, Parkinson's disease, schizophrenia, and post-traumatic stress disorder. All of these correlate well with the reduction in hippocampal volume, cognitive deficits, and mood dysregulation [74]. A recent 3-month prospective study by Yiping Lu et al. conducted in COVID-19 recovered patients found that there was grey matter enlargement in olfactory cortices and hippocampus bilaterally [75]. Yiping Lu et al. also found that the grey matter volume of the hippocampus was negatively related to loss of smell during the disease phase [75]. Anosmia over a course of time in upper respiratory tract infections was found to be associated with a decrease in the grey matter volume [GMV] of the central olfactory system due to loss of stimulation while enlargement of GMV is observed during recovery [76]. Functional compensation in the form of enlarged neurons and an increase in the dendritic spine and compensatory enhanced neurogenesis are believed to be the reason behind GMV enlargement during recovery [77]. Loss of memory that persisted 3 months after the active infection in COVID-19 recovered patients was found to be negatively related to hippocampal grey matter volume [75]. Memory acquisition depends on newborn neurons and impairment in the acquisition of memory occurs due to inhibition of adult neurogenesis in the hippocampus [78, 79].

Anosmia is regarded as the key feature of COVID-19 which either occurs as an only symptom or in association with other signs and symptoms [80, 81]. Earlier studies show that any impairment in olfactory neurogenesis is associated with anosmia since neurogenesis in the olfactory epithelium and olfactory bulb is essential for the sense of smell [82, 83]. Dysfunction or atrophy of the olfactory bulb was observed in COVID-19 patients by recent studies done using brain imaging reports [84, 85]. Pathogenic changes in COVID-19 seem to cause loss of dopaminergic neurons, defects in the dopamine system, and exacerbate the clinical features of Parkinson's disease [PD] [86, 87]. Anosmia is an important premotor symptom of PD which is not directly related to the neurodegenerative process in substantia nigra but appears to be related to defective adult neurogenesis [88, 89].

Understanding the process of adult neurogenesis in COVID-19 may reveal a critical role of the regenerative capacity of NPCs in combating the neuropsychiatric consequence of COVID-19. There are no studies or evidence to link COVID-19 with adult neurogenesis yet. Based on the factors like the presentation of neuropsychiatric symptoms in COVID-19, the occurrence of symptoms like anosmia, memory and

cognitive deficits in COVID-19, the neuro-invasive potential of SARS-CoV-2, ACE2 expression in sites of adult neurogenesis, increased levels of pro-inflammatory cytokines like IL-6, IL-1 β which inhibit adult neurogenesis and impact of earlier coronavirus infections, it might not be far-fetched to say that COVID-19 could have a possible impact on adult neurogenesis. There is a severe scarcity in research analysing the effect of SARS-CoV-2 infection on adult neurogenesis. The current chapter, which is speculative and based on a thorough literature search, discusses the possible changes in adult neurogenesis in COVID-19 emphasising the role of ACE2. If proven to be true in the future, the findings in this article will help in achieving early intervention to address the neuropsychiatric long-term consequence of COVID-19.

8. Role of ACE2 in adult neurogenesis in COVID-19

SARS-CoV-2 entry into the cell through ACE2 is followed by the downregulation of ACE2. A decrease in ACE2 will lead to dysregulation of RAS and various other complications. A recent study has found that ACE2 is expressed in young neurons and in human-induced pluripotent stem cell-derived neural progenitor cells [90]. ACE2 is found to have various neuroprotective functions. It converts neurotoxic amyloid protein A β into neuroprotective one in transgenic mice [91]. ACE2 activator, diminazene increased CREB, BDNF, glutamate, and nicotinic receptor and decreased the levels of apoptotic and inflammatory proteins in the AD model of D-galactose-ovariectomized rats [92]. All these factors play a major role in adult neurogenesis. ACE2 deficiency in mice was found to be accompanied by significantly impaired learning and memory [93]. Exercise-induced neurogenesis in the dentate gyrus was abolished in ACE2 deficient mice. Ang II, Ang [1-7], and Mas receptors were not found to be responsible and hence the mediator of this effect is not identified yet [94].

