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Review Article

Oxidative Stress-Mediated Blood-Brain Barrier (BBB) Disruption in Neurological Diseases

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The blood-brain barrier (BBB), as a crucial gate of brain-blood molecular exchange, is involved in the pathogenesis of multiple neurological diseases. Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and the scavenger system. Since oxidative stress plays a significant role in the production and maintenance of the BBB, the cerebrovascular system is especially vulnerable to it. The pathways that initiate BBB dysfunction include, but are not limited to, mitochondrial dysfunction, excitotoxicity, iron metabolism, cytokines, pyroptosis, and necroptosis, all converging on the generation of ROS. Interestingly, ROS also provide common triggers that directly regulate BBB damage, parameters including tight junction (TJ) modifications, transporters, matrix metalloproteinase (MMP) activation, inflammatory responses, and autophagy. We will discuss the role of oxidative stress-mediated BBB disruption in neurological diseases, such as hemorrhagic stroke, ischemic stroke (IS), Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury (TBI), amyotrophic lateral sclerosis (ALS), and cerebral small vessel disease (CSVD). This review will also discuss the latest clinical evidence of potential biomarkers and antioxidant drugs towards oxidative stress in neurological diseases. A deeper understanding of how oxidative stress damages BBB may open up more therapeutic options for the treatment of neurological diseases.

1. Introduction

BBB is a highly complex and dynamic structure composed mainly of brain microvascular endothelial cells (BMVECs), astrocytes, pericytes, and basement membrane, which plays a causative role in regulating central nervous system (CNS) homeostasis [1]. The BBB is selectively permeable to certain substances thereby preventing toxins and other macromolecules in the blood from reaching the brain. A variety of pathological factors can cause the destruction of the BBB, including oxidative stress, neuroinflammation, immune cells, and various pathogens [2, 3]. These pathological factors interact with each other, induce MMP activation, reduce tight connections between cerebrovascular endothelial cells, and degrade basement membranes all culminating to an increase in BBB permeability paving way for large molecules and harmful substances to reach brain tissue causing damage [4, 5].

Oxidative stress refers to a pathological state that produces a variety of toxic effects on cells due to the excessive accumulation of ROS and their related metabolites [6]. Accumulating evidence strongly suggests that ROS are the core factor of acute brain injury and also participate in the tissue repair in the long-lasting neurological recover time. After several minutes to several hours of cerebral ischemia or reperfusion, ROS were produced in large quantities, and they continued to rise within a few days until they gradually returned to normal around 20 days [7]. Further studies show that ROS produced by ischemia can activate hypoxia-inducible factor-1 (HIF) and downstream pathways, such as the Notch pathway, Wnt pathway, and hypoxia-induced growth factor changes, which are closely related to neural

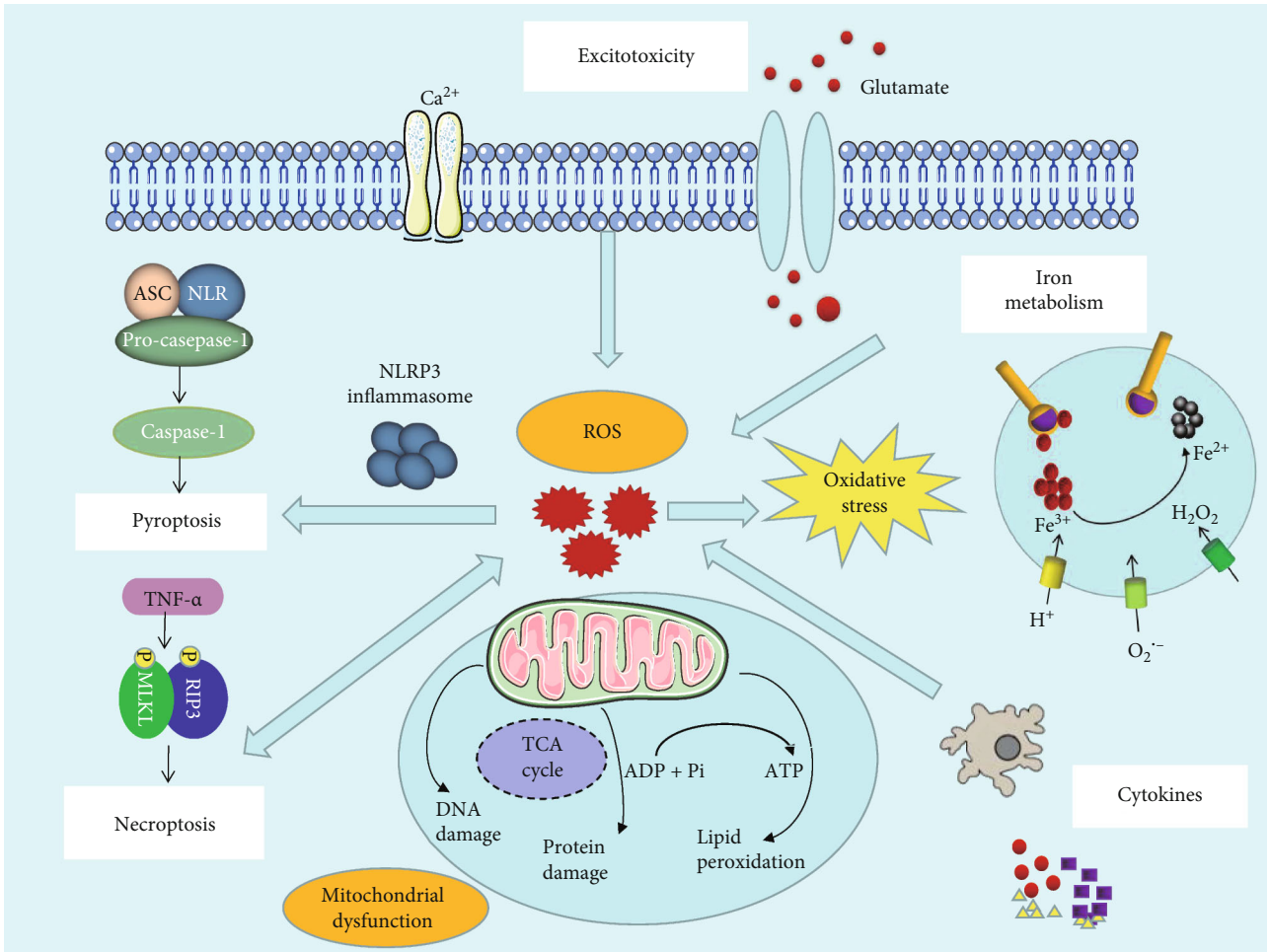

Figure 1: Schematic diagram of common pathological mechanisms that trigger oxidative stress. Primary mechanisms: (A) Formation of ROS. They are the main biomarkers of oxidative stress. A variety of enzymes including superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), nitric oxide (NO), and glutathione peroxidase (GPx) all belong to a group of molecules called ROS. (B) Mitochondrial dysfunction. ROS are mainly derived from oxidative phosphorylation (OXPHOS) occurring in the mitochondria. Secondary mechanisms: (C) Excitotoxicity. This occurs mainly through the excessive release of glutamate and the influx of Ca^{2+} to cause calcium overload in neurons, leading to the production of ROS. (D) Iron metabolism. When the amount of iron exceeds the cell's detoxification systems, the iron content increases, especially the ferrous (Fe^{2+}) content, and will promote the conversion of H_2O_2 to IOH through the Fenton reaction leading to an amplification of oxidative stress. (E) Cytokines. Inflammatory cells can release harmful compounds or cytokines, exacerbating oxidative stress. (F) Pyroptosis. ROS generation triggers the NLRP3 inflammasome to induce cell pyrolysis. (G) Necroptosis. The accumulation of intracellular ROS can cause necroptosis. In turn, TNF-induced necroptosis could also lead to ROS generation. Abbreviations: TCA cycle: tricarboxylic acid cycle; NLRP3: NLR pyrin domain-containing 3; RIP3: receptor-interacting protein 3; MLKL: mixed lineage kinase domain-like pseudokinase.

stem cell differentiation and migration in the long-lasting neurological recover time [8, 9]. Therefore, oxidative stress is extremely important in neurological diseases.

Increasing evidence shows that oxidative stress plays an essential role in the induction of BBB changes [10, 11]. ROS-related pathways that trigger BBB dysfunction include excitotoxicity, mitochondrial dysfunction, giant cell/microglial activation, extracellular transport, TJ modification, and MMP activation. This review will focus on the effects of oxidative stress-mediated BBB disruption in various neurological diseases with the goal of exposing novel therapeutic targets that can be exploited to treat neurological diseases in the future.

2. Molecular Mechanisms Involved in the Initiation of Oxidative Stress

At present, accumulating experimental and clinical evidence shows that oxidative stress plays a causative role in neurological diseases. The main primary mechanisms leading to the triggering of oxidative stress involve the formation of ROS and mitochondrial dysfunction, and the secondary mechanisms include excitotoxicity, iron metabolism, cytokines, pyroptosis, and necroptosis (Figure 1).

