Review Article

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Journal of Neurology and Neuroscience
ISSN 2171-6625

2021
Vol.12 No.4:366

The Potential Therapeutic Value of BDNF-TrkB Pathway in COVID-19 Associated Stroke

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Citation: Andhavarapu S, Bryant J, Gerzanich V, Simard MJ, Makar TK (2021) The Potential Therapeutic Value of BDNF-TrkB Pathway in COVID-19 Associated Stroke. J Neurol Neurosci Vol.12 No.4:366

Abstract

Infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared the coronavirus disease 2019 (COVID-19) pandemic by the World Health Organization (WHO) on March 11th, 2020. While most symptoms are those associated with the respiratory system, common symptoms also involve the nervous system. Stroke is a common complication of COVID-19, and it has been stated that future research should investigate the underlying mechanisms of COVID-19 associated thrombosis in order to develop preventative strategies for complications such as ischemic stroke. This is likely because SARS-CoV-2 binds to the angiotensin converting enzyme 2 (ACE2) receptor, and decreased activity of ACE2 promotes risk of stroke by causing an imbalance of the renin-angiotensin system. ACE2 is an enzyme that plays a role in the release of neurotrophic factors such as brain derived neurotrophic factor (BDNF), which plays a critical role in neurogenesis, cognitive function, and neurodevelopment. Earlier, it has been reported that the BDNF-TrkB system is neuroprotective during stroke. BDNF-TrkB signalling acts as a mediator of the renin-angiotensin system in the brain, and this regulatory effect may be disturbed during COVID-19 infection. This review consolidates the existing literature on the extensive role of the renin-angiotensin system and angiogenesis in COVID-19 and stroke with a focus on the BDNF-TrkB pathway. We hypothesize that the risk for stroke is higher in COVID-19 patients due to inhibition of BDNF that results from the downregulation of the ACE2 receptor during infection of SARS-CoV-2. In parallel, this review suggests that BDNF therapy may reduce the risk of stroke events and/or aid post-stroke recovery in COVID-19 patients.

Keywords: BDNF-TrkB pathway; COVID-19; WHO; Stroke; Renin-angiotensin system

Received: March 03, 2021; **Accepted:** April 22, 2021; **Published:** April 29, 2021

Introduction

Infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared the coronavirus disease 2019 (COVID-19) pandemic by the World Health Organization (WHO) on March 11th, 2020 [1]. Emerging in December 2019 in Wuhan City, China, the virus spread rapidly across the world and posed a threat to global public health [2]. Like the other known corona viruses such as SARS-CoV and the Middle East respiratory syndrome (MERS), SARS-CoV-2 most commonly affects the respiratory system, but is more virulent and has a steep mortality rate of 4-12% [2,3]. The most common symptoms are respiratory and include fever, chills, cough, sputum production, shortness of breath, sore throat, nausea or vomiting, and nasal congestion [4]. Other common symptoms, however, include the nervous system such as headache, nausea, vomiting, dizziness, myalgia, and fatigue, which suggest central nervous system (CNS) infection [5]. Other neurological COVID-19 sequelae are more severe such as encephalitis, demyelination (myelitis and encephalomyelitis); encephalopathy, seizures, polyradiculopathy, and cerebrovascular manifestations [6]. **Figure 1** summarizes the possible mechanisms underlying CNS involvement of SARS-CoV-2 infection. It is suggested that the likelihood of neurologic involvement and infection of the 2019 coronavirus is greater than prior coronaviruses [7]. Mao et al. conducted a retrospective case series of 214 patients with COVID-19 and found that a total of 36.4% of patients presented neurologic symptoms, suggesting that neurologic manifestations should be a greater area of focus

