




# COVID-19-induced neurological symptoms: focus on the role of metal ions

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Received: 16 February 2023 / Accepted: 23 February 2023 / Published online: 9 March 2023  
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## Abstract

Neurological symptoms are prevalent in both the acute and post-acute phases of coronavirus disease 2019 (COVID-19), and they are becoming a major concern for the prognosis of COVID-19 patients. Accumulation evidence has suggested that metal ion disorders occur in the central nervous system (CNS) of COVID-19 patients. Metal ions participate in the development, metabolism, redox and neurotransmitter transmission in the CNS and are tightly regulated by metal ion channels. COVID-19 infection causes neurological metal disorders and metal ion channels abnormal switching, subsequently resulting in neuroinflammation, oxidative stress, excitotoxicity, neuronal cell death, and eventually eliciting a series of COVID-19-induced neurological symptoms. Therefore, metal homeostasis-related signaling pathways are emerging as promising therapeutic targets for mitigating COVID-19-induced neurological symptoms. This review provides a summary for the latest advances in research related to the physiological and pathophysiological functions of metal ions and metal ion channels, as well as their role in COVID-19-induced neurological symptoms. In addition, currently available modulators of metal ions and their channels are also discussed. Collectively, the current work offers a few recommendations according to published reports and in-depth reflections to ameliorate COVID-19-induced neurological symptoms. Further studies need to focus on the crosstalk and interactions between different metal ions and their channels. Simultaneous pharmacological intervention of two or more metal signaling pathway disorders may provide clinical advantages in treating COVID-19-induced neurological symptoms.

**Keywords** Metal ions · Metal ion channels · SARS-CoV-2 · COVID-19-induced neurological symptoms · Neuroinflammation

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified for the first time in December 2019, which was responsible for the devastating infection of 2019 coronavirus disease (COVID-19) pandemic (Zhu et al. 2020). Early studies have focused on the respiratory system of COVID-19 patients, whose pulmonary symptoms have been well described (Guan and Zhong 2020; Huang et al. 2020). However, emerging evidence suggests that patients with COVID-19 have neurological symptoms and complications as well (Ellul et al. 2020; Helms et al. 2020; Jaywant et al. 2021; Méndez et al. 2022). Thus, understanding the mechanisms underlying COVID-19 neuropathology is critical for preventing neurological complications for COVID-19 patients.

Metal ions are widely distributed in the brain and play a pivotal role in the central nervous system (CNS) and neuronal function. It is well known that two types of metal

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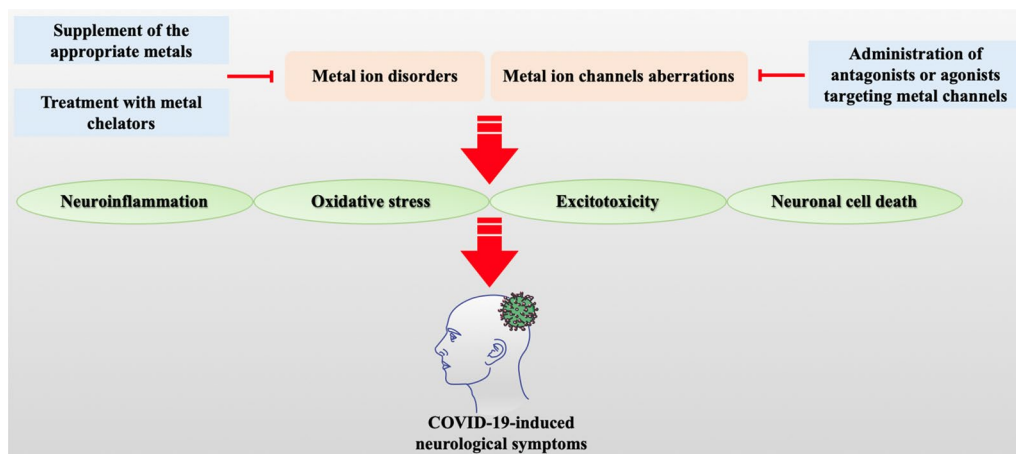
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ions are present in human: essential ions (such as sodium, potassium, calcium, iron and zinc) and nonessential ions (such as aluminum). Metal ions are involved in the development, metabolism, redox, and neurotransmitter delivery of the CNS with a strictly regulated metal absorption, efflux, distribution and storage (Black 1998; D'Ambrosi and Rossi 2015; Kauer and Gibson 2009; Masaldan et al. 2019; McDaid et al. 2020; Scheiber et al. 2014; Thirupathi and Chang 2019). In these processes, metal ions perform as the structural, catalytic, or regulatory ingredients of proteins including transcription factors, enzymes, transporter proteins and receptors. Because of their important functions, metal ions are enormously valuable to the brain. Lack of metals is associated with various degrees of damage to the CNS.

Although metals have physiological functions to the body, excessive amount of them are particularly neurotoxic to healthy nerve cells and tissues, which impairs nerve cell physiological activities and even causes cell death (Kawabata 2022; Sun et al. 2022). However, various pathological factors, such as SARS-CoV-2 infection and ischemia/hypoxia, may lead to excessive intake, uncontrolled release and metabolic disorders in metals, which are responsible for the pathogenesis of neurological symptoms due to COVID-19 infection and ischemic stroke (Alim et al. 2019; Almutairi et al. 2019; Danta 2020a; Pulido Perez et al. 2022; Vinceti et al. 2022). Therefore, metal homeostasis is important to neuro-homeostasis, which demands a precise balance among metal absorption, circulation, and storage.

Metal transport relies on various metal ion channels, which control the influx and efflux of metal ions. To date, diverse types of neurologically associated metal ion

channels have been identified including glutamate receptors, transient receptor potential (TRP) channels, iron transporter-related proteins and zinc transporters. Under physiological conditions, these channels keep a dynamic homeostasis to guarantee the functions of the CNS. Under pathological conditions (such as ischemia and hypoxia), transporter proteins are increased or decreased and become aberrantly activated or inactivated, causing metal overload or deficiency and affecting many cellular signaling. Generally, oxidative stress, neuroinflammation and excitotoxicity are well-established factors contributing to neurological disorders, and various studies have shown that abnormalities in transporter proteins usually cause and exacerbate neurological disorders (Denechaud et al. 2022; Wang et al. 2023; Zhang et al. 2022a). Considering the key roles of the metal ions and metal ion channels in neurological symptoms associated with COVID-19, big efforts are devoted to understand the regulatory mechanisms for transporter proteins and their correlation with intracellular metal homeostasis, especially to the downstream signaling pathways causing COVID-19-induced neurological symptoms. In this review, we summarized the latest studies regarding the metal ions, metal ion channels, and relevant pathogenesis in COVID-19-induced neurological symptoms. In addition, the strategies in targeting metal ions and their transport proteins are also discussed. Maintenance in metal homeostasis may illuminate potential novel therapeutic targets for COVID-19-induced neurological symptoms (Fig. 1).



**Fig. 1** Overview of this review article. In the case of SARS-CoV-2 infection, metal ion disorders and their channels aberrations induced neuroinflammation, oxidative stress, excitotoxicity and neuronal cell death, ultimately leading to a series of severe neurological symptoms.

Administration of metal ion modulators or their channel modulators restores the metal ion homeostasis, thereby ameliorating COVID-19-induced neurological symptoms

## Role of the major metal ions in the central nervous system

### Sodium (Na) and potassium (K)

The membrane translocation of metal ions is accountable for excitability and bioelectricity in nerves, muscles and other cells. Neurons are excitable cells whose physiological foundation is the transition between resting and action membrane potentials (Wicher et al. 2006). This transition is determined by the selective permeability of the plasma membrane to  $\text{Na}^+$  and  $\text{K}^+$  under different conditions (Khaliq and Raman 2006). In the condition of resting membrane potential, the plasma membrane is much more permeable to  $\text{K}^+$  than to  $\text{Na}^+$  in the excitable neurons, resulting in a resting membrane potential closer to the equilibrium potential of  $\text{K}^+$  ( $-90$  mV) than that of  $\text{Na}^+$  ( $+65$  mV) (Wang et al. 1994). Normally, the activity of the transporter  $\text{Na}^+/\text{K}^+$ -ATPase (also known as the  $\text{Na}^+$  pump) is critical for sustaining this asymmetric membrane translocation of  $\text{Na}^+$  and  $\text{K}^+$  (Scuri et al. 2007). Upon cells excitation, the plasma membrane at the axon hillock depolarizes with the assistance of opened voltage-gated  $\text{Na}^+$  channels. Gradually,  $\text{Na}^+$  returns to the cell, further depolarizing the membrane and eliciting an action potential in a positive feedback manner (Donnelly 2013). Once neurons are depolarized,  $\text{Na}^+$  channels are closed, accompanied by the opening of voltage-gated  $\text{K}^+$  channels, inducing repolarization (Chow and Leung 2020). As  $\text{K}^+$  flows out of the cell, the membrane potential declines and reverts to near resting potential. To achieve appropriate ion homeostasis,  $\text{Na}^+/\text{K}^+$ -ATPase performs a fundamental role in facilitating the efflux of three  $\text{Na}^+$  and the entry of two  $\text{K}^+$  into the cell by sacrificing the energy generated by the hydrolysis of one ATP molecule to provide energy for ion exchange and substance transport (Pivovarov et al. 2018). Thus, the  $\text{Na}^+/\text{K}^+$  gradient generated by  $\text{Na}^+/\text{K}^+$ -ATPase is the basis for trafficking of other ions, substrates and neurotransmitters between the intra- and extracellular compartments (Hernández 1992).