2.1. Formation of ROS. ROS are active substances produced when oxidative stress is imbalanced. Several important

molecules are involved in neurological diseases including nicotinamide adenine dinucleotide (NADPH), nitric oxide synthase (NOS), xanthine oxidase (XO), glutathione peroxidase (GPx), and catalase (CAT). Examples of ROS include superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), nitric oxide (NO), and hydroxyl radicals ($^{\bullet}OH$). All of these are unstable molecules that destroy cellular lipids and proteins, thereby activating intracellular ROS production [12]. Excessive amounts of ROS generation may be a critical factor contributing to oxidative stress in the pathogenesis of neurological diseases [13].

After excessive stimulation, NADPH and the electron transport chain will cause excessive production of ROS. NADPH is used as an electron donor to transfer electrons through the cell membrane, reducing molecular oxygen (O_2) to ROS [14]. NOX1 (NADPH oxidase 1) and NOX2 are the main sources of ROS in the pathophysiology of neurological diseases such as stroke [15], AD [16], and PD [17]. Thus, NOX-mediated oxidative stress has been identified as a primary contributor to BBB damage in neurological diseases [18, 19].

NOS is divided into inducible (iNOS), endothelial (eNOS), and neuronal (nNOS) [20]. NOS has four groups with redox-active structures, which can transfer electrons to O_2, and single electrons reduce O_2 to O_2^-, convert normal NOS into ROS ion-producing enzymes, and promote ROS production. Sustained oxidative stress results in NOS-mediated uncoupling of O_2. O_2^- is produced at the expense of NO. NO production from iNOS enzyme activation is a major factor in oxidative stress response. NO can dramatically affect the host's defense ability against various pathogens, but excessive production of NO may be detrimental and can cause neurological diseases [21, 22]. NOS activation leads to an increase in NO production [23]. NO and $ONOO^-$ may increase the permeability of the BBB by affecting TJ proteins or via the cyclic guanosine monophosphate-(cGMP-) protein kinase G (PKG) pathway [24, 25].

XO can activate xanthine dehydrogenase (XDH) through proteolysis to produce ROS during brain ischemia/reperfusion (I/R) [26, 27]. Although XDH mainly functions to produce hypoxanthine and xanthine to produce urate under normoxic conditions, XO promotes ROS production to induce brain damage under hypoxic conditions. Therefore, inhibition of XO has great advantages in reducing ROS production and protecting mitochondria from oxidative damage.

2.2. Mitochondrial Dysfunction. Mitochondria were identified as the center of the "free radical theory of aging," because they are not only the major source of ROS but also the major generators of energy in cells [28]. ROS are mainly derived from OXPHOS occurring in the mitochondria. Indeed, mitochondria producing ATP require cells to consume approximately 85% of O_2. Mitochondrial complex IV uses electrons derived from FADH2 or NADH to reduce O_2 to H_2O in the respiratory chain. The electron transport chain (ETC) activity will inevitably produce O_2^- [29]. The mitochondria are not only the major site of intracellular ROS production but are also the main target organelle of ROS-induced injury. The slower electron transfer of the mitochondrial respiratory chain results in increased ROS production and serious damage to the antioxidant system [30]. In addition, mitochondria are susceptible to nitrosation induced by $ONOO^-$ and NO·[31]. The latter can deleteriously alter the activities of enzymes such as Cyt-C oxidase and NAD dehydrogenase [32]. Furthermore, ROS-mediated ETC complex I, II, and III Fe-S center failure and the tricarboxylic acid cycle aconite lead to mitochondrial uncoupling [33]. The effects of reactive species on mitochondria and their metabolic processes ultimately lead to elevated levels of ROS, resulting in oxidation of DNA, mitochondrial proteins, and lipids [34, 35].

2.3. Mechanisms Responsible for ROS-Mediated Oxidative Secondary Damage

2.3.1. Excitotoxicity. Excitotoxicity refers to an abundance of excitatory amino acids (such as glutamic acid or excitatory toxins), which can lead to pathological responses through increased ROS and amino acid production. Glutamate is the core molecule in many neurological diseases [36–38]. It mainly promotes ROS generation in two ways. On the one hand, excessive release of glutamic acid leads to excessive activation of NMDARs and increased Ca^{2+} influx, resulting in calcium overload in neurons and disturbances in intracellular Ca^{2+} homeostasis that can lead to free radical production through multiple pathways. On the other hand, glutamate uncouples oxidative phosphorylation leading to increased Na^+ influx, enhances the activity of Na^+ and K^+-ATPase on the membrane, and consumes a large amount of energy, which in turn enhances mitochondrial respiratory function and promotes ROS production [39]. There is evidence that ROS are also involved in non-NMDA receptor-mediated glutamate neurotoxicity. Free radicals can inhibit glutamine synthetase, promote the release of glutamic acid, and inhibit glutamate reuptake. This leads to high concentrations of glutamic acid in the extracellular fluid exacerbating excitotoxicity [40]. That is, glutamate excitatory neurotoxicity is accompanied by ROS production, and ROS can intensify the excitotoxicity of glutamate through multiple pathways. In addition to inducing oxidative stress, excitotoxicity can aggravate BBB disruption by disrupting astrocyte function [41]. NO pathways can lead to mitochondrial disorders and increased BBB permeability following excitotoxicity [42, 43].

2.3.2. Iron metabolism. As an essential trace element of the human body, iron can be used as a catalyst in ROS production [44]. High iron levels in pathologically relevant brain regions and iron-mediated oxidative stress are the main factors involved in various neurological diseases [45–47]. When the amount of iron exceeds the cell's detoxification systems, the iron content, especially Fe^{2+}, increases and facilitates the conversion of H_2O_2 to IOH through the Fenton reaction. This promotes a preferable conversion rate in the Haber-Weiss cycle, resulting in the amplification of oxidative stress [48]. Ferritin, an iron storage protein, can act as a scavenger and a donor of free iron, a source of $^{\bullet}OH^-$. After the BBB is destroyed, the accumulated ferritin and free iron in brain capillary endothelial cells enter the penumbra together with

plasma ferritin. Iron-dependent oxidative stress in the penumbra can cause nervous system deterioration [49]. The imbalance of iron leads to the accumulation of free iron and the overload of iron in the brain, thus increasing ROS production. In this respect, excessive iron content in the brain has been reported in Huntington's disease (HD), PD, and AD [50, 51].

2.3.3. Cytokines. Inflammation is an interaction between the immune system and damaged tissues, which restores homeostasis through complex signaling pathways [52]. Inflammatory cells such as macrophages and neutrophils, immune factors, and chemokines can release harmful compounds or cytokines, thereby exacerbating oxidative stress to metabolically impair neurons, thus playing a critical role in neurological diseases. The signs of an inflammatory response include leukocyte infiltration and astrocyte and microglial activation [53]. After an injury, neutrophils, as a part of the inflammatory response, are recruited to the BBB [54]. In the process of inflammation, activated neutrophils are the main source of ROS, and enzymes such as NOX can catalyze ROS production [55]. The resulting ROS may negatively affect the integrity of the BBB through TJ protein modification or expression of inflammatory mediators [56]. Microglial phenotypes are also important for redox stability. After a cerebral infarction, NOX and NOS enzymes are activated, resulting in a sharp rise in ROS and RNS levels [57]. Under these conditions, ROS and RNS act as second messengers capable of regulating gene expression by inhibiting target phosphatases or inducing target kinases [58, 59]. Among these targets, nuclear factor-kappa B (NF-κB) in activated B cells is particularly sensitive to ROS and is essential for the acquisition of the proinflammatory M1 polarization.

2.3.4. Pyroptosis. Pyroptosis is a highly specific type of inflammatory programmed cell death different from necrosis or apoptosis, which was discovered recently. Accumulating research unveiled that pyroptosis plays a magnificent role in neurological diseases. Astrocytes induce the activation and proliferation of microglia, producing a large number of inflammatory mediators in the CNS. These inflammatory mediators can activate endothelial cells to produce a variety of tissue factors, increase excitatory amino acid toxicity, and promote the release of NO and ROS, thereby destroying intracellular lipids, proteins, and nucleic acids and triggering a variety of inflammatory cell signaling pathways, such as NF-κB and signal transducers and activators of transcription 3 (STAT3). These factors could induce caspase-1-independent pyroptosis downstream of noncanonical NLRP3 inflammasome activators, expand a cascade of inflammatory response, and aggravate neurological diseases [60, 61]. Studies have shown that ROS generation after cerebral I/R injury can destroy phagocytic cells and promote their rupture. The rupture may also trigger the NLRP3 inflammasome, and the rupture of lysosomes may damage cell integrity and activate the NLRP3 inflammasome signaling pathway to induce cell pyrolysis [62]. In addition, ROS are also an important factor in the regulation of NLRP3 inflammasome activation in TBI [63, 64]. They could be detected in neurons, astrocytes, and microglia in an injured brain, which contribute to inducing inflammatory response and neuronal death, as well as aggravating the neurological outcome [65, 66].