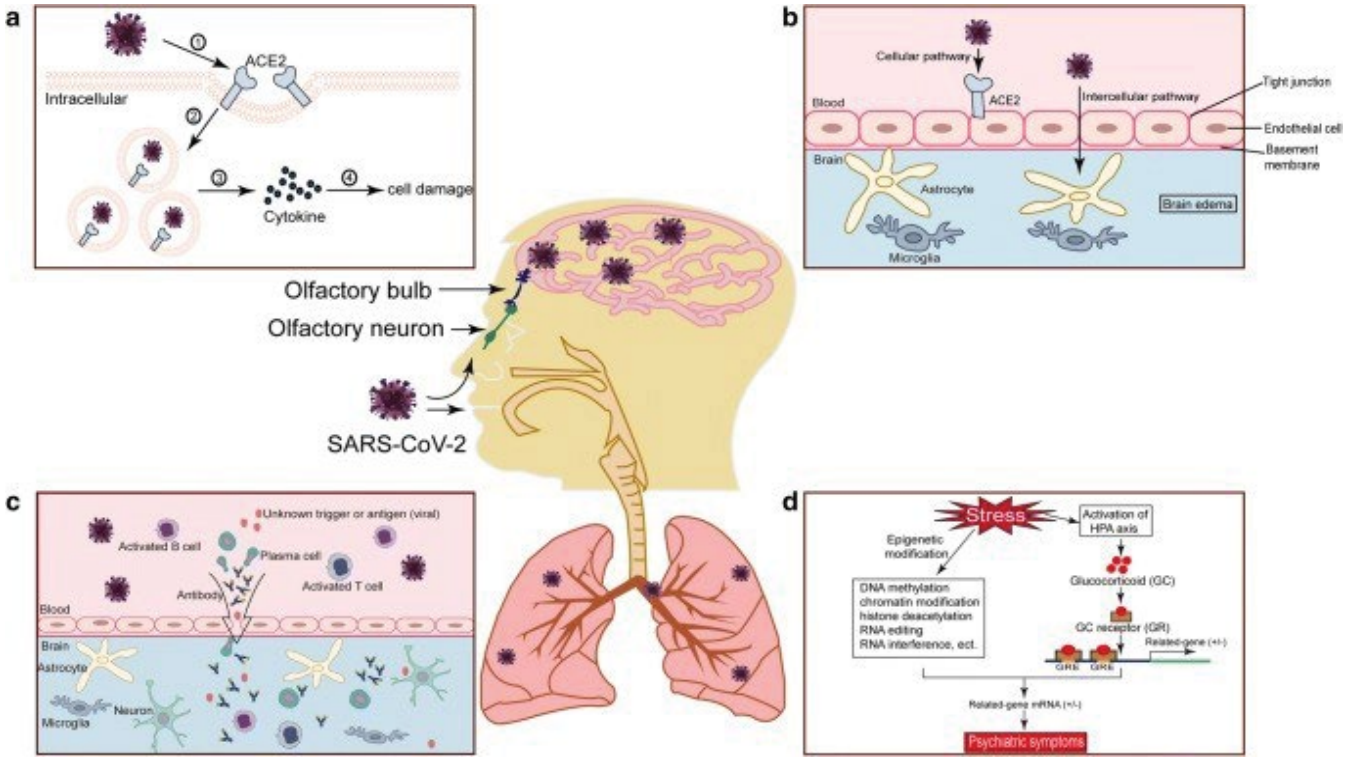

Figure 1 Possible mechanisms of SARS-CoV-2 infection-related CNS symptoms. (A) SARS-CoV-2 may enter the brain through the olfactory nerve endings and directly infect neurons via ACE2 protein on the surface of neurons. Axonal transport may promote the rapid spread of neurons to neurons. Also, cytokines secreted from infected neurons damage nearby neurons and glial cells. (B) SARS-CoV-2 may enter the blood vessels through mucosa and infected lungs. SARS-CoV-2 binds to ACE2 protein that is abundantly expressed in endothelial cells, disrupting endothelial cells and the blood-brain barrier and leading to cerebral edema and intracranial hypertension. (C) After SARS-CoV-2 infection, human immune cells produce antibodies against this coronavirus; however, some autoantibodies also attack endothelial cells of the vessels and neurons, resulting in autoimmune encephalitis. (D) Stress caused by panic or SARS-CoV-2 infection causes the release of corticotropin-releasing hormone (CRF) as well as the activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the over-activation of the HPA axis effectors glucocorticoids and GR and exhibit different behaviors. At the same time, environmental stress causes epigenetic modification changes on stress-related genes and leads to abnormal gene expression. Therefore, environmental stress from COVID-19 pandemic can cause psychiatric conditions such as depression, anxiety, psychiatric symptoms, or posttraumatic stress disorder (PTSD).

in COVID-19 research [6]. Most patients with such symptoms had cases of acute cerebrovascular diseases which was indicative of poor prognosis; viral encephalitis, meningoencephalitis, ischemic stroke, and hemorrhagic stroke are all neurological diseases that can be caused by infection of COVID-19 [6,8].

Stroke is often classified into two types: haemorrhagic stroke is defined as the rupturing of a cerebral blood vessel, and ischaemic stroke is caused by the blockage of a blood vessel within the brain [9]. During ischaemia, the brain tissue is starved of oxygen and glucose, leading to pathophysiological events characterized by inflammation, oxidative stress, and ionic dysregulation [10].

Literature Review

Various case series have suggested that stroke is an emerging complication of COVID-19 [6,11,12], and that future research should investigate the underlying mechanisms of COVID-19 associated thrombosis in order to develop preventative strategies for complications such as ischemic stroke [13]. This review consolidates the existing literature on the extensive role of the renin-angiotensin system and angiogenesis in COVID-19 and stroke. An emphasis of this review is the role of brain derived neurotrophic factor (BDNF) in the renin-angiotensin system and angiogenesis in relation to both COVID-19 and stroke pathologies. Extensive research has supported the potential therapeutic value of BDNF or its mimetics for the treatment of acute brain injuries including stroke. This review provides future directions for therapies that can prevent stroke events and/or aid post-stroke recovery in COVID-19 patients.