### Calcium (Ca)

$\text{Ca}^{2+}$  is an indispensable divalent cation that functions as a second messenger in modulating neurodevelopment, synaptic transmission, neuronal excitability, and neuronal morphology in the CNS (Chaudhuri et al. 2021; Lin et al. 2019). For instance,  $\text{Ca}^{2+}$  exerts a pivotal role in triggering long-term potentiation (LTP) and depression (LTD), as well as in synaptic information storage patterns that underlie memory formation and maintenance (Hell 2016;

Neveu and Zucker 1996).  $\text{Ca}^{2+}$  is also able to activate protein kinase including calpain and calcium/calmodulin-dependent protein kinase type II (CAMK II), to initiate downstream pathways (Coultrap et al. 2011; Tao et al. 2021). The wide variety of  $\text{Ca}^{2+}$  functions in the brain is only available when the gradient of  $\text{Ca}^{2+}$  concentrations tightly conserved in the cells (Dixon et al. 2022; Golovina et al. 1996). The concentration of  $\text{Ca}^{2+}$  in the cytoplasm is at least 10,000-fold lower compared to extracellular compartments and some intracellular compartments such as the endoplasmic reticulum (ER) and mitochondrion. This huge concentration gap is governed by mechanisms involving calcium channels, pumps, binding proteins, and other metal ions such as magnesium, which is considered to be a calcium antagonist (Yamanaka et al. 2019).

### Iron (Fe)

Iron, the most abundant essential element in humans, is widely spread in nearly all tissues and organs, such as the heart, liver, lungs, kidneys, spleen and brain. The absorption, circulation, storage, and regulation of iron cooperates intensively to uphold human iron homeostasis. Iron is present in several forms: functional iron that forms hemoglobin, myoglobin, enzymes, as well as functional proteins, and reserve iron in ferritin and hemosiderin (Thirupathi and Chang 2019). Being utilized by various key enzymes with its oxidation states and forming coordination bonds, iron is involved in the sustainment of normal physiological functions as an indispensable co-factor for proteins concerned with oxygen transport, cellular respiration, energy production, DNA synthesis and repair, as well as mitochondrial and immunological maintenance (Halcrow et al. 2021). Several studies have collectively confirmed that iron plays an important role in brain health due to iron-dependent enzymes and proteins, such as monoamine oxidase, tryptophan hydroxylase, and aldehyde oxidase, which are required for synapse development, myelination, and neurotransmitter transport (Bar-Am et al. 2015; Li et al. 2017; Specker et al. 2022). In addition, brain is energetically reliant on iron-dependent proteins associated with cellular respiration, as it consumes large amount of oxygen. Iron also exhibits strong redox activity and is frequently converted between divalent and trivalent states through reduction and oxidation by ferric reductase or Fenton reaction, respectively, to accommodate its absorption, transport and storage (Kapralov et al. 2020). For this reason, the distribution of iron in the brain is heterogeneous in time and space. The rate of iron accumulation in the brain varies during different stages of brain development and neurological disorders, which is coupled with oxidative stress, neuroinflammation, and cell death in the meantime (Feng et al. 2021b).

## Zinc (Zn)

Zinc is the second most abundant trace element after Fe in the brain and is localized in the hippocampus, amygdala, cerebral cortex, thalamus, and olfactory cortex. Zinc performs a major role in DNA synthesis, brain development and neurotransmission (Sun et al. 2022). Growing evidence suggests that aberrant zinc levels are involved in many devastating diseases. For example, zinc deficiency can lead to mental health problems, growth retardation and immune disorders, while excess zinc distorts lymphocytes state and inhibit copper uptake (Chen et al. 2021; Ogawa et al. 2018; Park et al. 2020). There are three main forms of zinc in humans: free zinc, vesicular zinc, and protein-bound zinc. Most prevalent zinc in the brain is free zinc or chelatable zinc (Maret 2015, 2019). The chelatable zinc is mainly conserved in the presynaptic vesicles of specific excitatory glutamatergic neurons and is excreted into synaptic clefts with glutamate during neuronal excitation (Carrillo et al. 2020; Lavoie et al. 2011). Upon reaching the postsynaptic membrane, the released  $Zn^{2+}$  pairs with diverse receptors, such as ionotropic glutamate receptors,  $\gamma$ -amino butyric acid (GABA) receptors, glycine receptors, and P2-type purinergic receptors, functioning as a second messenger in signal transduction, neurotransduction, and neurogeneration (Chuang and Reddy 2019; Kovács et al. 2018). Increasing evidence demonstrates that  $Zn^{2+}$  in synaptic clefts moderates dendritic function in an activity-dependent manner via N-methyl-D-aspartate receptors (NMDARs) (Krall et al. 2020). In parallel,  $Zn^{2+}$  regulates  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptor (AMPA) receptors with a negative feedback (Kalappa et al. 2015). It has also been reported that liberated  $Zn^{2+}$  diffuses to heterologous synapses for transmission spatio-temporal neural information and regulation of synaptic plasticity (Tlili et al. 2011; Vogler et al. 2020). These data suggest that strictly controlled levels of zinc are critical in neurodevelopment and neurometabolism.

## Copper (Cu)

Copper is the third most abundant trace element in the brain and it can be found in the thalamus, substantia nigra, striatum, and hippocampus. Copper is present in various redox enzymes such as cytochrome C oxidase (COX), Cu/Zn superoxide dismutase (Cu, Zn-SOD1), lysyl oxidase, uricase, dopamine hydroxylase and tyrosinase (Borisov and Forte 2021; Robinett et al. 2019). Possessing redox capability, copper facilitates the mitochondrial electron transport chain, neurotransmitter synthesis, myelination and clearance of reactive oxygen species (ROS) (Pezacki et al. 2022). The redox ability of copper is dependent on its capacity to operate as both electron “donor” and “acceptor”. Cuprous (Cu I) can redox into Cu II and Cu 0 through the single electron

transfer charge-disproportionation between the “donor” and “acceptor” (Hatori and Lutsenko 2016; Liang et al. 2022a). Upon combining with proteins to form ceruloplasmin, Cu also converts  $Fe^{2+}$  to  $Fe^{3+}$ , acting as a ferroxidase that contributes to Fe homeostasis (Hellman and Gitlin 2002). Another important function of copper is to serve as neurotransmitters (D'Ambrosi and Rossi 2015). Cu is also stored in presynaptic vesicles and released into synaptic clefts when a neuron is stimulated and subsequently connects to glutamate receptors and GABA receptors to modulate the neuronal excitability (D'Ambrosi and Rossi 2015; Tanaka and Kawahara 2017).

## Selenium (Se)

Selenium, an essential trace element, is the active center of several selenium-dependent enzymes such as glutathione peroxidase (1, 2 and 4), iodothyronine deiodinases, methionine-R-sulfoxide reductase, thioredoxin reductase, and selenoproteins (Alshammari et al. 2022). Therefore, selenium plays an important role in scavenging ROS, managing immunity, inhibiting inflammation, ferroptosis and endoplasmic reticulum (ER) stress (Genchi et al. 2023). Selenium and selenium-containing proteins contribute to the human defense system as potent antioxidants and serve an important biological role in human health.

In a word, metal homeostasis is a dynamic process that each metal ion in the body is inextricably relevant and impactful to each other. The roles of metal ions and their transport channels in the CNS are summarized in Table 1.