2.3.5. Necroptosis. Programmed necrosis (necroptosis) is a newly identified mechanism of regulated cell death combining features of both apoptosis and necrosis, which can be activated by several stimuli including oxidative stress, infection, inflammation, and activation of toll-like and cell death receptors [67–69]. Necroptosis has crucial functions in development and tissue homeostasis, yet emerging evidence has implicated this pathway in the development of several pathological conditions including various neurological diseases [70–72]. The accumulation of intracellular ROS can modify proteins, glucose, lipids, and nucleic acids in cells and tissues to cause dysfunction and cell death [73]. In turn, necroptosis could be activated by activating important metabolic enzymes including glycogen phosphorylase, glutamate ammonia ligase, and glutamate dehydrogenase 1; RIP3/RIP-like protein kinase 3 (RIPK3)/MLKL regulates tumor necrosis factor- (TNF-) induced ROS production [74]. Therefore, the participation of oxidative stress induced necroptosis as a common mediator of various neuronal demise. Pharmacological inhibition of necroptosis prevents mitochondrial dysfunction, oxidative injury, energetic failure, and dopaminergic neuronal loss in PD models [75]. Further studies demonstrated that upon TNF-induced necroptosis, the necrosome complex can translocate to the mitochondria and activate the pyruvate dehydrogenase and upregulate glycolysis and aerobic respiration leading to ROS generation [76].

3. Pathogenesis of Oxidative Stress-Mediated BBB Disruption

The BBB is a heterogeneous structure of the vasculature which is more susceptible to oxidative stress and neurovascular uncoupling damage in a specific region. Oxidative stress plays a pivotal role in the changes in the BBB. Oxidative stress can damage a variety of cells such as BMVECs, pericytes, and astrocytes, destroying the BBB. To some extent, as a result of vicious circles generated at molecular levels, it is difficult to separate or clearly indicate the cause and the effect of oxidative stress on BBB. A detailed description of the various pathological mechanisms of oxidative stress-mediated BBB disruption has been provided in the schematic illustration (Figure 2).

3.1. Tight Junctions. Tight junctions act as molecular gatekeepers of the paracellular space by mainly blocking water-soluble molecules, ions, blood-borne toxins, drugs, and pathogens from permeating the BBB channels [77]. The TJ chain of the brain endothelium consists of intact membrane proteins (claudins, obliteratin, and connecting adhesion molecules (jams)) [78], which are involved in intercellular contacts and interaction with cytosolic scaffolds ZO protein and actin cytoskeleton [79] and related proteins, including VE-cadherin [80], protein kinase [81], small GTPase [82], and heterotrimeric G protein [83]. Several lines of evidence indicate that TJ proteins are critical for the maintenance of BBB integrity.

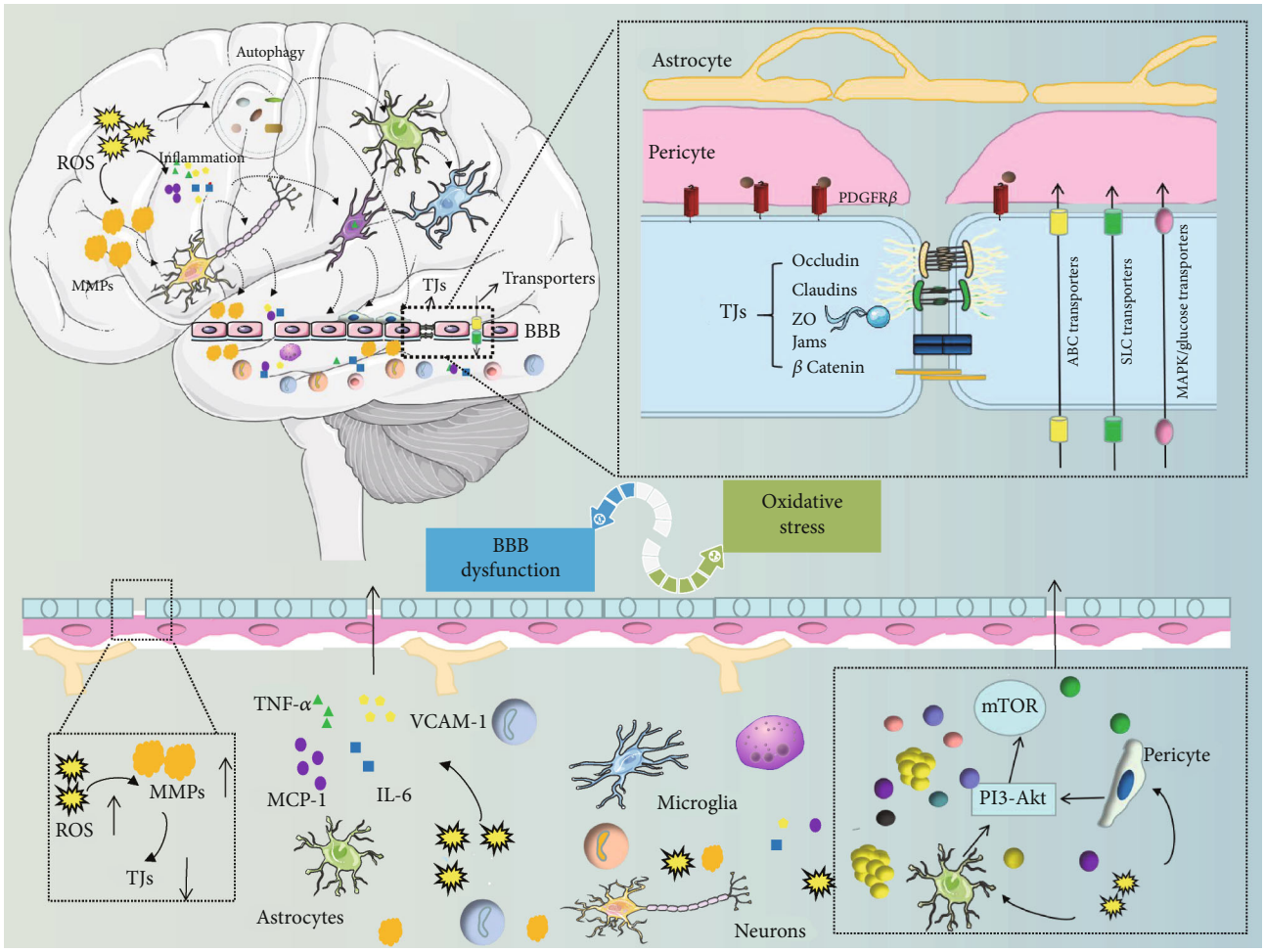

Figure 2: Schematic illustration of the main pathological mechanisms of oxidative stress-mediated BBB disruption. BBB is a highly complex and dynamic structure composed mainly of BMVECs, astrocytes, pericytes, and basement membrane. Oxidative stress can damage a variety of cells, such as BMVECs, astrocytes, and pericytes, and structures such as tight junctions (TJs) and basement membranes leading to the destruction of the BBB. (A) Many soluble carrier (SLC) transporters expressed in BMVECs allow substances such as peptides, amino acids, and glucose to selectively cross the BBB. ATP-binding cassette (ABC) transporters work by releasing toxic substances and drugs into the blood preventing them from entering the brain. (B) ROS can directly or indirectly promote MMP protein expression and can cause an increase in inflammatory factor levels, leading to BBB leakage possibly through degradation of TJ proteins and basement membrane proteins. (C) Tight junctions include TJ-related proteins such as occludin, claudin-5, and ZO-1. (D) Oxidative stress causes BBB disruption through induced lysosomal dysfunction, autophagy of the hippocampus, pericytes, and astrocytes, which may be involved in activating the AKT/mTOR signaling pathway. Abbreviations: IL-6: interleukin-6; MCP-1: monocyte chemoattractant protein-1; VCAM-1: vascular cell adhesion molecule-1; ZO: zonula occludens.

Pericytes and astrocytes associate with endothelial cells to mediate the formation of TJs essential to the function of the BBB. It has been reported that pericytes induce the synthesis of TJ proteins such as occludin, claudin-1, ZO-1, and ZO-2 by releasing proangiogenic protein factors, suggesting that the interaction between pericytes and endothelial cells can maintain the integrity of BBB [84]. Another type of cell that interacts with pericytes is astrocytes. Astrocytes regulate the integrity of TJs through signaling pathways such as WNT [85]. In vitro studies indicate that astrocytes can regulate TJ tightness and polarized distribution of transporters at the endothelial level [86]. Therefore, any changes in these proteins will affect the permeability of the BBB.

Occludin is the main structural protein of the TJs, and its expression level can represent the structural state of the BBB; for example, lower levels of occludin can signify BBB damage [87]. Experimental data showed that the expression and post-translational modification (phosphorylation) of occludin are tightly regulated, and its levels of expression reflect changes in BBB permeability [88]. Claudin protein may act as a regulatory target of the BBB and can alter the selective opening of tight junctions. The production of ROS can regulate the expression of claudin-5, increase the leakage of solute, and affect the BBB integrity [89–91]. Similarly, AMP-activated protein kinase (AMPK) activation was shown to reduce the expression of occludin and improve the functions of the BBB impaired by LPS through suppression of NADPH oxidase-derived ROS in mice [92]. The JAM subtype regulates cell bypass permeability of the BBB, especially in immune cells (i.e., neutrophils and monocytes/macrophages)

[93]. Malfunctioning of BMVECs of the BBB can be directly caused by the absence of JAM proteins in the TJs [94]. In addition to claudin and occludin, ROS can also change the permeability of the BBB by affecting the distribution of ZO protein. Exposure to hydrogen peroxide led to the redistribution of ZO-1 from the TJ_S to the cytosol, resulting in decreased transepithelial electric resistance (TEER) and increased BBB permeability [95]. That is, the expression, phosphorylation, and distribution of TJ proteins are important factors affecting BBB permeability. Therefore, any change of these parameters caused by ROS may compromise the integrity of the BBB. Increasing evidence suggests that there is a correlation between BBB disruption, oxidative stress, alteration of TJ complexes, and the progression of various neurological diseases [96, 97].