The renin-angiotensin system and angiogenesis in brain

The renin-angiotensin system (RAS) is a peptide hormone system integral in maintaining water and electrolyte balance, blood pressure and cardiovascular homeostasis, and systemic vascular resistance [14]. Chronic activation of the RAS can lead to

oxidative stress, endothelial dysfunction and inflammation [15]. The RAS includes angiotensin (AGT), renin, angiotensin I (Ang I), angiotensin II (Ang II), ACE, ACE2, angiotensin type-1 receptor (AT1R), angiotensin type-2 receptor (AT2R), and the MAS receptor. Renin, which is released when there is a drop in blood volume or blood pressure, hydrolyses circulating angiotensinogen to produce Ang I. Ang I is then converted to Ang II, which plays an important role in vasoconstriction and pro-inflammation by stimulating AT1R and AT2R [16]. This mechanism is considered the classical axis. The alternative axis involves ACE2, a RAS peptidase that is key in maintaining the system's homeostasis by acting as a negative regulator [17]. Ang II is degraded by ACE2 and converted into the vasodialiatic and anti-proliferative Ang 1-7 to counteract the activity of ACE. The components of the classical axis are present in the parenchyma of the brain, and with findings showing the presence of ACE2 in neurons, astrocytes, and in the cerebrovasculature, it is now also suggested that the alternative axis is also present in the brain [18] **(Figure 2)**.

Angiogenesis is a life-long process describing the production of blood vessels from pre-existing vasculature [19]. Over the last few decades, research has focused a great deal on the therapeutic potential of controlling angiogenic processes in a variety of diseases including ischemic heart disease [19]. Angiogenesis in the brain is highly regulated by various growth factors derived from the neuroectoderm which bind to endothelial tyrosine kinase receptors. A pathological hallmark of various brain disorders is the triggering of angiogenesis, which results from neurovascular remodeling. This characteristic is emerging to be a promising biomarker for indicating disease severity and progression [20]. Some major growth factors that play a role in angiogenesis are the vascular endothelial growth factor (VEGF) and BDNF. While inhibiting angiogenesis may hold therapeutic potential in cancerous diseases, pro-angiogenic therapies may be effective in stroke patients [21].