## Metal ion-related pathogenesis

### Neuroinflammation

Inflammation in the CNS, also termed neuroinflammation, is a vital segment of neurological pathology intended to repair brain injuries and restore brain homeostasis (Candelario-Jalil et al. 2022). However, excessive neuroinflammation inflicts destructive damage to the CNS (Hou et al. 2021). Mounting evidence highlights that COVID-19 causes a range of neurological symptoms by inducing neuroinflammation (Fig. 2), and the pathogenesis of stroke is also closely associated with neuroinflammation (Anthony et al. 2022; Beckman et al. 2022). In general, neuroinflammation is induced by the release of damage associated molecular patterns (DAMPs) from injured or dead cells. Later, free DAMPs in the form of adenosine, heat shock proteins (HSPs), high mobility group box 1 (HMGB1), and interleukin-1 $\alpha$  (IL-1 $\alpha$ ) are enrolled by associated immune cells that can induce various downstream signaling pathways (Liu et al. 2021; Villadiego et al. 2018; Zhang et al. 2022b). A number of immune cells, such



**Table 1** Roles of metal ions and their transport channels in the central nervous system

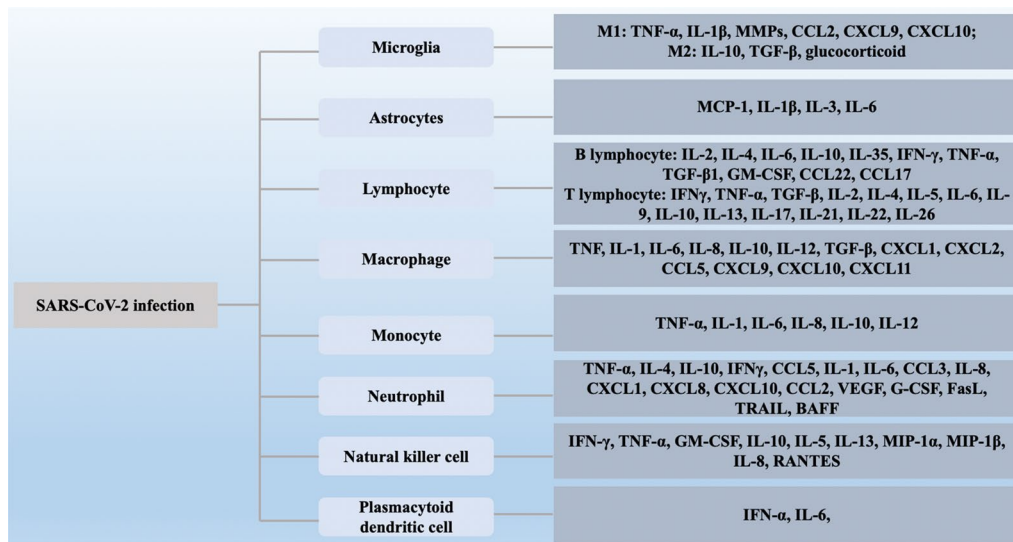
Metal ions	Metal transport channels	Physiological effects	References
Sodium (Na)	Voltage-gated Na <sup>+</sup> channels; Na <sup>+</sup> /K <sup>+</sup> -ATPase	Involving in membrane depolarization to induce action potential	(Donnelly 2013; Khaliq and Raman 2006)
Potassium (K)	Voltage-gated K <sup>+</sup> channels; Na <sup>+</sup> /K <sup>+</sup> -ATPase	Involving in membrane polarization to induce resting potential	(Chow and Leung 2020; Khaliq and Raman 2006)
Calcium (Ca)	Voltage-dependent Ca <sup>2+</sup> channels; glutamate receptors; Ca <sup>2+</sup> -ATPase pump	Functioning as a second messenger regulating neurodevelopment, synaptic transmission, neuronal excitability, and neuronal morphology	(Chaudhuri et al. 2021; Hell 2016; Lin et al. 2019; Neveu and Zucker 1996)
Iron (Fe)	Divalent metal ion transporter 1 (DMT1); ferroportin (FPN); transferrin receptor 1 (TFR1)	Acting as a ligand factor for a variety of enzymes involved in oxygen transport, cellular respiration, energy production, DNA synthesis and repair, as well as mitochondrial and immunological maintenance	(Halcrow et al. 2021; Thirupathi and Chang 2019)
Zinc (Zn)	Metallothioneins (MTs); SLC30A (also named ZnT) family; SLC39A (also named ZIP) family	Involving in DNA synthesis, brain development and neurotransmission	(Sun et al. 2022)
Copper (Cu)	Copper-transporting ATPase (including ATP7A and ATP7B); copper transport protein (including ATOX1 and CTR1)	Involving in the mitochondrial electron transport chain, neurotransmitter synthesis, myelination and clearance of ROS	(Borisov and Forte 2021; Pezacki et al. 2022; Robinett et al. 2019)

as microglia, astrocytes, macrophages, and T lymphocytes, are activated during the release of DAMPs (Garofalo et al. 2022). In parallel, inflammation-related cytokines, interferons or chemokines including chemokine-chemokine ligand 2 (CCL2) and monocyte chemoattractant protein-1 (MCP-1) are spurred to recruit immune cells, leading to infiltration of leukocytes (Gutiérrez et al. 2022; Zhang et al. 2018).

Metal ions are thought to be relevant to neuroinflammation. Some pathways such as voltage and receptor gated Ca<sup>2+</sup> influx promote a large increase in free cytosolic calcium, which causes mitochondrial calcium overload and in turn compromises the ATP production, further promoting ROS release (Bertero et al. 2021). In addition, elevated levels of intracellular Ca<sup>2+</sup> activate various proteases, lipases, kinases, phosphatases, and endonucleases (Metwally et al. 2021; Tone et al. 2022). These toxic elements thus induce a series of inflammatory cascades, leading to mobilization of microglia and astrocytes and increased production of cytokines and chemokines (Mehta et al. 2023). As a calcium antagonist, Mg<sup>2+</sup> can facilitate the alleviation of neuroinflammation by suppressing calcium influx via NMDARs (Zhu et al. 2018).

Iron accumulation is a major signature of activated microglia and neuroinflammation, which has been observed in several neurological disorders (Lu et al. 2022). It has been proposed that excess iron activates microglia by promoting NF-κB-mediated transcription of pro-inflammatory cytokines (Feng et al. 2021b). A recent study has further confirmed that excess irons provoke both morphological activation and transcriptomic changes of microglia using induced pluripotent stem cells (iPSCs) derived microglia, and this activation reduced both pro- and anti-inflammatory pathways (Kenkhuis et al. 2022). Additional studies have identified the interaction between inflammation and iron accumulation in neuronal cells. For example, Urrutia et al. have reported that the rise in inflammatory factors including TNF-α and IL-6 causes the upregulation of DMT1 and downregulation of FPN, resulting in iron accumulation (Urrutia et al. 2013).

Zinc is indispensable for immune stability, and it is able to work as a transcriptional repressor, suppressing NF-κB and restricting the function of TNF-α (Foster and Samman 2012; Voelkl et al. 2018). Therefore, intracellular zinc deficiency may boost NF-κB expression and trigger deleterious neuroinflammation. Consistently, subsequent evidence has indicated that changes in immune markers, including a decrease in MCP-1 and an increase in naive CD4<sup>+</sup> T cell markers, worsen during zinc deficiency (Lu et al. 2012). In addition, zinc contributes to the suppression of IFN-γ, IL-17 and TNF-α in immune activated T cells (Guttek et al. 2018). These findings suggest that zinc deficiency is associated with immune dysfunction and neuroinflammation. However, Kauppinen et al. have reported that Zn<sup>2+</sup> promotes the



**Fig. 2** Schematic diagram of COVID-19-induced neuroinflammation. SARS-CoV-2 activates different immune cells in the brain via infecting other organs and inducing inflammatory storms on the one hand, and directly invading the brain through the BBB on the other hand. These activated immune cells then secrete cytokines to induce neuroinflammation. *TNF* tumor necrosis factor, *IL* interleukin, *MMPs* matrix metalloproteinases, *CCL* C–C motif chemokine, *CXCL* C–X–C motif chemokine, *TGF* protransforming growth factor, *MCP-1* mono-

cyte chemoattractant protein-1, *IFN* interferon, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *VEGF* vascular endothelial growth factor, *G-CSF* granulocyte colony-stimulating factor, *FasL* factor related apoptosis ligand, *TRAIL* tumor necrosis factor related apoptosis inducing ligand, *BAFF* B-cell activating factor of the TNF family, *MIP-1β* macrophage inflammatory protein 1 beta, *RANTES* regulated upon activation normal T cell expressed and secreted factor

activation of microglia at the late stage of cerebral ischemic injury, indicating the double-edged sword effect of zinc (Kauppinen et al. 2008). Therefore, the effect of zinc on neuroinflammation depends on its basal level and the different disease courses.