ACE2 expression is stronger in the enterocytes of the small intestine and colon, which is even higher than in the lungs. Neural ganglia cells in the colon of the enteric nervous system also express ACE2 receptors. Intestinal ACE2 plays a major role in the transport of neutral amino acids via B0AT1, neutral amino acid transporter. ACE2/B0AT1 complex regulates the composition and function of gut microbiota. ACE2 knockout animals showed lower levels of serum neutral amino acid levels like tryptophan, and impaired gut microbiota composition along with reduced expression of small intestinal antimicrobial peptides [95]. Enteric infection is an important presentation of COVID-19. Faeces of COVID-19 patients were found to have Viral mRNA [96, 97]. SARS-CoV-2 entry via the enteric route into host cell leads to ACE2 shedding due to S priming which may lead to gut microbiota dysbiosis [98]. Depletion of gut microbiota by prolonged antibiotic treatment resulted in impairment in cognitive function and hippocampal neurogenesis in adult mice [99]. The existence of a strong link between gut microbiota and the development of mental disorders, depression, and anxiety which are associated with impaired adult neurogenesis has been explored in recent studies [100].

Neuroinflammation directly impairs adult hippocampal neurogenesis. Pro-inflammatory cytokine IL-1 β , IL-6, IFN- α causes a reduction in neural cell proliferation and suppresses adult hippocampal neurogenesis [101–103]. SARS-CoV-2 entry into the brain triggers an immune response by activating microglia, astrocytes, and other immune cells. This leads to increased production of cytokines in the brain. Cytokine storm which is a deadly hyperinflammatory response is considered to be a hallmark feature of COVID-19 pathogenesis [104]. Hypercytokinemia of IL-6, IL-10, and TNF- α was observed in COVID-19 patients. Increased levels of IL-6 correlate with mortality and the need for ventilator support [105, 106].

Thus, there are different possible mechanisms through which SARS-CoV-2 affects adult neurogenesis via ACE2. This chapter, however, will focus on the role of ACE2 in possible alterations in adult neurogenesis in COVID-19 via neurotransmitters.

9. ACE2 and neurotransmitters involved in adult neurogenesis

Neurotransmitter signalling is found to play a major role in the formation of new neurons in addition to its clear and indisputable role in communication between neurons. Starting from embryogenesis, neurotransmitters are involved in neuronal proliferation. In adult neurogenesis, they influence various steps including proliferation, differentiation, and migration. In addition to the direct action of neurotransmitters on adult neurogenesis, they also influence other factors that regulate neurogenesis like neurotrophic factors and growth factors [107].

9.1 ACE2 and serotonin

Serotonin is a crucial monoaminergic neurotransmitter that acts as a mood stabiliser and is associated with feelings of happiness, well-being, and contentedness. In the brain, it is synthesised by the Raphe nuclei neurons in the brain stem from tryptophan using neuron-specific tryptophan hydroxylase 2 enzymes. Vesicular monoamine transporter 2 [VMAT] packs the synthesised serotonin into vesicles. Serotonin transporters [SERT] re-uptake serotonin back to presynaptic neurons after its release, thereby regulating its extracellular levels [108]. The serotonergic fibres from raphe nuclei have projections throughout the brain and especially to the granule cells and interneurons of the dentate gyrus of the hippocampus. Serotonin is known to play a major regulatory role in adult hippocampal neurogenesis. Selective serotonin reuptake inhibitors [SRRI] are commonly used antidepressants that act by increasing serotonin levels in the brain causes clinical improvement associated with an increase in adult hippocampal neurogenesis characterised by increased neuronal proliferation and number of newborn neurons [109]. Malberg et al. in 2000 were the first to show that chronic treatment with fluoxetine improved adult hippocampal neurogenesis [109]. In the dentate gyrus, serotonin is known to promote neuronal development and its depletion was found to cause reduced dendritic spine density of granule cells [110–113]. Chronic treatment with SSRI, fluoxetine was found to increase the survival of newborn neurons in the dentate gyrus [109, 114]. In stress models like inescapable stress, cold restraint stress in the animal model, fluoxetine administration was found to exhibit neurogenic and neuroprotective roles in the hippocampus [114, 115]. Accelerated synaptogenesis and increased long-term potentiation [LTP] in the hippocampus were also observed by long-term treatment by fluoxetine [116].

Recent studies have found that ACE2 plays a major role in the biosynthesis of serotonin [5HT]. The precursor for 5HT is an essential amino acid, tryptophan which can cross the blood–brain barrier and whose intestinal absorption was found to be reduced by 70% in case of ACE2 deficiency. Thus, ACE2 has an indirect modulatory role in 5HT synthesis in the brain [117]. There are recent studies that show that 5HT synthesis in the brain is dependent on ACE2, which acts by modulating 5HT metabolism and ACE2 deficiency leads to decreased serum tryptophan levels and decreased serotonin levels in the brain [94].