Previously, it has been proposed that the RAS may be an important

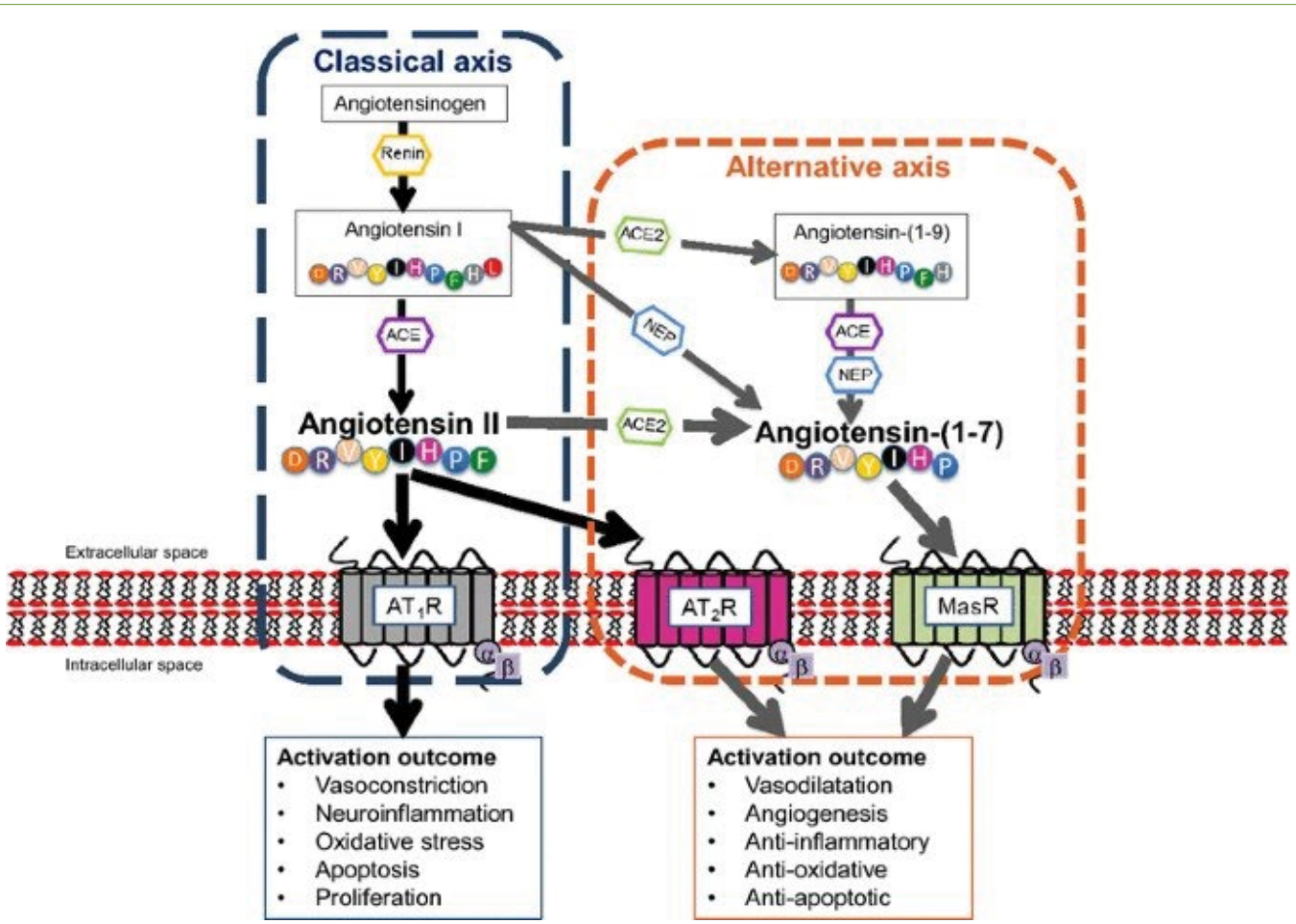

Figure 2 Simplified overview of the renin angiotensin system (RAS). Angiotensinogen is cleaved by renin generating Angiotensin I (Ang I) which is then formed into Angiotensin II (Ang II) via the actions of angiotensin converting enzyme (ACE). Ang II preferentially binds to Angiotensin II type I receptor (AT1R) ('classical axis') inducing vasoconstriction, inflammation, oxidative stress, apoptosis and cell proliferation. Ang II can also activate the Angiotensin II type II (AT2R) and is metabolised by angiotensin converting enzyme 2 (ACE2) to generate Angiotensin-(1-7). Ang-(1-7) activates the Mas receptor (MasR). Ang-(1-7) can be formed by the actions of ACE or neprilysin (NEP) on Angiotensin-(1-9) or Angiotensin I. AT2R and ACE2/Ang-(1-7)/MasR form the 'alternative axis' and its activation is thought to counteract the detrimental effects induced by AT1R by leading to vasodilation, angiogenesis and preventing inflammation, oxidative stress and apoptosis.

regulator of developmental and pathologic angiogenesis. VEGF is known to be the primary stimulator for the pro-angiogenic activity of Ang II, which is mediated by AT1R stimulation. These effects may also be due in part to greater expression of pro-angiogenic transcription factors and the activation of epidermal growth factor receptor (EGFR). AT2R, on the other hand, inhibits angiogenesis [22]. There is also extensive evidence surrounding the proangiogenic abilities of upstream peptidases that play a role in cleaving angiotensin II into smaller, functionally active proteins [23]. For example, membrane-associated protease aminopeptidase A (APA) is a cell surface constituent that is responsible for cleaving the NH2-terminal aspartate residue of the 8–amino acid angiotensin molecule to the 7–amino acid angiotensin III, which typically also binds to angiotensin type I and type II receptors. Angiotensin III is also functionally very similar to angiotensin II [24]. It's been found that APA is important in the angiogenic response in murine models of tumor pathologies [25], and that inhibiting APA activity inhibits tumor angiogenesis [26,27], suggesting that angiotensin III also holds proangiogenic activity.

ACE2, the renin-angiotensin system, and angiogenesis in COVID-19

Both *in vitro* and *in vivo* studies have demonstrated that ACE2 is a functional receptor for SARS-CoV-2 invasion [28,29], and ACE2 expression is directly associated with degree of infectivity [30]. It has been suggested that endogenous Ang II can prevent COVID-19 infection, as it competes with the virus to bind to ACE2 by binding to ATR1 and causing internalization of the ACE2 receptor [31,32]. In turn, ACE2 is destroyed via AT1R initiated ubiquitination and entry of lysosomes [33]. During infection, the S glycoprotein on the surface of the virus binds to ACE2 with the help of cellular protease TMPRSS2, resulting in the downregulation of ACE2 [34]. Due to the reduced ACE2, Ang II is formed at higher rates by ACE, activating the classical RAS axis. This over-activation of the classical RAS pathway can lead to lower vasodilation, angiogenesis, anti-inflammatory, anti-apoptotic, and antioxidant resources [34-36]. **Figure 3** briefly describes the RAS in the context of COVID-19 infection.

ACE2 is heavily expressed in the heart, kidneys, and testes and moderately expressed in the lungs, liver, intestine, and brain [17]. Hamming et al showed that ACE2 is also expressed in the CNS on the neuronal cell membrane, which is likely the mechanism of neurological symptoms and injury caused by SARS-CoV-2. The virus enters the neuron when the spike protein's S1 unit on the coronavirus surface attaches to the surface of target cells by binding to the neuronal ACE2 receptor, resulting in the activation of the spike protein via serine protease TMPRSS2 [37]. Another pattern of CNS invasion that was identified in prior corona viruses is the disruption of the blood-brain-barrier (BBB); SARS-CoV-2 can attack endothelial cells in cerebral blood vessels, which highly express ACE2, resulting in intracranial hypertension, cerebral edema, and increased BBB permeability [4,38,39].