Both COVID-19 and stroke can cause varying degrees of BBB damage, while heavy metals such as lead and cadmium are able to shuttle through the BBB and eventually accumulate in the brain, inducing neuroinflammation. It has been shown that cadmium induces the dismissal of IL-6 and IL-8 from astrocytes through activating MAPK and NF-κB pathways, leading to neuroinflammation and neuronal death (Phuagkhaopong et al. 2017). In a rat model, Liu et al. have reported that lead exposure contributes to increased microglial activation and inferior long-term potentiation (LTP) (Liu et al. 2015). This might be one of the explanations that COVID-19 is able to trigger more severe neurological symptoms in patients with metal ion disorders.

### Oxidative stress

Oxidative stress is provoked by overproduction of ROS, which leads to oxidative damage on lipids, biological membranes, proteins, and DNA (Feng et al. 2021a). ROS are highly reactive molecules comprising superoxide anion radicals ( $O_2^{\cdot-}$ ), hydroxyl radical ( $OH^{\cdot}$ ), hydrogen peroxide ( $H_2O_2$ ), and hypochlorous acid ( $HOCl$ ) (Knaus 2021). They

are products mainly from nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondria electron transport chain, and the Fenton or Haber–Weiss reaction (Wu et al. 2022). Metal ions play an essential role in the production, distribution and metabolism of ROS. There is emerging evidence that ROS are generated in mitochondria via an electron transport chain consisting of complex I–IV and mobile carriers (coenzyme Q [CoQ] and cytochrome c [Cyt<sub>c</sub>]) (Nolfi-Donagan et al. 2020). Under physiological conditions, the electrons derived from nicotinamide adenine diphosphate hydride (NADH) and flavin adenine dinucleotide (FAD) in the complex I and II, are transferred to complex III, and ultimately converge on complex IV, where oxygen is reduced to water (Turrens 2003). Iron is involved in the electron transport chain as a component of complex I, transferring electrons. Then, redox-active metal ions encompassing  $Cu^{+/2+}$  or  $Fe^{2+/3+}$  are able to convert  $H_2O_2$  into the more harmful  $OH^{\cdot}$  following overproduction of  $O_2^{\cdot-}$  in the electron transport chain, which is known as the Fenton reaction (Husain et al. 2008; Thiriveedi et al. 2020).

In response to ischemic and hypoxic stimuli, the metabolism of neuronal cells shifts from aerobic to anaerobic glycolysis with the production of hydrogen ions and lactic acid (Chen et al. 2018; Tan et al. 2021). Excessive production of these byproducts lowers intracellular pH, leading to a buildup of intracellular  $Na^+$  levels through the export of intracellular  $H^+$  and import of extracellular  $Na^+$  by the  $Na^+/$

H<sup>+</sup> exchangers (NHE) (Rotte et al. 2012). Subsequently, the plasma membrane Na<sup>+</sup>/Ca<sup>2+</sup> exchanger is triggered to expel redundant Na<sup>+</sup> and transport extracellular Ca<sup>2+</sup> into the cytoplasm (Schnetkamp 1995). Ca<sup>2+</sup> overload can provoke mitochondrial permeability transition pore (mPTP) opening, which further triggers ROS generation (Seidlmayer et al. 2015). Simultaneously, the opened mPTP is capable of damaging mitochondrial membrane potential, liberating Cyt c and metal ions such as Ca<sup>2+</sup>, Cu<sup>+/2+</sup> or Fe<sup>2+/3+</sup>, Mg<sup>2+</sup> and Zn<sup>2+</sup>, inhibiting ATP production, causing a cascade reaction in neighboring mitochondria, and eventually inducing neuronal cell death.

Under physiological circumstances, antioxidants are in charge of scavenging ROS via enzymatic reactions that transform toxic free radicals into less-toxic or non-toxic species, involving superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) (Bai et al. 2021; Wen et al. 2021). In terms of mechanisms, SOD catabolizes O<sub>2</sub><sup>•−</sup> into O<sub>2</sub> and H<sub>2</sub>O<sub>2</sub>, peroxidase breaks down not only H<sub>2</sub>O<sub>2</sub> but also other organic hydroperoxides, and GPx converts H<sub>2</sub>O<sub>2</sub> into H<sub>2</sub>O and O<sub>2</sub> with the assistance of glutathione (Chen et al. 2022; Rattanawong et al. 2021). It has been demonstrated that a few metal ions play crucial roles in composing these antioxidants, including Zn-Cu-SOD and Ca-peroxidase (Mohandass et al. 2021; Weydert and Cullen 2010). In addition, the enzyme synthesizing SOD is Mn-dependent (Zelko et al. 2002). When metal ion homeostasis is disrupted in COVID-19 or stroke, the antioxidants fail to remove extra ROS, ultimately causing oxidative stress.

## Excitotoxicity

Glutamate and aspartate are the dominant excitatory neurotransmitters in the CNS and high concentrations of glutamate or aspartate lead to the damage of brain cells, referring to as excitotoxicity (Lai et al. 2014). Emerging evidence has emphasized the ionic underpinnings of excitotoxicity. K<sup>+</sup> overload and acidosis have been reported as prodromal events in the ischemic cascade resulting in ionic disturbances (Lipton 1999). Elevated K<sup>+</sup> facilitates the release of glutamate, thereby catalyzing Na<sup>+</sup>/Ca<sup>2+</sup> channels linked to NMDARs and further increasing intracellular Na<sup>+</sup> and Cl<sup>−</sup> concentrations as well as the passive influx of H<sub>2</sub>O that causes cytotoxic edema (Dumuis et al. 1993). Furthermore, extracellular glutamate can also activate AMPARs and mGluRs, a critical step in the inflammatory cascade (Lu et al. 2017; Ribeiro et al. 2017). Thereafter, NMDARs work through a single ion channel, which in turn improves intracellular Ca<sup>2+</sup> levels. In the physiological state, Mg<sup>2+</sup> obstructs the channel pore of NMDARs. Whereas with the release of glutamate from presynaptic sites and AMPARs activation, Mg<sup>2+</sup> is completely depleted from NMDARs as the postsynaptic membrane is partially depolarized, resulting

in an influx of Na<sup>+</sup> and Ca<sup>2+</sup> into the cells and mitochondrial calcium overload, further impairing ATP production (Arvanian et al. 2004; Wollmuth et al. 1998). Calcium overload in neurons generates a cascade of downstream death signaling pathways, involving calpain activation, ROS production, and mitochondrial insults.

Interestingly, extracellular and intracellular zinc and copper signaling may play a neuroprotective role against glutamate-induced excitotoxicity. As we mentioned before, copper and zinc were coupled to glutamate for transmission during synaptic activity (Gasperini et al. 2015; Krall et al. 2020). In the synaptic cleft, the two metals modulate excitatory neurotransmission by suppressing the activity of NMDARs and AMPARs. Other metals such as Fe, Mn, Al, and Pb also seem to engage in excitotoxicity through regulating intracellular levels of Ca<sup>2+</sup> or related receptor activity. Nevertheless, more work needs to be done to identify the roles of metals in excitotoxicity.

## Neuronal cell death

As a consequence of oxidative stress, excitotoxicity and/or neuroinflammation, neuronal cells will ultimately die and the death is classified into three main different types: apoptosis, necrosis and autophagic cell death. For a long time, necrosis was considered passive and unregulated. However, in recent years, specific forms of necrosis have been identified as highly regulated and are referred to as regulated necrosis, including necroptosis, pyroptosis, ferroptosis, parthanatos, and cyclophilin D (CypD)-dependent necrosis.