3.2. Transporters. Transporters, an important component of maintaining the strength of the BBB, can protect the CNS from exposure to circulating chemicals by regulating the exchange between the CNS and blood and controlling the ability of many endogenous and exogenous substances through pores [98]. These transporters mainly include ABC and SLC transporters. Among these, ABC transporters are the most important involved in limiting the permeability of several toxins and therapeutic agents [99]. In particular, ABCB1 (P-gp), ABCC (MRPs), and ABCG2 (BCRP) as exogenous efflux pumps driven by ATP participate in the extrusion of drugs from cells, thus limiting the delivery of small-molecule drugs to the brain [100]. Oxidative stress-induced signaling pathways that affect the expression of ABC transporters may be essential regulators in the pathogenesis and treatment of CNS diseases. After detoxification by binding to molecules like glutathione (GSH), glucuronic acid, and sulfate, toxic compounds can then be extruded by ABC transporters.

As discussed above, ROS participate in cytotoxicity and play a pivotal role in the signal transduction of multiple transcription factors, such as HIF-1, NF-κB, and nuclear factor E2-related factor 2 (Nrf2) [101]. In turn, these transcription factors could regulate the expression of ABC transporters. NF-κB activation is associated with the overexpression of P-gp in the brain caused by epilepsy [102]. Nrf2 is a cell sensor of oxidative stress. It was found that with the activation of oxidative stress, the expression levels of Nrf2 and the activity of P-gp, Mrp2, and Bcrp increased in the BBB [103]. Strikingly, reactive astrocytes display an increased expression of P-gp and Mrp1 in multiple sclerosis (MS) lesions [104].

Compared with ABC transporters, SLC transporters act as the "metabolic gate" of cells and mediate the transport of various necessary metabolites and nutrients, including glucose, neurotransmitters, inorganic/metal ions, and amino acids [105]. Of the known SLC transporters that transport drugs across the BBB, the most common target transporters are members of the SLC21A/SLCO family, which includes organic anion transporters (human and rodent Oatps). OATP/Oatp is the prototype transporter of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins), which has antioxidant and neuroprotective functions that could be of great advantage in neurological diseases [106, 107].

In addition to ABC and SLC transporters, ROS can also change BBB permeability by modulating AMPK. AMPK has been reliably confirmed to target transporters, including glucose transporter types 1 and 4 (i.e., GLUT-1 and GLUT-4), K^+, and Cl^- channels in the epithelium [108, 109] and Na-K-Cl (NKCC2) cotransporters [110]. AMPK is also known to be involved in critical cell stress signaling responses in the BBB [111]. The interaction between pericytes and astrocytes is essential for maintaining BBB integrity and AMPK protein kinase activity and influencing the expression of glucose transporters GLUT-1 and GLUT-4 and glucose uptake [112].

3.3. Matrix Metalloproteinases. Zinc-containing proteolytic matrix metalloproteinases (MMPs) can degrade the extracellular matrix and the epithelial basement membrane thus affecting the integrity of the BBB [113]. Endothelial cells, basement membranes, and TJs are essential for the normal functioning of the BBB. In turn, any disruptive changes in the BBB can compromise its integrity leading to neurological disease progression [114]. It has been suggested that inhibiting MMPs prevents the digestion of basement membrane proteins and TJs thus preventing BBB compromise [115]. Therefore, MMP activity is the key mediator of BBB permeability [116, 117]. ROS directly downregulate TJs and indirectly activate MMPs that promote the opening of the BBB [118, 119]. Oxidative stress-induced activation of MMPs and aquaporin leads to the loosening of the perivascular units and vasculature, promotes vascular or cellular fluid edema, enhances BBB leakage, and leads to neuroinflammatory progression [120–122]. The structural changes of pericytes and astrocytes increase the permeability of BBB, which leads to the entry of microbial pathogens into the brain, the accumulation of neurotoxic substances, and the induction of oxidative stress [123]. In addition, oxidative stress can activate the secretion of MMP-9 and other factors by pericytes and astrocytes, degrade the basement membrane, change the expression and distribution of TJ proteins, and aggravate the damage of BBB [124].

3.4. Inflammation. Excessive oxidative damage occurs when inflammatory cells release large amounts of ROS at the inflammatory site. Beyond that, increased intracellular ROS levels accelerate the proinflammatory response. ROS activate a variety of redox-sensitive transcription factors and are involved in the inflammatory response, leading to BBB damage. NF-κB, as a major regulator of the inflammatory response, is mainly activated in a redox-dependent manner. Activation of NF-κB by ROS can increase intercellular adhesion molecule-1 (ICAM-1) and VCAM-1 expression [125]. The activation of the Ca^{2+} signaling pathway by ICAM-1 can lead to changes in the cytoskeleton in BMVECs, leading to BBB damage [126]. Macrophage/microglial activation appears to be an early stage of injury, and before BBB breakdown, inhibition of its activation prevents BBB dysfunction [127]. Activated macrophages/microglia can induce the expression of cytokines (i.e., TNF-α and Egr-1), leading to

BBB destruction [128, 129]. Release of IL-1β in astrocytes leads to immune cell recruitment, BBB destruction, edema, and loss of neurons [130]. MCP-1 from astrocytes and microglia can attract microglia to sites of injury and stimulate monocyte migration through the BBB [131]. Crosstalk among BMVECs, pericytes, and astrocytes occurs through soluble factors, including cytokines [132]. Oxidative stress leads to the death of pericytes and further destruction of BBB. Pericytes can mediate inflammatory cascades and white matter damage and eventually increase nerve damage [133]. TGF-β, IL-6, glial cell line-derived neurotrophic factor, and basic fibroblast growth factor released by astrocytes can change the barrier characteristics of BMVECs. In contrast, leukemia inhibitory factors released by BMVECs can induce astroglial differentiation, further aggravating BBB injury [134].

3.5. Autophagy. Autophagy is a cellular degradation pathway that transports damaged, denatured, or senescent proteins and damaged organelles to the lysosome for digestion and degradation. Therefore, under physiological and pathological conditions, the autophagy pathway can be critical for neuronal homeostasis and can play the role of a local housekeeper [135]. Some recent findings suggested that oxidative stress caused BBB disorders through induced lysosomal dysfunction, autophagy activation in the hippocampus, pericytes, and astrocytes [136–138]. In in vivo and in vitro subarachnoid hemorrhage (SAH) models, mTOR inhibition has a potent protective effect on neuronal damage after SAH by reducing excessive mitochondrial fission [139]. Studies have found that oxidative stress induces damage to the frontal cortex and hippocampal neurons. The mechanism for this damage may involve the activation of the AKT/mTOR signaling pathway to regulate autophagy and inhibit neuronal apoptosis [140]. Studies have found that in astrocytes exposed to H_2O_2, 2-(2-benzofuranyl)-2-imidazoline (2-BFI) can exert cytoprotective effects by enhancing lysosomal stability under conditions of oxidative stress [141]. A study indicated that autophagy was activated during starvation and protected the endothelial barrier integrity by scavenging ROS and inhibiting the redistribution of claudin-5 [89]. A novel mechanism of autophagy disturbance secondary to nitrosative stress-induced tyrosine nitration of transient receptor potential M2 (TRPM2) during pericyte injury both in vitro and in vivo has been revealed [142]. A prolonged oxidative stress in astrocytes inhibits LC3 lipidation and impairs autophagosome formation and autophagic flux, despite concomitant activation of several proautophagic signals [143]. ROS can induce autophagy under conditions of oxidative stress, and autophagy can reduce the damage caused by oxidative stress. Therefore, both ROS and autophagy can jointly maintain the stability of the intracellular environment and the structural and functional integrity of brain cells and the BBB [144, 145].

4. Oxidative Stress-Mediated BBB Disruption in Neurological Diseases

Recent researches have suggested that oxidative stress-mediated BBB disruption is an important process in various neurological diseases, including IS, hemorrhagic stroke, TBI, AD, PD, ALS, and CSVD (Table 1).