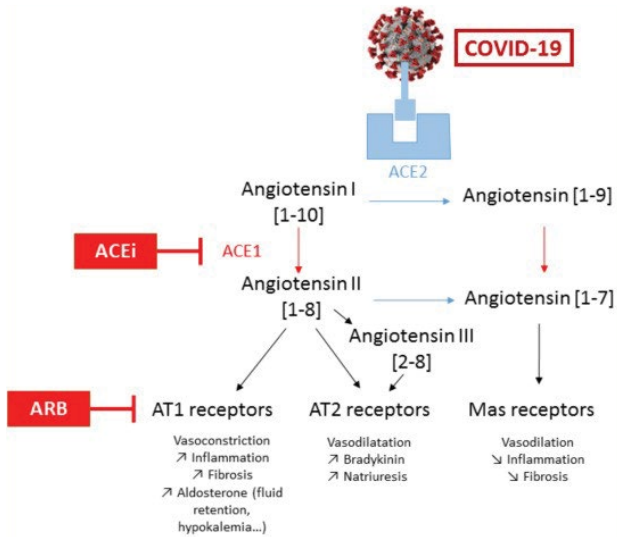

Figure 3 General view of the renin-angiotensin-aldosterone system in the context of COVID-19 infection. ACE1: angiotensin-converting enzyme 1; ACE2: angiotensin-converting enzyme 2; ARB: angiotensin II receptor blocker; ACEi: angiotensin-converting enzyme inhibitor.

One study comparing the lungs of patients who died from COVID-19 with the lungs of patients who died from acute respiratory distress syndrome found that the COVID-19 lungs presented more than 2.7 times as much new vessel growth predominantly via intrasucceptive angiogenesis than influenza lungs [40]. Moreover, one prospective study found that angiopoietin-2 was the best predictive biomarker for ICU admission and was also associated with lung injury in COVID-19 patients. Angiopoeitin-2 is a key player in the angiopoietin/tie-2 pathway, which regulates angiogenesis [41]. These findings suggest the role of pulmonary angiogenesis in COVID-19 pathology, perhaps a compensatory mechanism.

The renin-angiotensin system and angiogenesis in stroke

It is thought that over-activation of the classical RAS axis, which can lead to pro-inflammatory activity, vasoconstriction, and angiogenesis, plays a role in the pathogenesis of acute ischemic stroke (IS) [28]. It has been found that mice overexpressing renin and angiotensinogen genes have larger infarcts that control mice, suggesting a direct association between AT2 and the severity of ischemic injury in an experimental model [42]. Moreover, the stimulation of the AT1 receptor has been found to increase ischemic brain damage, reduce cerebral blood flow, and enhance oxidative stress [43].

Conversely, the alternative RAS axis may be protective during IS by promoting anti-inflammatory activity, vasodilation, and antioxidant activity via the activation of the MAS receptor and AT2R, thus counteracting the classical RAS axis [44,45]. Various studies shed light on the protective effects of the alternative

RAS axis, including anti-hypertensive, anti-thrombosis, anti-atherosclerotic, neuroprotective, and improved angiogenesis effects [35]. The overexpression of ACE2 in endothelial progenitor cells and neuronal cells has been found to be neuroprotective in models of ischemic stroke [46,47]. Moreover, it has been found that Ang (1-7) is neuroprotective and anti-inflammatory in rodent models of ischemic stroke [48-50]. This evidence suggests the RAS imbalance during stroke pathology is a potential therapeutic target.

Studies with both animal models and human stroke patients have demonstrated that angiogenesis is strongly correlated with improved functional outcome after ischemic stroke [51-54]. In rodents, angiogenesis genes and proteins are immediately upregulated in ischemic areas [55]. In patients, those who had greater cerebral blood vessel density had higher survival rates and improved recovery [56]. During this proangiogenic state, numerous growth factors including BDNF and VEGF play a role in the recovery process by accentuating angiogenesis [57-59]. These growth factors also aid in the survival of neuronal, endothelial, and glial cells in the insulted area [60]. Given this, research has investigated how dynamically altering these factors may have therapeutic value in stroke patients. For example, administering VEGF within 5 minutes of reoxygenation in a rat model of hypoxic ischemia reduced brain injury [61]. In addition to neurotrophic factors, angiogenic factors including angiopoietins and thrombospondins are also upregulated in ischemia [62,63].