There is no doubt that metal ions play an important role in regulating neuronal cell death. Novel evidence demonstrates that exposure to excessive amounts of metals, such as Ca, Fe, Zn, Cu, Pb, and Cd, leads to neuronal cell death (Gleitze et al. 2021; Lu et al. 2022; Tsvetkov et al. 2022). It is well accepted that the occurrence of ferroptosis depends on iron. Actually, zinc is also critical for ferroptosis in breast and renal cancer cells (Chen et al. 2021). It has been shown that ferroptosis is inhibited when zinc chelators are administered. Conversely, additional zinc treatment boosted ferroptosis despite the presence of an iron chelator. Mechanistically, by investigating the genes associated with zinc and ferroptosis, the authors identified SLC39A7, which encoded ZIP7 that regulated zinc transport from ER to cytosol, as a novel genetic determinant of ferroptosis (Chen et al. 2021). In addition to iron-dependent ferroptosis, a recent authoritative study uncovered a copper-dependent programmed cell death that, unlike known death mechanisms, relied on mitochondrial respiration. In this study, the authors presented robust evidence confirming copper-dependent death through direct binding of copper to lipoylated components of the tricarboxylic acid (TCA) cycle, resulting in accumulation of lipid acylated proteins and proteotoxic stress and ultimately

cell death (Tsvetkov et al. 2022). It is still unknown whether there is a unique mechanism for neuronal cell death induced by zinc or copper. Nevertheless, there is substantial evidence that metal dysregulation disrupts the CNS in various ways, including releasing excessive ROS, triggering excitotoxicity, inducing neuroinflammation, and ultimately leading to neuronal cell death (Fig. 3).

## Metal dysregulation in COVID-19-induced neurological symptoms

### COVID-19-induced neurological symptoms

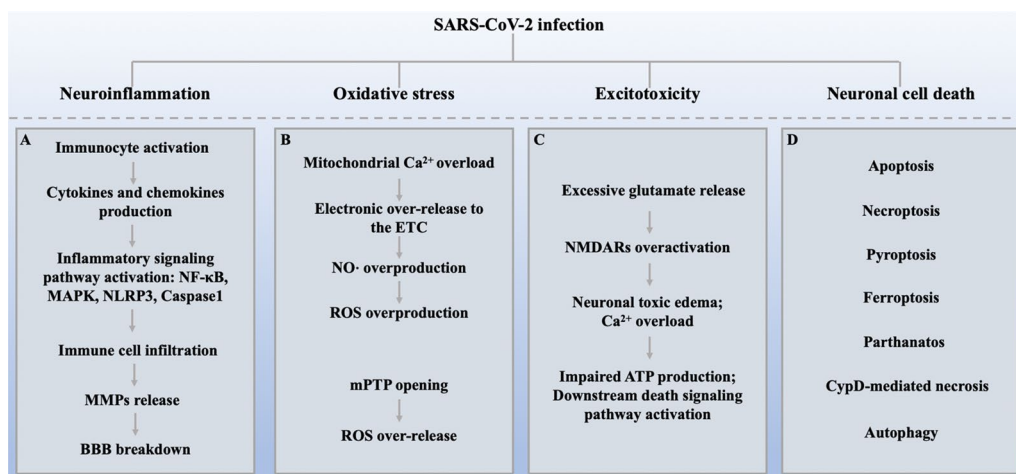
There is evidence that SARS-CoV-2 invades host cells via utilizing prominent spike proteins that attach to cell membrane receptors, including angiotensin-converting enzyme 2 (ACE-2) and CD147 (basigin), in combination with the processing of primer/transmembrane serine proliferase 2 (TMPRSS2) involving the viral spike protein (Scialo et al. 2020; Wang et al. 2020; Wu et al. 2021). SARS-CoV-2 is also able to access 293/hACE2 cells in a receptor non-dependent manner via endocytosis, in which PIKfyve, TPC2, and cathepsin L are essential for this entry (Ou et al. 2020).

A large number of reports have provided a full description of the pulmonary symptoms of COVID-19 (Guan and Zhong 2020; Huang et al. 2020; Zhu et al. 2020). However, besides

the typical respiratory and gastrointestinal symptoms, COVID-19 infection might be also accompanied by neurological manifestations that may persist for a long time (Ellul et al. 2020). In the period of COVID-19, patients with no previous neuropsychiatric history suffered attention difficulties, insomnia, fatigue, hysteria and delusions, even changes in behavior such as suicide (Becker et al. 2020; Ceban et al. 2022; Farooq et al. 2021; Fricchione et al. 2022; Pappa et al. 2020). Patients admitted to the intensive care unit (ICU) have been revealed with agitation (69%) and corticospinal tract signs (67%), suggesting a definite association between COVID-19 and encephalopathy (Helms et al. 2020).

A number of recent studies have highlighted that adult patients with COVID-19 further developed a variety of neurological symptoms, such as stroke, dementia, hallucinations, seizures, and encephalopathy (Poloni et al. 2021; Stein et al. 2021; Uginet et al. 2021; Xu et al. 2022). In addition, Frontera et al. conducted a prospective study on the prevalence of new neurological disorders among COVID-19 patients in the New York City metropolitan area, which showed that 13.5% of COVID-19 patients developed neurological disorders (Frontera et al. 2021). These reports indicate a specific propensity of COVID-19 for the central and peripheral nervous system.

Radiographic evidence showed that a reduction in gray matter thickness and tissue contrast were observed in up to 80% of hospitalized patients (Chou et al. 2021; Douaud et al. 2022). From autopsies of COVID-19 decedents, many



**Fig. 3** Schematic diagram of the pathophysiology involved in COVID-19-induced neurological symptoms. **A** Neuroinflammation: excessive immune cells activation and chemokines and cytokines release promote inflammatory cell infiltration and BBB damage. **B** Oxidative stress: mitochondrial  $\text{Ca}^{2+}$  overload leads to excessive ROS production and mPTP opening causes excessive ROS and Cyt C release. **C** Excitotoxicity: excessive glutamate release activates NMDARs, which subsequently induces calcium overload and activates downstream death signaling pathways. **D** Neuronal cell death:

involving apoptosis, necroptosis, pyroptosis, ferroptosis, parthanatos, CypD-mediated necrosis, and autophagy. *NF-κB* nuclear factor kappa-B, *MAPK* mitogen-activated protein kinase, *NLRP3* NOD-like receptor thermal protein domain associated protein 3, *MMPs* matrix metalloproteinases, *BBB* blood–brain barrier, *ETC* electron transport chain, *mPTP* mitochondrial permeability transition pore, *ROS* reactive oxygen and species, *NMDARs* N-methyl-D-aspartate receptors, *CypD* cyclophilin D



investigators have reported postmortem neuropathological findings: hypoxia, microglia activation, astrocyte lesions, mild lymphocytic infiltration, as well as microhemorrhages and hemorrhages (Egbert et al. 2020; Mesci et al. 2022; Samudiyata et al. 2022; Thakur et al. 2021). Moreover, Khan et al. have recently discovered that ciliary cells of the respiratory mucosa and parasitic cells (non-neurons) of the olfactory mucosa are the major target cells of COVID-19, which is supposed to be the main pathway affecting olfactory sensory neurons, resulting in the sequelae of COVID-19 olfactory dysfunction (Khan et al. 2021). However, whether COVID-19 can directly infect the CNS remained controversial.

Some studies did not detect viral RNAs or proteins in the CNS tissue of COVID-19 decedents although their brains exhibited postmortem neuropathology, whereas some studies detected COVID-19 virus in autopsies of patients who died from COVID-19 (Mesci et al. 2022; Pellegrini et al. 2020; Soung et al. 2022; Thakur et al. 2021). The reason for this discrepancy might be due to the differences in basic diseases and severity of infection. In support of this view, another report has demonstrated that the S1 spike protein of COVID-19 virus is able to cross the blood brain barrier (BBB) in mice and enter the CNS, initiating a neuroinflammatory process (Pellegrini et al. 2020; Zhang et al. 2021b). These data suggested that COVID-19 virus was capable of infecting the brain and triggering long-term neurological manifestations. Patients with neurodegenerative disorders suffer from increased BBB permeability, which potentially facilitates the neural invasion of SARS-CoV-2. Based on these reports, it is reasonable to speculate that SARS-CoV-2-induced neuroinflammation may increase susceptibility to neurodegeneration in patients who do not yet develop these diseases. Despite the emerging evidence, a comprehensive overview of the cellular and molecular mechanisms of SARS-CoV-2 brain infection and the consequent impact on CNS is still not available.