4.1. Ischemic Stroke. Ischemic stroke is a destructive cerebrovascular disease that has become the leading cause of long-term disability and the fourth leading cause of death worldwide [173]. Oxidative stress plays a critical role in I/R-induced brain injury [174, 175]. Various mechanisms in the body can trigger oxidative stress, including mitochondrial dysfunction, excitatory toxins, and glutamate release, and defects in the antioxidant system, and enzymes and phagocytes can activate oxidative stress [176, 177]. Mitochondria are both important intracellular organelles for energy metabolism organelles, the main intracellular source of ROS [178], and important targets for I/R injury [179, 180]. During cerebral ischemia, inflammatory factors, oxidative stress, and calcium overload stimulate the mitochondria, causing them to produce large amounts of ROS, thereby initiating the mitochondrial necrosis program and causing cell death. In addition, macrophages, endothelial cells, and other immune cells produce large amounts of ROS during the cerebral ischemia phase [181], which in turn induce the expression of NF-κB, NOS, and proinflammatory factors, triggering the upregulation of vascular endothelial cell adhesion molecules and causing BBB permeability.

The occurrence of ischemic stroke and subsequent reperfusion reduces the integrity of the BBB and increases cell permeability, causing brain edema [182]. Inflammatory factors can directly damage neurons by permeating the compromised BBB, aggravating I/R injury [183]. Importantly, I/R injury involves changes in endothelial barrier function and recruitment of immune cells, both of which are conducive to oxidative stress and the BBB disruption. Using experimental models of cerebral ischemia, abundant evidence indicates that molecules such as NOX, NOS, or GPx can reduce oxidative stress and protect the BBB and brain from I/R injury [184, 185]. Recent research showed that stanniocalcin-1 attenuates I/R injury by reducing oxidative stress and BBB permeability [186]. Dihydrocapsaicin downregulated ROS, NOX2, NOX4, NF-κB, and MMP-9 levels to reduce oxidative stress and increase TJ protein expression, thereby protecting the BBB and brain from I/R injury [147].

4.2. Hemorrhagic Stroke. When compared with ischemic stroke, hemorrhagic stroke is more detrimental, with higher mortality and morbidity [187]. The pathophysiological processes of cerebral injury after intracranial hemorrhage (ICH) can be divided into primary mechanical injury and secondary brain injury, involving oxidative stress, BBB disruption, excitotoxicity, neuroinflammation, and neuronal apoptosis [188, 189]. Increasing evidence suggests that oxidative stress plays a role in the pathological process of ICH and in the important stages of the pathophysiological response to ICH [190]. Multiple pathways can induce ROS production after ICH, the two main pathways. First, blood cell breakdown products such as hemoglobin, ionized iron, and thrombin can induce free radical generation [191]. Increased extracellular iron levels during ischemia can lead to excessive activation of glutamate receptors, thereby promoting iron

Table 1: Oxidative stress-mediated BBB disruption in neurological diseases.

Diseases	Model	Targets		Pathways	Mechanisms	Ref
		Oxidative stress	BBB			
IS	MCAO, rat	MDA, GSH, and NADPH	ZO-1 and occludin	REK	Oxidative stress and tight junctions	[146]
	MCAO, rat	NOX2, NOX4, ROS, MDA, GPx, and NO	Occludin, MMP-9, Nrf2, and Nqo1	MAPK	MMP, oxidative stress, and inflammatory response	[147]
	OGD/R, BMVECs	ROS	ZO-1 and claudin-5	PI3K/Akt/Nrf2	Oxidative stress	[148]
	MCAO, rat; OGD/R, primary cortical neurons	NO, MDA, and ROS	IL-6 and TNF-α	NF-κB	Neuroinflammation and oxidative stress	[149]
	MCAO, rat; OGD/R, BMVECs	ROS	ZO-1	mTOR	Cell autophagy and oxidative stress	[150]
Hemorrhagic stroke	Autologous blood injection, rat	ROS	ATP, Bcl-2, Bax, caspase-3, and caspase-9	DJ-1/Akt/IKK/NF-κB	Apoptosis, oxidative stress, and inflammatory response	[151]
	Collagenase injection, rat	ROS, GSH-px, and SOD	ZO-1 and occludin	MAPK	Oxidative stress	[152]
	LPS-activated, microglia	ROS, NOX2, and NOX4	CD86, Arg1, CD206, IL-1α, IL-1β, TNF-α, and FeSO4	Not mentioned	Oxidative stress, inflammatory response, and iron metabolism	[153]
	Autologous blood injection, rat; OxyHb, primary rat cortical neurons	ROS, NOX1, and NOX2	TNF-α, MMP-9, NQO1, Bcl-2, Bax, caspase-3, CD14, CD68, γ-H2AX, and XRCC1	HO-1	Oxidative stress, apoptosis, inflammation, mitochondria injury, and DNA damage	[154]
TBI	Free fall brain trauma, rat	ROS, SOD, and 4-HNE	MMP-9, ZO-1, and occludin	JNK	MMP inhibition and oxidative stress	[155]
	A cryogenic injury, mice; biaxial stretch SI, BMVECs	ROS	GFAP, IL-6, IL-β, and ICAM-1	Nrf2/HO-1 and NF-κB	Oxidative stress and inflammatory response	[156]
	Controlled cortical, mice	SOD, CAT, and GSH	TNF-α, NLRP3, caspase-1, IL-1β, and IL-6	AMPK and Nrf2	Oxidative stress, inflammation, and apoptosis	[157]
	Controlled cortical, mice	SOD, GPx, and MDA	NQO1 and Bax	Nrf2-ARE	Oxidative stress and apoptosis	[158]
AD	Neuronal damage, neurons	ROS, 4HNE, H_2O_2, SOD, MDA, and GPx4	MMP	Nrf2/HO-1	MMP inhibition and oxidative stress	[159]
	H_2O_2-induced N2a, SH-SY5Y cells	ROS	Fe^{2+} and Fe^{3+}	Nrf2/HO-1	Iron metabolism and oxidative stress	[160]
	Injection of D-galactose and Aβ25-35-ibotenic acid, rats	SOD, MDA, and GSH-Px	5-HT, methionine, glutamine, and tryptophan	AMPK-SIRT	Oxidative stress and energy metabolism	[161]
	H_2O_2-induced, PC12 cells	ROS	Caspase-3, MMP	ASK1-JNK/MAPK	MMP inhibition, apoptosis, and oxidative stress	[162]
	Aβ-induced, rats and SH-SY5Y cells	ROS	TXNIP	Not mentioned	Oxidative stress	[163]
PD	People, blood	ROS	P-gp	Not mentioned	Oxidative stress	[164]
	H_2O_2-induced, rat and PC12 cells	SOD and catalase	Caspase-3 and Hsp-70	Nrf2/HO-1	Oxidative stress and apoptosis	[165]

Table 1: Continued.

Diseases	Model	Targets: Oxidative stress	Targets: BBB	Pathways	Mechanisms	Ref
	6-OHDA-treated, mice	DA, ROS, and SOD	IL-1β and TNF-α	PI3K/AKT and IKK/IκBα/NF-κB	Neuronal inflammation and oxidative stress	[166]
	6-OHDA-induced, mice and SH-SY5Y cells	ROS and GSH	Caspase-3, Bax, and Bcl-2	Nrf2/HO-1	Oxidative stress and apoptosis	[167]
	MPTP-induced, mice and PC12 cells	ROS	Mitochondrial membrane potential and caspase-3	ROS/JNK	Oxidative stress and apoptosis	[168]
ALS	hSOD1-linked, Drosophila and NSC-34 cells	GSH and GCLC	HSP70	Nrf2/STAT3	Oxidative stress	[169]
	SOD1 mutation, B6SJL-Tg 1Gur/J mice	COX, LDH, thiol groups, and lipid dienes	Cav-1, respiratory capacity rate, and cholesterol	Not mentioned	Mitochondrial bioenergetics and oxidative stress	[170]
CSVD	Spontaneously hypertensive, rat	SOD, GSH, MDA, and CAT	IL-6, TNF-α, IL-1β, Bcl-2, caspase-3, and VEGF	STAT3/VEGF	Oxidative stress and inflammatory response	[171]
	Spontaneously hypertensive, rat	SOD, GSH, MDA, and CAT	TNF-α, IL-6, IL-1β, MCP-1, and COX-2	Not mentioned	Oxidative stress and inflammatory response	[172]

Abbreviations: OGD/R: oxygen-glucose deprivation/reperfusion; MCAO: middle cerebral artery occlusion; OxyHb: Oxygen hemoglobin; SI: stretch injury; SH-SY5Y: human neuroblastoma cells; 4HNE: 4-hydroxynonenal; DA: dopamine; GCLC: glutamate-cysteine ligase catalytic; Bcl-2: B cell lymphoma-2; Bax: Bcl-2-associated X protein; Arg1: arginase 1; XRCC1: X-ray repair crosscomplementing gene 1; GFAP: glial fibrillary acidic protein; NQO1: NAD(P)H:quinone oxidoreductase; 5-HT: 5-hydroxytryptamine; TXNIP: thioredoxin-interacting protein; VEGF: vascular endothelial growth factor; Hsp-70: heat shock protein 70; Cav-1: caveolin-1; COX-2: cyclooxygenase-2; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; HO-1: heme oxygenase-1; SIRT: sirtuin; ASK1: apoptosis signal-regulating kinase 1; PKC: protein kinase C.

uptake in neurons and subsequent excessive production of membrane peroxides [192]. Experimental results show that deposition of free iron can trigger oxidative stress, leading to nerve damage, cytotoxicity, and poor outcomes after thrombolytic therapy following an acute stroke [193, 194]. In addition, the use of nonspecific ROS scavengers and NADPH oxidase inhibitors can reduce ROS production and neurotoxicity, improve cerebral vascular function, and reduced cerebral amyloid angiopathy-related microhemorrhages [153, 195]. Also, infiltration of macrophages, excessive microglial activation, and neutrophils releasing large amounts of ROS, NO, and the activation of a series of cascades mediate direct and indirect neuronal damage and promote neuronal apoptosis, astrocyte necrosis, and cerebral edema after ICH [196, 197]. These overlapping mechanisms interact to cause BBB disruption, loss of neurons, and glial hyperplasia leading to permanent neurological deficits [198, 199]. Therefore, ROS and BBB play a key role in brain injury after a hemorrhagic stroke.