COVID-19 associated stroke

Recent reports have suggested that COVID-19, although primarily a respiratory illness, can also lead to hypercoagulability and thrombotic complications [64-66]. Various case series have suggested that stroke is an emerging complication of COVID-19 [6,11,12]. For example, in the study conducted by Mao et al., 5.7% of severe COVID-19 patients had a stroke [6]. Moreover, one retrospective cohort study of 2132 COVID-19 patients found that the incidence of ischemic stroke in COVID-19 was approximately 1.5%, which is 7.5 times higher the incidence in influenza patients, which was used as the comparison group for what is generally expected from viral respiratory infections [13]. The authors of this study also concluded that future research should focus on the exact mechanisms of COVID-19 associated thrombosis to develop preventative strategies for complications such as ischemic stroke [13].

SARS-CoV-2 induces down regulation of ACE2 through receptor endocytosis, which can over-activate the classical RAS axis and, in turn, under-activate the alternative RAS signalling in the brain. With reduced expression of ACE2, ACE1 is not regulated and uncontrolledly generates Ang II. This tips the RAS balance in favor of the pathological characteristics that contribute to stroke pathophysiology [67]. COVID-19 induced inflammation and hypoxemia may also contribute to the pathogenesis of ischemic stroke [68].

Administration of human recombinant soluble ACE2 is a promising treatment for targeted COVID-19 therapy and has been deemed safe in a pilot clinical trial in ARDS [69,70]. Recombinant ACE2 works by preventing SARS-CoV-2 induced ACE2 depletion and competing with the virus' S protein for binding to ACE2 in the lungs and endothelial cells. Virus-mediated depletion of ACE2 in neurons and brain endothelium increases the susceptibility of acute stroke in COVID-19 patients, and recombinant ACE2 may mitigate this. Angiotensin (1-7) is another treatment that targets the RAS and is in clinical trial right now. Other recommended treatments include AT1R blockers and ACE inhibitors [67].

Brain Derived Neurotrophic Factor (BDNF)

BDNF is a member of the neurotrophin family, which includes secreted proteins that play important roles in the growth, differentiation, survival, and recovery of the nervous system such as nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and VEGF [71]. Neurotrophins bind to primarily two receptors: high-affinity tyrosine kinase receptors (Trks) and low-affinity p75NTR.

Subsequently, homodimers are formed and autophosphorylation induces downstream signalling cascades throughout the cell [71].

BDNF specifically is a ligand of the Tropomyosin-receptor-kinase B (TrkB) receptor and is essential in maintaining normal cognitive function, neuronal modulation of dendritic branching and spines in the cortex, long-term potentiation in the hippocampus, synaptic plasticity, and neurite outgrowth [72,73]. BDNF is highly expressed in the CNS as well as the liver and kidney [74]. Several studies have reported BDNF's neuroprotective properties and effects during both chronic neurodegenerative diseases and acute neurological injuries. In parallel, several neurological diseases are also associated with lower levels of BDNF or BDNF dysfunction [75-78]. These characteristics are derived the phosphatidylinositol 3-kinase (PI3K)/Akt and the mitogen activated protein kinase/extracellular- signal-regulated kinase (MAPK/ERK) pathways, both of which are downstream signalling pathways downstream of TrkB activation [79].

BDNF regulation of the renin-angiotensin system and angiogenesis in the brain

Previously, it has been shown that Ang II significantly stimulates the expression of BDNF in the human and rat adrenocortical cells [80]. RAS activity that is associated with progressing hypertension can be regulated by BDNF; BDNF is a mediator of blood pressure (BP) responses to central Ang II activity, and has the ability to increase hypothalamus blood pressure by modulating angiotensin signalling [81-84].

Increased BDNF production is characteristic of the neuroprotective effects associated with AT1R blockers and AT2R agonists [85,86]. In microglia, BDNF downregulates ROS and proinflammatory cytokine production and polarizes these cells towards the M2 phenotype, resulting in further inducement of microglial-derived BDNF, majority of which is produced by M2 microglial that also expresses AT2R [87]. In primary neurons, Namsolleck et al shed light on AT2's role in neuronal differentiation, and that AT2 increases BDNF and TrkB mRNA levels [88,89]. In astrocytes too, astrogliosis is suppressed by BDNF release mediated by AT2R, suggesting that increasing BDNF production by modulating the RAS to target cognitive impairment by inducing antioxidant and

antiinflammatory effects as well as promoting cell survival is promising [89]. An example of an AT1R blocker is candesartan, which has been shown to ameliorate cognitive impairment. Candesartan enhances angiogenesis in the brain in part due to increased expression of BDNF and TrkB, and knocking down BDNF reverses these beneficial effects [85,86,90]. It must also be noted that ACE2 deficiency is associated with a decrease in BDNF [91].