### **Metal dysregulation in COVID-19-induced neurological symptoms**

It is well accepted that virus is able to disrupt  $\text{Ca}^{2+}$  homeostasis in host cells and in turn to modulate signal transduction (Danta 2020a). Although there is no sufficient laboratory data to support the direct relationship between  $\text{Ca}^{2+}$  and SARS-CoV-2, several recent studies on other sequentially homologous coronaviruses, including severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV), have revealed the enhanced fusion with host cells via  $\text{Ca}^{2+}$ , thereby increasing the infection rate (Danta 2020b; Straus et al. 2020). Furthermore, viruses can also seize calcium channels and pumps, such as voltage-gated calcium channels

(VGCCs), receptor-operated calcium channels, store-operated calcium channels, TRP channels, and  $\text{Ca}^{2+}$ -ATPase in host cells to release more intracellular  $\text{Ca}^{2+}$  for their life cycle (Qu et al. 2022). In agreement with these findings, Chen et al. have shown that interactions between viruses and VGCCs contribute to virus-host cell fusion entry (Chen et al. 2019). Therefore, it is very likely that SARS-CoV-2 can also distort  $\text{Ca}^{2+}$  homeostasis when it attacks the body, which facilitates disease progression. Some highly lipophilic calcium channel blockers (CCBs), such as nimodipine and memantine, have been reported to be effective on AD dementia due to their ability to easily pass the BBB (López-Arrieta and Birks 2000; McShane et al. 2019). In particular, some CCBs have also been found to inhibit various viral infections such as Japanese encephalitis virus (JEV), dengue virus (DENV), West Nile virus (WNV), Zika virus (ZIKV), and even Ebola virus (EBOV) (Chen et al. 2019). Ribeiro et al. have also proposed that P2X7 receptor may be over-activated via SARS-CoV-2-induced extracellular ATP overload, leading to an increase in  $\text{Ca}^{2+}$  influx and glutamate release (Ribeiro et al. 2021). As a result, severe oxidative stress and cytokine storm occurs in the brain, eventually causing neuronal death. These reports shed some light on novel strategies for prevention of SARS-CoV-2 infection or the neurological diseases it causes via targeting calcium signaling pathways.

Zinc also exhibits a Yin-Yang role in COVID-19. Numerous reports have revealed that zinc deficiency facilitates the risk of viral infections and the development of severe forms of disease (Balboni et al. 2022; Dhawan et al. 2022). Observational clinical studies and animal experiments have demonstrated that appropriate zinc administration could counteract the disease progression (Ben Abdallah et al. 2022). For example, in a randomized clinical study, 470 newly diagnosed COVID-19 patients were enrolled and the effect of high-dose zinc (50 mg per day divided into two doses) was examined on the two primary endpoints, admission to the ICU and death. The results showed that the risk ratio for ICU admission in the zinc supplementation group was 0.43 and short-term mortality was 0.68, with additional benefits for the length of stay and the duration of symptoms in outpatients (Vinceti et al. 2022). In addition, a recent survey revealed that taste impairment was associated with the reduced salivary zinc levels in COVID-19 patients (Abdelmaksoud et al. 2021). These reports indicate that zinc should be considered as a preventive and adjuvant treatment for COVID-19 to reduce susceptibility and disease severity. Besides the transient protection of COVID-19 by zinc supplementation, its long-term effects on the CNS remain to be determined.

There is evidence that iron metabolism disturbances also occur in COVID-19 patients. COVID-19-induced inflammation promotes an accumulation of intracellular iron, resulting in low levels of circulating iron available for metabolism

(Habib et al. 2021; Mahroum et al. 2022). A clinical study from Muhammad et al. showed a significant decrease in serum iron, total iron binding capacity (TIBC) and transferrin levels as well as a notable increase in ferritin and transferrin saturation in COVID-19 patients (Muhammad et al. 2022). In another study, iron and transferrin were reported to be associated with mortality in COVID-19 patients (Suriawinata and Mehta 2022). Even though not confirmed, it can be hypothesized that iron-related biomarkers play important roles in causing oxidative stress in various tissues of COVID-19 patients, further triggering the activation of cytokine storm, and ultimately inducing ferroptosis.

The role of selenium in fighting against COVID-19 and relevant neurological symptoms should not be underestimated. On the one hand, selenoproteins and selenium-containing organisms can prevent SARS-CoV-2 infection via suppressing the expression of ACE-2 receptors; on the other hand, they can exert anti-COVID-19 effects by inhibiting inflammation, oxidative stress, cytokine storm and 3CLPro, the main protease of SARS-CoV-2 (Alshammari et al. 2022). Clinical evidence showed that serum selenium concentrations were significantly higher in COVID-19 survivors than that in non-survivors (Moghaddam et al. 2020). Moreover, selenium concentrations in patient toenail samples were correlated with the COVID-19 severity index (CSI) (Larvie et al. 2023). These results suggest that selenium plays a potential role as a neuroprotective agent in treating COVID-19. In summary, long-term inflammation, BBB breakdown, and microglia activation may contribute to neurotransmitter alterations, and neuronal impairment, thus interpreting the neuropsychiatric symptoms of COVID-19. Dysregulation of metal homeostasis is involved in a range of neurological complications and sequelae in COVID-19 patients and targeting metal-related signaling pathways for treating COVID-19 infection should be performed with appropriate compatibility. Thus, appropriate drug combinations may be a promising approach for improving neurological injury caused by COVID-19. The roles of metal ions in COVID-19-induced neurological symptoms are summarized in Table 2.

## Treating COVID-19-induced neurological symptoms via targeting metal dysregulation

Due to the pivotal roles of metal ions in COVID-19-induced neurological symptoms, targeting the metal-related signaling pathways might be a potential strategy to mitigate the neurological symptoms. The initial thought was to directly remediate the neural metal content by giving appropriate metals or metal chelator. A recent study has shown that zinc administration may ameliorate disease progression in COVID-19 by reducing the inflammatory factor levels of patients (Dhawan et al. 2022). In another

**Table 2** Roles of metal ions in COVID-19-induced neurological symptoms

Metal ions	Contents	Mechanisms or potential mechanisms	Related neurological symptoms	References
Na and K	Unknown	Inducing cerebral osmotic pressure dysregulation; inducing action potential disturbance	Attention difficulties, insomnia, fatigue, hysteria, delusions, behavior changes, hallucinations, stroke, and seizures	(Khaliq and Raman 2006; Wicher et al. 2006)
Ca	Increase	Promoting virus-host cell fusion; inducing oxidative stress and cytokine storm, eventually causing neuronal death	Stroke, dementia, hallucinations, insomnia, fatigue, hysteria, delusions, and seizures	(Arvanian et al. 2004; Bertero et al. 2021; Danta 2020a; Seidlmayer et al. 2015)
Fe	Increase	Inducing oxidative stress; activating cytokine storm; causing ferroptosis; causing A $\beta$ peptides accumulation; triggering hyperphosphorylated tau entanglement	Stroke, dementia, seizures	(Chen et al. 2021; McIntosh et al. 2019; Rao et al. 2021)
Zn	Decrease	Facilitating the risk of viral infections and the development of severe forms of disease; correlation with astrocyte functions; decreasing antioxidant capacity	Stroke, dementia, seizures	(Balboni et al. 2022; Ben Abdallah et al. 2022; Dhawan et al. 2022)
Cu	Unknown	Inducing oxidative stress; inducing A $\beta$ oligomers, deposition, and lipid peroxidation	Stroke, dementia, seizures	(Pezacki et al. 2022; Williams et al. 2016)
Se	Decrease	Inducing oxidative stress, lipid peroxidation, ferroptosis, and neuroinflammation	Stroke, dementia, seizures	(Alim et al. 2019; Pereira et al. 2022; Schweizer et al. 2021)

report, patients with low selenium intake exhibited more severe COVID-19-related symptoms and selenium intake below 65 µg/day might increase the severity of COVID-19 (Zhang et al. 2020). Growing evidence has also demonstrated the role of iron chelators in COVID-19. Poonkuzhi Naseef et al. revealed that deferiasirox, an iron chelator, was able to save COVID-19 critically ill patients, mitigated disease progression, and improved survival (Poonkuzhi Naseef et al. 2022). In addition, deferiprone (L1) might adjunctively treat COVID-19 through binding transferrin, involving in immune response and mobilization of iron in highly inflamed cells (Poonkuzhi Naseef et al. 2022). Unfortunately, single administration of iron chelators could cause a variety of serious neuropathological consequences, such as myelinopathy (McCarthy et al. 2022). These data indicated that it was extremely difficult to master the proper timing and dosage of metals *in vivo* by simple supplementation or chelation, and that inadequate or excessive amounts of these drugs gave rise to insufficient efficacy or more serious side effects. Therefore, it is necessary to monitor the dynamics of metal ions *in vivo* so as to adjust therapeutic strategies timely.