ROS can trigger multiple interconnected molecular and cellular pathways involved in BBB disruption after ICH. Studies in animal models have shown that ROS can also upregulate MMP-9 expression, degrade TJ proteins, and activate microglia, leading to BBB disruption following ICH [200, 201]. There is also emerging evidence that ROS are maintained at a stable level via a stable ROS production balance and a balance of mitochondrial oxidative phosphorylation and antioxidant mechanisms [202]. A recent study showed that the overexpression of E3 ubiquitin ligase ring finger protein 34 in mice exacerbates ICH-induced neurological deficits and brain injury, hematoma volume, and BBB disruption by facilitating mitochondrial dysfunction-mediated oxidative stress [203]. More importantly, the presence of multiple inflammatory mediators such as IL-6 and lipopolysaccharides has been noted after ICH. These can induce the production of ROS, activate microglia and astrocytes, and disrupt the BBB causing brain edema [204, 205]. Thus, oxidative stress and BBB disruption are also pivotal in the underlying pathological process of ICH.

4.3. Traumatic Brain Injury (TBI). TBI is the main cause of mortality and morbidity in children and young adults [206, 207], and it is currently estimated to be the third largest cause of global disease burden [208, 209]. Accumulating evidence strongly suggests that oxidative stress is a major threat in the development of TBI [210]. Besides, it has been reported that biomarkers of oxidative stress accumulate in patients with TBI [211].

ROS production may lead to lipid peroxidation, protein crosslinking, DNA breakage, mitochondrial electron transport chain damage, and disruption of the structure and function of brain cells [212]. Lipid peroxidation, a sequence of

oxidative stress in TBI, also triggers the formation of aldehyde byproducts including propenal (acrolein) and 4-HNE from neurotoxic reactions. These byproducts aggravate the production of ROS/RNS, mitochondrial dysfunction, and BBB dysfunction and permeability. Finally, aldehyde byproduct accumulation will lead to intracellular Ca^{2+} overload leading to the activation of proteolytic degradation of neuronal cytoskeletal proteins [213, 214]. NOX is the main source of ROS after TBI [215]. A recent study has confirmed that the deletion of NOX4 decreases the severity of TBI [216]. The absence of NOX2 can reduce the expression of M1-like markers in microglia/macrophages which initiate damage of the cerebral cortex [217]. Studies have indicated that ICAM-1 can increase markers of oxidative stress, promote microglial transformation into the activated phenotype, promote BBB permeability, and increase the neuropathological index [218]. Increasing exposure of endothelial cells to ROS can increase the function of contraction and adhesion molecules, resulting in functional impairment of the BBB [219]. Impairment of pericyte-endothelium crosstalk results in BBB disruption following TBI [10].

In TBI, MMPs, ROS, and inflammatory cytokines including TNF-α, IL-1β, and TGF-β are activated [220]. ROS promote blood vessel and cellular edema through oxidative stress-induced MMP activation and aquaporin release and increase the BBB permeability, leading to the progression of neuroinflammation [122]. Ultimately, similar to the destruction of the BBB in TBI, circulating neutrophils, macrophages, and lymphocytes are recruited to the injured sites to further exacerbate the inflammatory response. In the early stage of TBI, the brain parenchyma upregulates the expression of leukocyte adhesion molecules on brain endothelial cells [221]. Leukocytes can further damage the BBB by secreting cytokines and chemokines, promoting ROS generation, and hydrolyzing proteases, in addition to other mechanisms [222].

4.4. Alzheimer's Disease (AD). AD is a multifactorial neurological disease, characterized by the formation, aggregation, and accumulation of amyloid-beta (Aβ). As mentioned above, oxidative stress can cause BBB dysfunction through neurotoxicity, mitochondrial dysfunction, heavy metal deposition, etc. In turn, the BBB can also trigger oxidative stress and neuroinflammation, enhance the activity of secretases, and finally promote the generation of Aβ. With gradual accumulation of Aβ in the brain and the presence of oxidative stress, BBB dysfunction may become a vicious circle, leading to cognitive impairment and dementia.

Studies have shown that Aβ-induced oxidative imbalance is related to elevated levels of byproducts of protein oxidation, lipid peroxidation, and DNA/RNA oxidation levels [223–225]. Also, oxidative stress is a crucial determinant of Aβ accumulation, triggering mitochondrial dysfunction and apoptosis [226, 227]. Studies have shown that damaged mitochondria can produce ROS and other active substances, which can lead to abnormal phosphorylation of tau protein [228–230]. The latest progress in the study of the gene expression profile of an AD brain shows that the production of brain insulin and insulin signal transduction are significantly impaired, indicating that an AD brain shows the characteristics of a diabetic brain; that is, brain insulin depletion can lead to the initiation of mitochondrial dysfunction and increase oxidative stress and the sensitivity to brain insulin [231].

In a recent study, the mouse microglial cell line BV2 was used to establish the H_2O_2-mediated oxidative stress injury model of cells, which led to MMP-9 degradation, apoptosis, and BBB destruction [232]. The expression of nNOS was increased in astrocytes around β-amyloid plaques in humans [233]. Other teams also reported increased expression of eNOS and iNOS in the neurofibrils, suggesting that the production of NO and peroxynitrite by reactive astrocytes plays a critical role in the pathogenesis of AD [234, 235]. Since oxidative stress/nitration stress and NO production by active astrocytes and microglia in neurofibrillary tangles are markers of AD, even in the early stages, targeting ROS production as a therapy could be potentially important for curbing disease progression.

4.5. Parkinson's Disease (PD). PD is characterized by selective damage of dense dopaminergic (DA) neurons in the substantia nigra and the loss of DA levels in the striatum nigra in the brain [236]. Accumulating evidence strongly suggests that ROS are crucial determinants leading to the loss of DA neurons in a PD brain, low GSH, mitochondrial dysfunction, neuroinflammation, and disorders of metal metabolism [237]. In addition, there are several polyunsaturated fatty acids in the brain that can undergo lipid peroxidation under conditions of oxidative stress releasing toxic products [238]. Similarly, evidence of elevated ROS levels in the brains of PD patients includes the occurrence of lipid, protein, and DNA oxidation as documented in numerous studies [239, 240].

Although most of the DA released at the end of the synapse is reabsorbed by DA neurons, astrocytes may reabsorb some dopamine. Astrocytes play an active and key role in the development of PD, and they mediate the survival and function of neurons [241]. A recent study has indicated that dopamine-induced activation of the pentose phosphate pathway in astrocytes reduces oxidative stress and exerts a neuroprotective role in PD [242]. Oxidative- or ROS-induced molecules, such as α-synuclein, neuromelanin, and active MMP-3, from damaged substantia nigra dopaminergic neurons trigger microglial activation. The active form of MMP-3 is increased in response to oxidative stress in dopaminergic cells. MMP-3 leads to the activation of microglia, thus producing RNS and ROS [243]. It was found that MMP-3 induced by oxidative stress can also result in BBB degradation and neutrophil infiltration, further resulting in neuroinflammation [244].

4.6. Amyotrophic Lateral Sclerosis (ALS). ALS is one of the most devastating neurological diseases. Autopsy and laboratory studies in ALS have shown that oxidative stress plays a critical role in motor neuron degeneration and astrocyte dysfunction [245, 246]. Increased oxidative stress biomarkers in cerebrospinal fluid, plasma, and urine indicated abnormal oxidative stress outside of the CNS [247]. Recent studies suggest that oxidative stress is part of the neuroinflammatory

response and may be triggered by a combination of mitochondrial dysfunction and pathophysiological activation of astrocytes and microglia in G93A-SOD1 rats and mice [248]. Considerable experimental evidence suggests that ROS generation in motor neurons in response to excitotoxic activation can induce oxidative damage of glutamate transport in surrounding astrocytes, leading to excitatory stress expansion and, thereby, triggering the development of ALS [249, 250]. The end of the stellate cells lining the BBB is rich in two proteins, aquaporin 4 (AQP4) and inward rectifying potassium channels (Kir) [251]. Both channels are important for maintaining a functional BBB astrocyte lining. Studies have found that the ability of astrocytes to maintain water and potassium homeostasis is hindered in the ALS model. The imbalance in homeostasis affects the BBB, disrupts the microenvironment of neurons, and causes neuronal dysfunction and death [252]. A recent study has indicated that the pivotal mechanism that promotes the pathogenesis of ALS, which involves the Ets-2 transcription factor of the Bts-xL gene, protects glial cells from oxidative stress [253].