BDNF has also recently emerged as a mediator of angiogenesis. Using a femoral artery ligation model, Kermani et al. found that exogenous delivery of BDNF to ischemic tissue significantly promoted angiogenesis, indicated by improved blood flow recovery and capillary density [92]. In fact, these effects were comparable to the effects of VEGF and were mediated by TrkB. Moreover, exogenous BDNF delivery also resulted in the recruitment of TrkB expressing CD11b+ myeloid cells and Sca-1+ hematopoietic cells, indicating two distinctive angiogenic mechanisms [93]. Another study found that mice with a mutant variant of BDNF after cerebral ischemia exhibited impaired angiogenic activity, resulting in a worsened outcome in comparison to wild type mice with cerebral ischemia [94].

Therapeutic potential of BDNF in stroke comorbidities

Extensive research has provided evidence for the neuroprotective effects of BDNF in various neurological disorders, and recent research has also shed light on its potential for therapies to treat stroke. High risk and poor recovery for stroke have been linked with low levels of circulating BDNF, and stroke treatments which alter BDNF levels have been proven to have clinically positive outcomes [95]. One prospective study using a community-based sample to assess the association of serum BDNF and the risk of clinical stroke or subclinical vascular brain injury found that lower serum BDNF levels is associated with increased risk of incident stroke [96]. BDNF activates the TrkB receptors, and in turn, activates downstream PI3K/Akt and MAPK/ERK pathways. During stroke, neuronal apoptosis is a key contributor to neuronal cell death and brain damage, and it has been shown that increased BDNF expression and the BDNF-TrkB-ERK pathway can protect neuronal cells from apoptosis, injury, and ischemia in the rat model of middle cerebral artery occlusion (MCAO) [97-102]. There also exists literature supporting the role of BDNF-TrkB signalling in the protection of ischemic neurons from ferroptosis and necroptosis, both of which are cell death types that participate in stroke pathology [103-106].

Evidence also suggests that the BDNF -TrkB signaling pathway can promote neurogenesis and neurite outgrowth, functional recovery, and neuroplasticity during post-stroke rehabilitation [95]. Neurite outgrowth and neurogenesis are essential for post-injury brain regeneration [107,108], and it was found that these processes are facilitated via the BDNF-TrkB pathway in the rat MCAO model as well as cortical cell cultures [109,110]. Research has also suggested that testosterone, which has been proven to exert beneficial effects during treatment of stroke, promotes neurogenesis, neurite outgrowth, and even functional recovery by activating the BDNF-TrkB pathway and upregulating BDNF in the serum and brain [111]. During post-stroke rehabilitation, functional recovery is a critical endpoint in both preclinical models and clinical trials, and BDNF levels have been positively correlated with functional recovery. In both the rat MCAO model and an intracerebral hemorrhage mouse model, intracerebral transplantation of

BDNF-overexpressing human mesenchymal stem cells promoted functional recovery [112,113]. In the photothrombotic ischemia model, daily intravenous applications of BDNF during just the first 5 days improved sensorimotor recovery and stimulated neurogenesis [108].

Erythropoietin (EPO) is a cytokine that has been found to be neuroprotective in ischemia and brain injury models by reducing neuronal apoptosis and inflammatory cytokines while increasing neurogenesis and angiogenesis. One study investigating the administration of recombinant human EPO (rhEPO) in the post-ischemic rat MCAO model found that rhEPO increased the levels of BDNF and the density of cerebral microvessels in the brain [114]. Moreover, one study found that the long-term recovery mediated by AT1R blockers is associated with BDNF. Candesartan is an AT1R blocker that has been shown to promote recovery in stroke models [85]. Interestingly, the study found that candesartan induced a pro-angiogenic effect via a BDNF dependent manner, and knocking down BDNF diminished the angiogenic effect [86,115]. These findings suggest the role of BDNF in promoting angiogenesis during post-stroke rehabilitation.

While BDNF has many neuroprotective properties, it has many limitations when being considered as a potential therapeutic agent. BDNF has a short serum half-life, large molecular size, and poor blood-brain barrier (BBB) penetration [116]. Moreover, diffusion of BDNF into the parenchyma of the targeted tissues is not possible during intracranial administration due to its physical "stickiness". Finally, the manufacturing process for BDNF is expensive and limited to an extent by current technology [117]. Therefore, over the recent years, several alternatives such as improved delivery methods and TrkB agonists have emerged.

Previous studies have demonstrated that the genetic modification of BDNF improved the longevity and specificity of its delivery in stroke models [118-120]. Another study conducted by Harris et al. found that the intravenous administration of a nanoparticle polyion complex formulation of BDNF improved brain uptake and reduced tissue loss [121]. The development of new TrkB agonists has especially been found to be promising in mimicking the function of BDNF for treatment of stroke. 7,8-DHF is an orally bioavailable small molecule that has a high affinity tropomyosin receptor kinase B (TrkB) agonist [122]. 7,8-DHF has been extensively studied in a variety of neurodegenerative diseases such including Alzheimer's disease [123], traumatic brain injury [124], Parkinson's disease [125], multiple sclerosis [126], and stroke [109,127]. It has been demonstrated that this compound induces the phosphorylation of TrkB and in turn activates the downstream signalling pathways Akt and ERK [128]. **Figure 4** summarizes the various methods to enhance the activation of the TrkB receptor and how it may mediate stroke recovery.