9.2 ACE2 and dopamine

Dopamine is involved in executive functions, volition, motor control, motivation, pleasure/reward, and attention/concentration [118]. The role and mechanism

of action of dopamine in adult neurogenesis are not elucidated fully. Dopamine was found to modulate cell proliferation in the embryonic brain [119]. Hippocampus and sub-ventricular zone [SVZ] which are the neurogenic niche containing neural stem cells receive dopaminergic projections from the substantia nigra and ventral tegmental area. Dopamine receptors are also widely expressed in these two areas and play a regulatory role in adult neurogenesis and neural plasticity [120, 121]. Earlier studies show that depletion of dopamine in the rat model reduces both proliferation and survival of neural precursor cells in the sub-granular zone [SGZ] of the dentate gyrus [122, 123]. Dopaminergic denervation in substantia nigra caused a significant reduction in the proliferation of neural stem cells in SGZ and SVZ which was reversed by D2 receptor stimulation in rodents [123]. In humans, post-mortem studies have revealed that the number of neural precursor cells in SGZ and SVZ was reduced in patients with Parkinson's disease [124]. Dopamine was also found to increase the type 2A early progenitor cell in the hippocampus of rodents via D1 like receptors [118]. Dopamine receptor agonist pramipexole increases the proliferation and survival of newborn neurons in SVZ, olfactory bulb [119].

RAS plays a major role in dopaminergic vulnerability through AT1 receptors. Dysregulation of RAS due to the downregulation of ACE2 induced by SARS-CoV-2 may increase the vulnerability of dopaminergic neurons and subsequently dopamine levels [125]. Interactions between dopamine and angiotensin receptors that are counterregulatory in nature are observed in substantia nigra and striatum [125]. The gene for ACE2 was found to coexpress and coregulate with that of dopa decarboxylase [DDC] in non-neuronal cells, which is a major enzyme of dopamine, serotonin, and histamine biosynthesis. DDC converts L-3,4-dihydroxyphenylalanine [L-DOPA] into dopamine which subsequently forms norepinephrine and epinephrine and L-5-hydroxytryptophan into serotonin. This coexpression and coregulation link between the genes for ACE2 and DDC gives rise to the possibility of a functional link between the actions of ACE2 and DDC [i.e.,] in the synthesis of Ang [1-7] and dopamine and serotonin mediated by ACE2 and DDC, respectively [126]. Following the infusion of Ang [1-7] in the hypothalamus of rats, brain dopamine levels increased which emphasises the link between ACE2 and DDC. SARS-CoV-2 induced downregulation of ACE2 could cause the decreased synthesis of serotonin and dopamine [94, 127].

The SARS-CoV-2 infection has been found to cause loss of dopaminergic neurons and deficits in the dopamine system [86, 128]. ACE2 expression is high in dopaminergic neurons and the downregulation of ACE2 by SARS-CoV-2 may cause depletion of dopaminergic neurons and dopamine levels. This is evident from the worsening of symptoms observed in COVID-19 patients with Parkinson's disease [PD], requiring increased dopamine replacement therapy [129]. ACE2 deletion in the knockout mouse model caused a significant reduction in dopamine D1 mRNA expression in substantia nigra [130].

9.3 ACE2 and norepinephrine

Norepinephrine is an important catecholamine that is involved in alertness, arousal, sleep-wake cycle, memory storage, and emotions. It modulates various functions of the hippocampus like learning, memory, and mood. Noradrenergic axon terminals arising from the locus coeruleus densely innervate the neurogenic niche in the adult hippocampus [131]. Norepinephrine along with the other monoaminergic neurotransmitters plays a major role in adult neurogenesis. Norepinephrine was found to activate the stem cells and neural precursor cells via β 3-adrenergic receptors where non-proliferating latent precursor cells develop the ability to respond to mitogens and generate neurospheres. It also increases the proliferation of early progenitor

cells in the adult hippocampus via β 2-adrenergic receptors [132, 133]. Depletion of norepinephrine significantly decreased the proliferation of progenitor cells of granule cells in the hippocampus [134]. Antidepressants that selectively increase norepinephrine were found to increase adult hippocampal neurogenesis [132].

Downregulation of ACE2 by SARS-CoV-2 may affect the activity of DDC due to the coexpression and coregulation between the genes for ACE2 and DDC. This could lead to a decrease in the biosynthesis of dopamine and subsequently norepinephrine [126].