4.7. Cerebral Small Vessel Disease (CSVD). CSVD refers to a variety of clinical manifestations such as hypertension, acute stroke, and cognitive dysfunction caused by pathological changes in the cerebral microcirculation (including small blood vessels or microvessels) [254, 255]. The pathogenesis of cerebral microangiopathies involved endothelial dysfunction, BBB disruption, oxidative stress, amyloid deposition, and decreased blood perfusion [256, 257].

Among these mechanisms, BBB disruption and oxidative stress are considered to be important pathophysiological mechanisms of CSVD [258, 259]. BBB injury, as an early feature of CSVD, involves vascular endothelial dysfunction, TJ destruction, and degradation of the extracellular matrix [260]. Increased BBB permeability plays a critical role in normal aging, dementia, white matter, lacunar infarction, and CSVD. Aging and hypertension have a synergistic effect on aggravating BBB injury, which will eventually promote oxidative stress in brain tissues [261]. For example, the expression of NO was increased compromising areas of the BBB. Peripheral cytopathy leads to disruption of the BBB and microvascular disruption as well. The mechanism leading to this disruption may be related to the end of astrocytes detached from the brain microvessels, the leakage of plasma proteins, and the decreased expression of endothelium adhesion connexin [262]. In addition to endothelial cell injury, the decrease in pericyte coverage in aged hypertension mice further reduces the integrity of the BBB [263]. Ischemic injury induces increased expression of MMPs, which impairs BBB integrity by changing the structure of TJ proteins and pericyte damage [264, 265]. A study found that white matter damage, cognitive damage, brain atrophy, TJ protein expression, and microglial proliferation were downregulated in a mouse model of persistent cerebral hypoperfusion. These indicated that impaired BBB plays a role in the pathogenesis of CSVD [266].

Excessive ROS are generated during tissue injury, triggering neuron edema and release of excitatory transmitters, which activate excitatory toxic cascades leading to the activation of inflammatory cells, exacerbating focal neurovascular injury [267]. Endothelial dysfunction may be caused by oxidative stress and inflammation. Conditions such as hypertension, diabetes, hypercysteineemia, smoking, and infection produce large amounts of ROS [268, 269]. In hypercholesterolemic apolipoprotein E gene-knockout mice, NOX2 knockout can block the production of ROS and damage of the cerebral vasodilation [270]. Similarly, the absence of NOX2 can prevent obesity-induced cerebral small blood vessel dysfunction [271]. The cerebrovascular network is one of the main goals of the process of local oxidative stress. Local oxidative stress can trigger damage to the vasculature and changes in BBB and blood flow and can promote changes in neurodegeneration in brain tissues [272]. A recent study indicated that salvianolic acid B ameliorated oxidative stress and neurocyte apoptosis, attenuated BBB disruption, and restored cognitive deficits and angiogenesis in a rat model of CSVD via the STAT3/VEGF signaling pathway [171]. Oxidative stress is involved in disrupting microvascular integrity, loss of integrin, and leakage of plasma proteins, which collectively destroy the integrity of the BBB [273].

5. ROS Can Affect the Integrity of the BBB via Mechanisms Interconnecting Multiple Organ Systems

In addition to the main factors described earlier that ROS can cause BBB disruption, recent studies also show that ROS can affect the BBB via mechanisms interconnecting multiple organ systems (Figure 3).

5.1. Microflora Gut-Brain Axis. With the recognition of a two-way communication system between the gut and brain, there is evidence that the "microbiota gut-brain axis" plays a major role in neurological diseases [274, 275]. The microflora gut-brain axis is considered a two-way neuroendocrine system and plays a pivotal role in oxidative stress response. Dietary ingestion of antioxidants, such as probiotics [276], prebiotics, and polyphenol [277], can influence gut microbiota composition, thereby contributing to the integrity of the BBB. *Megasphaera massiliensis* MRx0029 has antioxidant effects on differentiated SH-SY5Y neuroblastoma cells [275]. Chronic stress-induced gut dysfunction exacerbates intestinal hyperpermeability and disruption of TJ proteins such as ZO-1, occludin, and claudin-1 in a rotenone-induced mouse model of PD [278]. Alpha-synuclein (α-syn) deposition and related neurodegeneration in the intestinal nervous system can increase intestinal permeability, local inflammation, and oxidative stress, causing constipation in patients with PD. It is believed that chronic low-grade inflammation in the gut is the trigger factor for BBB leakage, activation of immune cells, and CNS inflammation [279].

5.2. Myocardial I/R Injury. Circulatory damage due to acute myocardial infarction and reperfusion injury can also interfere with systemic blood flow [280, 281]. Therefore, when myocardial I/R injury occurs, several important organs, including the brain, are also affected [282, 283]. Importantly, myocardial I/R injury may lead to the onset of oxidative

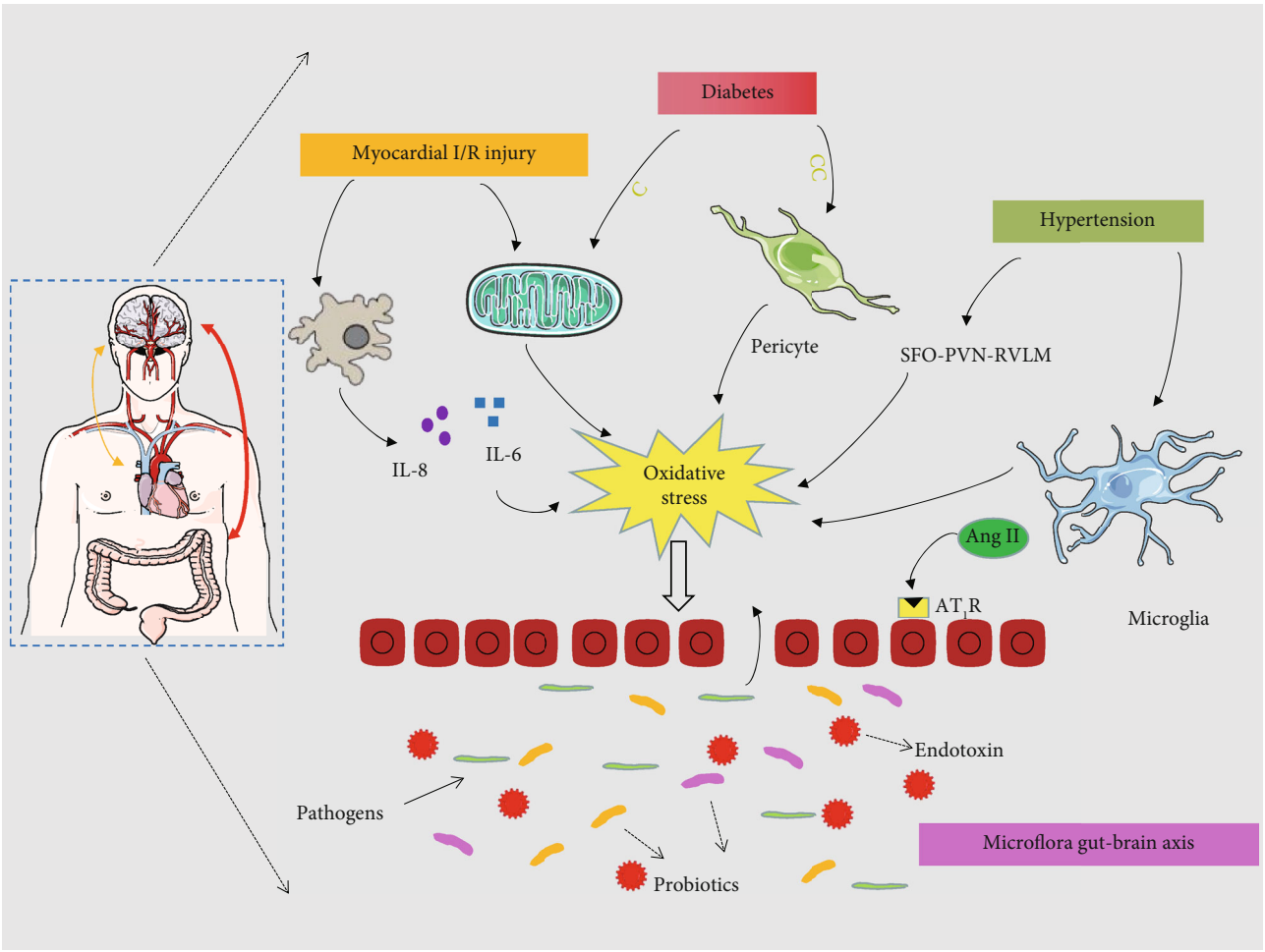

Figure 3: Schematic illustration of how ROS can affect the BBB via mechanisms interconnecting multiple organ systems. (A) Microflora gut-brain axis. Probiotics and pathogens can affect the composition of the intestinal flora and, thus, affect the integrity of BBB. (B) Myocardial I/R injury. It causes oxidative stress in the brain through mitochondrial dysfunction and inflammation, leading to BBB dysfunction. (C) Hypertension. Endothelial dysfunction, microglial activation, Ang II-mediated pathways, and the subfornical organ-paraventricular nucleus of the hypothalamus-rostral ventrolateral medulla pathway (SFO-PVN-RVLM pathway) may contribute to ROS production leading to the destruction of the BBB during hypertension. (D) Diabetes. Increased mitochondrial oxidative stress can be caused by hyperglycemia. This induces peripheral blood cell loss and is a prerequisite for BBB destruction.

stress in the brain, BBB dysfunction, mitochondrial swelling, brain cell apoptosis, and brain death [284]. Recent studies have also confirmed that myocardial I/R injury causes BBB decomposition, increased oxidative stress, and mitochondrial disruption [285]. In addition to myocardial I/R injury, neurological abnormalities after cardiac surgery are very common. Neurological complications after cardiac surgery are one of the most serious complications [286]. Glial cell injury with the two CSF markers (S-100B and GFAP) increased respectively by 35% and 25%, and IL-6 and IL-8 increased by 3.5 and 12 times, respectively, in 10 patients who underwent aortic valve replacement, indicating that cardiac surgery with cardiopulmonary bypass can lead to brain inflammation, glial cell damage, and BBB disruption [287].