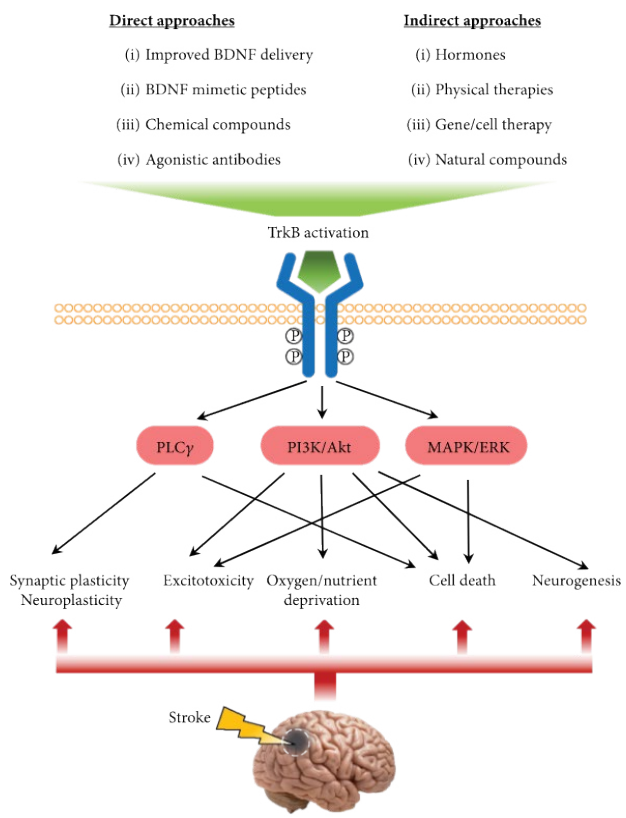

Figure 4 Summary of approaches to enhance TrkB activation and their effect on stroke treatment and recovery. Multiple strategies could be utilized to activate the TrkB receptor to serve in the treatment and recovery of stroke comorbidities. Direct approaches include the modification and improvement of BDNF for better delivery and the development of BDNF mimetic peptides, small molecule compounds, and specific agonistic antibodies. Indirect approaches include hormones, physical therapies, and natural compounds that can stimulate the endogenous expression of BDNF and gene/cell therapy to overexpress BDNF. TrkB receptor activation directly triggers and stimulates downstream signaling cascades, which subsequently protect neuronal cells and facilitate post stroke brain recovery. While the PLCγ pathway has been suggested to play a role in neuroplasticity and in cell death, the PI3K/Akt and MAPK/ERK pathways mainly protect neurons from excitotoxicity and cell death, chiefly apoptosis. The PI3K/Akt signaling is also reported to support neuronal survival under oxygen/nutrient deprivation and to contribute to neurogenesis during rehabilitation.

BDNF levels during COVID-19 infection

In one study, the serum samples of several patients with mild, moderate, or severe SARS-CoV-2 infection were obtained upon hospital admission and periodically during hospitalization [129]. A correlation between low serum BDNF levels and the severity of SARS-CoV-2 infection was discovered, and during the recovery stage for these patients, BDNF levels were restored. Moreover, the researchers observed an inverse relationship between BDNF levels and ferritin levels. This is important because acute phase reactants such as ferritin have previously been established to be elevated in severe COVID-19 patients [130-132]. These findings suggest that serum BDNF may be used as a disease severity biomarker and low BDNF may be involved with the neurological involvement of the virus and perhaps the increased risk for stroke events in COVID-19 patients.

Potential therapeutic value of BDNF in COVID-19 associated stroke

As suggested by various case series, stroke is an emerging complication of SARS-CoV-2 infection. SARS-CoV-2 downregulates the expression of the ACE2 receptor, which, by reactivating the classical RAS axis and under-activating the alternative RAS axis, contributes to the risk of incurring stroke.

Conclusion and Future Directions

Previously, ACE2 deficiency has been correlated with low levels of BDNF in the brain. This correlates with the recent finding that COVID-19 disease severity is directly associated with levels of serum BDNF. Given that higher risk of stroke is associated with low levels of circulating BDNF, it is possible that COVID-19-associated stroke may be due in part to decreased BDNF. Future research should investigate whether activation of the BDNF-TrkB pathway in animal models of COVID-19 can ameliorate the neurological complications and perhaps reduce the risk of stroke. Given that BDNF acts as a regulator of the RAS and angiogenic activity, both of which play a key role in the pathogenesis of COVID-19 and stroke, an emphasis of this research should lie on how BDNF affects these processes during COVID-19 associated stroke. By doing so, we can seek to understand the potential of the BDNF-TrkB pathway as a preventative or recovery treatment for COVID-19 associated stroke.

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