With the clarification of metal metabolic mechanisms, therapeutic protocols via targeting metal ions have become increasingly diverse. One possible strategy is to target the metal ion channels. Various antagonists or agonists targeting different metal ion channels have been developed (Table 3). Unfortunately, all of them are still only used as research tools so far. Therefore, selectively targeting the downstream pathways might be another feasible option. For instance, targeting the pro-death signaling of NMDARs downstream has shown great promise in neuroprotection (Yan et al. 2020). Different downstream pathways of NMDARs have been identified, including the GluN2B-PSD95-nNOS pathway, the GluN2B-DAPK1 pathway, the NMDAR-PTEN complex, and the NMDAR-Src-Panx1 complex (Sun et al. 2015; Tu et al. 2010; Weiling et al. 2016; Zhou et al. 2010). Through developing small molecule inhibitors and interfering peptides, many experiments have shown that targeting these signaling pathways improved the neurological function after stroke and reduced the ischemia/hypoxia-induced neuronal death. Since many scholars assume COVID-19 as a pathological model of human inflammation combined with hypoxia, analogous to the pathological features of ischemic stroke (Fig. 4), it is reasonable to speculate that targeting the downstream pathways of NMDARs also works for treating COVID-19-induced neurological symptoms.

Growing evidence indicates that iron deposition-induced ferroptosis causes neurological disorders (Ou et al. 2022). Thereby, targeting ferroptosis-relevant pathways represents a novel therapeutic approach for treating COVID-19-induced neurological symptoms. Currently available ferroptosis inhibitors mainly focus on preventing iron overload and

inhibiting lipid peroxidation (Liang et al. 2022b). A recent study by Tuo et al. has shown that intranasal administration of ferritinase inhibitors, ferritinase-1 and lipoproteinase-1, immediately after cerebral ischemia in mice reduced neuronal damage, and the protective effect continued until 6 h after reperfusion (Tuo et al. 2022). By intravenous injection, Feng et al. have revealed that tirazol mesylate, an inhibitor of iron-dependent lipid peroxidation, alleviated hypoxic-ischemic brain injury in neonatal piglets (Feng et al. 2000). Furthermore, desferrioxamine (DFO), a powerful iron chelator, has also been reported to improve neurological function in ischemic rats and stroke patients (Papazisis et al. 2008; Selim 2010). It is worth mentioning that different organic and inorganic selenium compounds including methylselenocysteine, selenocystine, selenomethionine, selenocystamine, ebselen, sodium selenite, and sodium selenate are all effective in preventing erastin- and RSL3-induced iron toxicity and exerting antioxidant effects. Among them, methylselenocysteine or selenocystamine could reduce brain injury in stroke mice (Tuo et al. 2021). Due to similarity between stroke-induced brain injury and COVID-19-induced neurological symptoms as we mentioned before, it is reasonable to posit that targeting the iron-relevant pathways and applying the relevant antioxidants might also benefit the COVID-19-induced neurological symptoms.

## Conclusion

In summary, maintenance of metal homeostasis is essential for neurological function. Metal metabolic dysregulation, aberrant activation or suppression of metal ion channels, and disruption of the ion-relevant signaling pathways may contribute to COVID-19-induced neurological symptoms (Balboni et al. 2022; Habib et al. 2021; Poonkuzhi Naseef et al. 2022; Suriawinata and Mehta 2022). So far, significant advances have been achieved in understanding different metal-relevant signaling pathways, offering us new directions to combat COVID-19-induced neurological symptoms (Gleitze et al. 2021; Sun et al. 2022; Thirupathi and Chang 2019). Thus, restoration of metal homeostasis is an effective strategy to prevent neurological damage. Despite the fact that preclinical studies have demonstrated the potential neuroprotective effects of a few metallo-modulators, they have obvious limitations, such as side effects and narrow therapeutic windows. This can be explained by the fact that multiple metal dysregulation can be triggered simultaneously in complex disease processes. The crosstalk between different metal dysregulation and the downstream signaling pathways merits further investigation, which implies that any single metal modulator may require combination with other drugs. However, the application of current discoveries based on animal or cellular experiments to the clinical

**Table 3** Potential mechanisms of metal ion channels in COVID-19-induced neurological symptoms and their agonists and antagonists

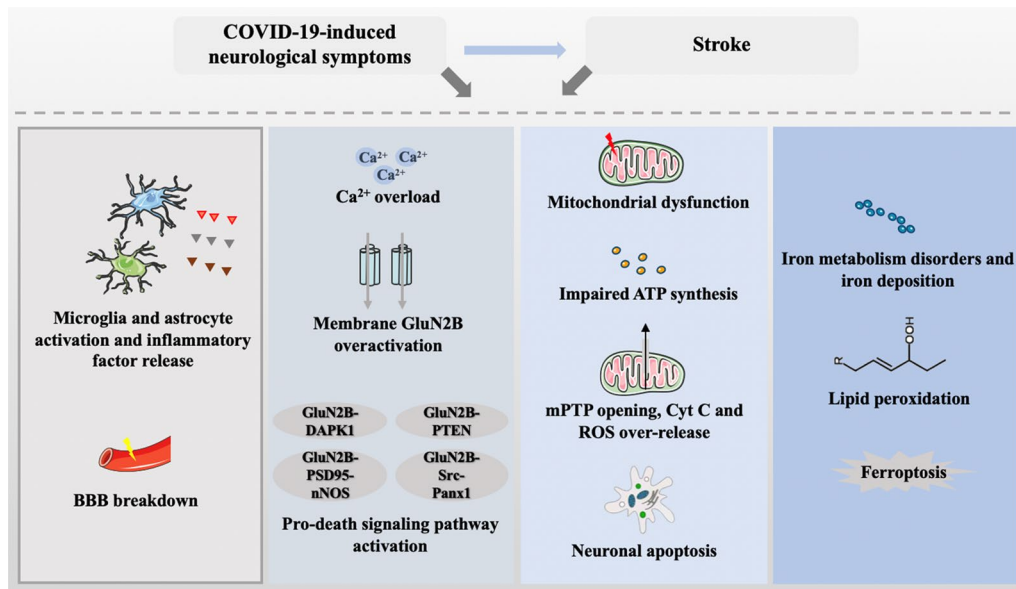
Metal ion channels	Potential mechanisms	Agonists	Antagonists	References
Na <sup>+</sup> /K <sup>+</sup> -ATPase	Inhibition of Src signaling cascades; activation of NADPH oxidase; increasing the generation of ROS; activation of NLRP3; activation of AMPK/mTOR and ERK1/2 signaling pathways; indirectly increase intracellular Ca <sup>2+</sup> by shifting NCX to the reverse mode	Citroviridin (Microsomes); Strophanthidin (0.1–1 nmol/L); Sodium oleate	Citroviridin (brain synaptosome); Strophanthidin (1–100 μmol/L); Digoxin; Marinobufogenin; Oleandrin; Istaroxime; Aquastatin A; Prilocaine hydrochloride; Prilocaine; Istaroxime hydrochloride; Chlorprocaine; Phlorizin; Gitoxin; Ginsenoside; Bufalin; Nerifolin; Rostafuroxin;	(Liu et al. 2013; Nam and Keum 2020; Zhang et al. 2012)
IP3R	Ca <sup>2+</sup> overload; ER stress	Unknown	2-Aminoethyl diphenylborinate; (-)-Xestospongin C;	(Ye et al. 2021)
RyRs	ER Ca <sup>2+</sup> leakage	RyRs activator 1; RyRs activator 2	Dantrolene	(Huang et al. 2017)
SERCA	Lower ER resting Ca <sup>2+</sup> concentration	Istaroxime hydrochloride; CDN1163	Thapsigargin; Cyclopiazonic acid; Annonacin; Paxilline, JTV-519 hemifumarate; (-)-Xestospongin C	(Lee et al. 2019)
Na <sup>+</sup> /Ca <sup>2+</sup> exchanger	Increasing intracellular Ca <sup>2+</sup>	FeCl <sub>3</sub> ; neuorouina	SEA0400; CGP37157; SM-6586; ORM-10103; KB-R7943; bepridil; GLU-XIP; CB-DMB	(Schnetkamp 1995)
ATP7B	Disrupting Cu/Fe homeostasis	Unknown	Tetrathiomolybdate	(Cai et al. 2022)
ATOX1	Involving in apoptosis signaling pathways; inhibiting amyloid formation	Unknown	DC_AC50; DA-PROTAC	(Jin et al. 2022)
GluN1	Binding soluble amyloid-β oligomers; altering neurophysiology	(RS)-(Tetrazol-5-yl)glycine; NSC339614 potassium; UBP646	TCN 201; UBP608; UBP618	(Taniguchi et al. 2022)
GluN2A	Promoting Ca <sup>2+</sup> overload and neuronal cell death during the early stage of ischemia; activating PI3K/AKT/ERK and CREB signaling pathways to inhibit neuronal cell death	(RS)-(Tetrazol-5-yl)glycine; UBP646	TCN 201; TCN 201-d5; TCN 213; UBP608; UBP618	(Li et al. 2021)
GluN2B	Activating GluN2B-FSD95-nNOS/GluN2B-DAPK1/GluN2B-PTEN/NMDAR-SFK-Panx1/Ca <sup>2+</sup> signaling pathway;	UBP646	Rislenemdaz; BZAD01; Conantokin G; EVT-101; UBP618; BMS-986163; BMS-986169; BMT-108908; Praeruptorin C	(Sun et al. 2015; Tu et al. 2010; Weiling et al. 2016; Zhou et al. 2010)
TRPC1	Inhibiting Aβ production	Unknown	Pico145	(Li et al. 2018)
TRPC3	Inducing intracellular Ca <sup>2+</sup> overload	GSK1702934A; OptoBI-1	TRPC3/6-IN-1; GSK2332255B; Pyr10; Pyr3; Pyr6	(Doleschal et al. 2015)
TRPC5	Inducing intracellular Ca <sup>2+</sup> overload	Englerin A; AM12	Pico145; TRPC5-IN-1; TRPC5-IN-4; TRPC5-IN-2; TRPC5-IN-3; HC-070; Evfacotrep; ML204	(Dattilo et al. 2008)
TRPC6	Activating NF-κB and CREB signaling pathway; Increasing both inflammatory responses and apoptosis in astrocytes	TRPC6-PAM-C20; Hyperforin DCHA	GSK2332255B; TRPC6-IN-3; TRPC6-IN-1; SAR7334 hydrochloride; DS88790512; Larixyl acetate	(Yao et al. 2009)