9.4 ACE2 and glutamate and GABA

Glutamate is the predominant excitatory neurotransmitter of the CNS. It plays a vital role in both embryonic brain development and adult neurogenesis. Its extracellular levels are especially higher in the neurogenic niche when compared to other areas of the brain [135, 136]. It has trophic effects on the developing neurons before synapse formation like proliferation, migration, and maturation. It causes an increase in the proliferation of neural progenitor cells [NPC]. The NPCs express NMDA metabotropic glutamate receptors, stimulation of which caused increased intracellular calcium and activation of NeuroD1, proneural gene [137]. Glutamate signalling plays a positive role in maintaining the proliferation of NPCs and the survival rates of newborn neurons [137, 138].

Gamma-aminobutyric acid [GABA] is a principal inhibitory neurotransmitter in the CNS. It is produced from glutamate by the action of the enzymes glutamate decarboxylase GAD65 and GAD67 [139]. Dysfunction in the GABAergic system is implicated in major depressive disorder and anxiety [140]. However, in the developing brain, GABA exerts an excitatory effect, that is, GABA is excitatory in immature neurons. Tonic discharge from GABAergic neurons is necessary for maintaining the quiescent state of NPCs. The absence of GABAergic excitability will cause impairment in neuronal maturation and synapse formation while an excess of it over newborn neurons will lead to seizures [141]. In SGZ, GABA mediates depolarisation of progenitor cells which is involved in the incorporation of AMPA receptors in immature granule cells, which is critical for learning and formation of memory [142]. It has a negative influence on neuroblasts. It inhibits the proliferation and migration of neuroblasts. It also inhibits the proliferation of NPCs [143–145]. It also promotes the differentiation of hippocampal NPCs. GABAA receptor agonist, phenobarbital caused a reduction in NPC proliferation and increase in differentiation which resulted in an increased number of newborn neurons [146]. Thus, it plays crucial role in different stages of adult neurogenesis. GABA and glutamate signalling play a major role in adult neurogenesis. Selective activation of the receptor subtypes of GABA and glutamate expressed in NPCs plays a pivotal role in self-replication and fate commitment of the developing neurons into a particular progeny [147].

A recent study has found ACE2 to be located mainly in excitatory neurons of the brain and to a lesser extent in inhibitory neurons like GABAergic neurons [148]. This indicates that SARS-CoV-2 once enters the brain has the potential to access the glutamatergic and GABAergic neurons. The consequence of this is not known however, viral entry may trigger apoptotic pathways and cause excitatory-inhibitory imbalance, and lead to neuronal death [149]. Cytokine release from infected neurons and other activated microglia and astrocytes may also cause a decrease in glutamate and GABA [150]. These effects are implicated along with impaired adult neurogenesis in neurodegenerative diseases like Parkinson's disease and Alzheimer's disease. Seizure is one of the neurological symptoms in COVID-19 patients, in which an increase in glutamate levels and decrease in GABA levels in the cerebral cortex and hippocampus is an implicated mechanism [151]. This further emphasises the possible impact of SARS-CoV-2 on glutamate and GABA.

Thus, SARS-CoV-2 induced downregulation of ACE2 in COVID-19 is potentially detrimental to adult neurogenesis. ACE2 deficiency affects the levels and actions of the neurotransmitters serotonin, dopamine, norepinephrine, GABA, and glutamate which play crucial roles in adult neurogenesis.

10. Conclusion

SARS-CoV-2 has been found to have a high affinity to ACE2 receptors. Such high affinity has been linked to affect neurogenesis through a variety of mechanisms. The present chapter has clearly postulated the link between this deadly virus and its effect on monoaminergic neurotransmitters as well as GABA and glutamate which play a major role in adult neurogenesis. As ACE2 receptors are expressed in the hippocampus, decreased neurogenesis in this region could be one of the major factors behind the neuropsychiatric disorders associated with patients affected with COVID-19. Awareness and early intervention to prevent and treat long-term psychiatric consequences of COVID-19 are crucial. We should be aware of the possibility that in the long term, COVID-19 may be associated with cognitive and psychiatric disorders in those who recovered. Despite having a mild course of disease in children and adolescents, immunological response to the infection in this population may affect synaptic pruning which may lead to various issues that may not be immediately apparent. Insights into the various machinations of adult neurogenesis in COVID-19 can be used to engineer the process to help with the pathological changes in the brain inflicted by the disease.

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