Table 3 (continued)

Metal ion channels	Potential mechanisms	Agonists	Antagonists	References
TRPV1	Participating in mTOR-AKT-HIF-1 $\alpha$ signaling pathways; inducing neuroinflammation	Vanillin; Capsaicinoid; MSP-3; N-Oleoyldopamine; Olvanil; (R)-Methanandamide (AM-356); Capsaicin; MDR-652	PeActx peptide; TRPV1 antagonist 3; Resolvin D2; A-784168; SB 452533; JTS-653	(Lu et al. 2021)
TRPV2	Inhibiting CaMKII/CREB/GSK signaling pathway	Probenecid	Tramilast	(Thapak et al. 2022)
TRPV4	Inducing Na <sup>+</sup> , K <sup>+</sup> , and Ca <sup>2+</sup> disorders thus causing cerebral edema	TRPV4 agonist-1; TRPV4 agonist-1 free base; 4 $\alpha$ -Phorbol 12,13-didecanoate; GSK1016790A	HC-067047; TRPV4 antagonist 3; GSK205; HC-067047; GSK2798745	(Bothwell et al. 2019)
TRPM2	Enhancing GluN2B signaling pathways	Adenosine 5'-diphosphoribose sodium	N-(p-aminocinnamoyl)anthranilic acid	(Alim et al. 2013)
TRPM4	Dysregulating Ca <sup>2+</sup> , Mg <sup>2+</sup> , and Zn <sup>2+</sup> signaling pathways	Unknown	9-Phenanthrol; TRPM4-IN-1; TRPM4-IN-2; TRPM4-IN-5; glibenclamide	(Yan et al. 2020)
TRPM7	Dysregulating Ca <sup>2+</sup> , Mg <sup>2+</sup> , and Zn <sup>2+</sup> signaling pathways; inducing PI3K/AKT/mTOR signaling pathways	Unknown	Carvacrol; Ginsenoside Rd; sphingosine	(Gotru et al. 2018; Nadolni et al. 2020)
DMT1	Inducing iron transport disorders; causing ferroptosis	Unknown	DMT1 blocker 1; DMT1 blocker 2	(Zhang et al. 2021a)
FPN	Inducing iron deposition; inhibiting myelination	Unknown	VIT-2763	(Schulz et al. 2012)
TFR	Inducing iron deposition and ROS production	Unknown	AG-18; Deferasirox	(Weinreb et al. 2013)

*IP3R* inositol 1,4,5-trisphosphate receptors, *RyRs* ryanodine receptors, *SERCA* sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase, *ATP7B* ATOX1, copper-transporting ATPase, *GluN* NMDA receptor, *TRPC* transient receptor potential cation channel subfamily V, *TRPM* transient receptor potential cation channel subfamily M, *DMT1* divalent metal ion transporter 1, *FPN* ferroportin, *TJR* transferrin receptor, *Syc* proto-oncogene tyrosine-protein kinase Src, *NADPH* nicotinamide adenine dinucleotide phosphate, *ROS* reactive oxygen species, *NLRP3* NOD-like receptor thermal protein domain associated protein 3, *AMPK* adenosine 5'-monophosphate (AMP)-activated protein kinase, *mTOR* mammalian target of rapamycin, *ERK1/2* extracellular regulated protein kinases 1/2, *NCX* Na<sup>+</sup>/Ca<sup>2+</sup> exchanger, *ER* endoplasmic reticulum, *PI3K* phosphatidylinositol-3-hydroxykinase, *AKT* protein kinase B, *CREB* cAMP-response element binding protein, *NF- $\kappa$ B* nuclear factor kappa-B, *DAPK1* death-associated protein kinase 1, *PTEV* phosphatase and tensin homolog, *PSD95* postsynaptic density protein-95, *mGOS* neuronal nitric oxide synthase, *Panx1* Pannexin-1, *SFK* Src family kinases, *HIF-1 $\alpha$*  hypoxia inducible factor-1 $\alpha$ , *CaMKII* calcium-calmodulin (CaM) dependent protein kinase II, *GSK* glycogen synthase kinase



**Fig. 4** Similarities between COVID-19-induced neurological symptoms and ischemic stroke. The pathological similarities between the neurological symptoms caused by COVID-19 and ischemic stroke mainly include: microglia and astrocyte activation and BBB breakdown;  $\text{Ca}^{2+}$  overload activates GluN2B and its downstream death signaling pathway; mitochondrial dysfunction leads to impaired ATP synthesis, ROS overproduction and neuronal apoptosis; iron overload

results in lipid peroxidation and neuronal ferroptosis. *BBB* blood-brain barrier, *GluN2B* NMDA receptor 2B, *DAPK1* death-associated protein kinase 1, *PTEN* phosphatase and tensin homolog, *PSD95* postsynaptic density protein-95, *nNOS* neuronal nitric oxide synthase, *Src* proto-oncogene tyrosine-protein kinase *Src*, *Panx1* Pannexin-1, *mPTP* mitochondrial permeability transition pore, *Cyt C* cytochrome C, *ROS* reactive oxygen species

setting (such as COVID-19-induced neurological symptoms) requires considerable effort.

**Acknowledgements** This work was supported by National Natural Science Foundation of China (No. 82073849 to Xiu-Ju Luo, China, No. 82204389 to Kai-Di Ren, No. 82173815 to Jun Peng, China), Natural Science Foundation of Hunan Province, China (No. 2021JJ30032 to Xiu-Ju Luo).

**Author contributions** Yi-Yue Zhang, Jun Peng and Xiu-Ju Luo conceived this review. Yi-Yue Zhang and Kai-Di Ren wrote the manuscript. Jun Peng and Xiu-Ju Luo revised the manuscript.

**Funding** The study was supported by National Natural Science Foundation of China (grant nos. 82073849, 82204389, 82173815) and Natural Science Foundation of Hunan Province (grant no. 2021JJ30032).

**Data availability** Enquiries about data availability should be directed to the authors.

## Declarations

**Conflict of interest** The authors declare no conflicts of interest.

**Consent for publication** This publication is approved by all the authors.

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