5.3. Hypertension. Hypertension carries the highest risk for cardiovascular and cerebrovascular diseases [288, 289]. Damage to target organs, such as the heart, brain, kidney, and peripheral blood vessels, caused by uncontrolled hypertension affects the structure and function of these important organs [290]. In recent years, numerous studies have shown that hypertension is the most important cerebrovascular risk factor [291, 292]. The main mechanisms involved in hypertension-induced organ damage include endothelial cell activation, platelet activation, renin-angiotensin system activation, and oxidative stress. Endothelial dysfunction occurring under conditions of uncontrolled hypertension may be a potential underlying factor leading to vascular inflammation and BBB destruction [293].

Ang II-mediated proinflammatory effect is now widely recognized as a key mechanism for promoting excitatory hypertension in sensory nerves, and growing evidence supports that microglia are the key cellular targets that mediate the proinflammatory effect of central Ang II [294, 295]. Besides, recent studies also support that this mechanism contributes to the destruction of the BBB in hypertensive states

Table 2: Potential biomarkers towards oxidative stress in neurological diseases.

Biomarkers	Diseases	Sources	Methods	Ref
NcRNAs				
miR-27b	AIS	Rat striatum and PC12 cells	qRT-PCR	[313]
miR-210	IS	Ischemic penumbra regions of the right cerebral cortex	qRT-PCR	[314]
miR-186	AD	Hippocampal neuronal cells	qRT-PCR	[315]
lncRNA SOX21-AS1	AD	Hippocampal neuronal cells	qRT-PCR	[316]
Exosomes				
α-SYN and DJ-1	PD	CSF and plasma	Differential centrifugation	[319]
CTRP9	Stroke	Plasma	ELISA	[320]
Uric acid	AIS	Serum	Bayer technician	[322]
F2-isoprostanes	AIS and AD	Plasma, serum, urine, saliva, and cerebrospinal fluid	GC-MS, LC-MS, and HPLC	[325, 326]

Table 3: Antioxidant drugs towards oxidative stress in neurological diseases.

Antioxidant drugs	Targets	Clinical use	Ref
Edaravone	ROS, MDA, SOD, Nrf2/HO-1, GFAP, and TJs	AIS and ALS	[327, 328]
N-Acetylcysteine	Nrf2/HO-1, GSH, SOD, MDA, TAS, vitamin A, vitamin C, and vitamin E	PD, ALS, AD, and TBI	[334, 351–354]
Minocycline	GSH, MDA, NO, iNOS, eNOS, DPPH, MMP-9, MAP2, GFAP, CD11b, and Iba1	IS and AIS	[355–357]
Metformin	ROS, SOD, MDA, GSH, CAT, 8-iso-$PGF_{2\alpha}$, glutathione, glutamate, catalase, Nrf2/HO-1, and AMPK/mTOR	TBI, AD, and acute stroke	[339, 340, 342]
Fingolimod	NO, iNOS, cNOS, tNOS, SOD, MDA, GSH, and GSH-Px	RRMS and stroke	[358–360]
Idebenone	MDA, NO, GSH, and CAT	AD and HD	[361–363]
Dimethyl fumarate	SOD, MDA, GSH, GPx, NADPH, GFAP, Iba1, and Nrf2/HO-1	RRMS and stroke	[364, 365]

[296]. Ang II-mediated ROS production in the SFO-PVN-RVLM pathway is also considered to be a key factor in the sympathetic excitability of hypertension [297]. In this sense, in addition to the release of various proinflammatory cytokines, activated microglia also produce and release ROS [298]. Besides, studies have shown that hypertension can aggravate cerebrovascular oxidative stress caused by mild craniocerebral injury through the protective effect of the mitochondrial-targeted antioxidant peptide SS-31 [299]. Renovascular hypertension also significantly increases brain AT1R and oxidative stress in the brain and plasma [300].

5.4. Diabetes. Recent evidence has demonstrated that diabetes is a potential cause of neuropsychiatric disorders such as stroke [301], cerebral microangiopathy [302], diabetes-related cognitive decline [303], and BBB disruption [304]. Diabetes-related cognitive decline is characterized by impaired cognitive function and neurochemical and structural abnormalities, mainly involving neuronal damage caused by glucose-driven oxidative stress [305, 306]. In diabetes, increased mitochondrial oxidative stress is a mechanism for hyperglycemia-induced pericyte loss as a prerequisite causing BBB disruption [307]. It was shown that decreased GSH and SOD and elevated HNE in tissues of the early brain of diabetic mice, as well as a decreased number of late pericytes, led to BBB disruption [308]. Studies have shown that neurons and glial cells in different brain regions (such as the hypothalamus, lateral amygdala, and cerebral cortex) of diabetic rats promote the expression of iNOS, IKK, IKB, and NF-κB, while also inhibiting the expression of microglial CD11b and astrocyte GFAP [309]. Glycosylation of methylglyoxal with amino acids can generate superoxide radical anions [310]. Therefore, methylglyoxal damage to proteins can be mediated by oxidative stress generated by ROS, which may cause protein carbonyl formation [311]. Increased methylglyoxal and decreased GSH in diabetes lead to increased BBB permeability and increased I/R damage in the brain of mice [312].

6. Clinical Approaches towards Oxidative Stress in Neurological Diseases

Numerous studies have been conducted on various antioxidant agents. We here discuss the latest clinical evidence of potential biomarkers (Table 2) in neurological diseases such as noncoding RNAs (ncRNAs), exosomes, C1q and tumor necrosis factor-related protein 9 (CTRP9), uric acid, and F2-isoprostanes, and antioxidant drugs (Table 3) have been extensively investigated, such as edaravone, N-acetylcysteine (NAC), minocycline, metformin, fingolimod, idebenone, and dimethyl fumarate (DMF). They may provide more strategies for the treatment of neurological diseases.

6.1. Potential Biomarkers. ncRNAs are a class of functional RNAs that regulate gene expression in a posttranscriptional manner. ncRNAs, including microRNAs, long noncoding

RNAs (lncRNAs), and circular RNAs (circRNAs), can be used as diagnostic biomarkers and are emerging as novel therapeutic targets for neurological diseases. The study by Xu and colleagues showed that the inhibition of miR-27b could alleviate brain injury and upregulate the expression of Nrf2, Hmox1, SOD1, and Nqo1 after ICH via the Nrf2/ARE pathway [313]. Knockdown of miR-210 attenuated neuronal death and the antioxidant stress response effects of vagus nerve stimulation in the cortex following transient MCAO [314]. Recently, a study has defined the potential role of miR-186 as an inhibitor of AD development by downregulation of IL2 through the suppression of the JAK-STAT signaling pathway [315]. lncRNA SOX21-AS1 acted on oxidative stress-induced neuronal injury in AD mice via the Wnt signaling pathway by targeting FZD3/5 and may be a novel biomarker for enhanced AD treatment [316]. Accumulating evidence suggests that secreted exosomes may serve as vehicles for the transport of a wide range of proteins and immune markers, thereby potentially initiating or exacerbating pathogenic processes by fusing with recipient cells, including neurons [317, 318]. Since oxidative stress and mitochondrial dysfunction influence the underlying mechanisms of misfolded α-syn aggregation [319], biomarkers such as DJ-1 (oxidative stress sensor) and α-syn have the potential as clinical tools for early and accurate diagnosis of PD.

CTRP9 is a novel cytoprotective cytokine with antioxidant effects, which is highly expressed in brain tissue. It has been reported that high concentration of CTRP9 can reduce the risk of cerebral infarction and is an independent protective factor for cerebral infarction [320]. Uric acid is a potent water-soluble antioxidant that targets free radicals caused by oxidative damage, including hydroxyl radicals and superoxide [321]. In a prospective study involving 881 consecutive patients, uric acid levels were inversely associated with the extent of neurological deficits on admission and the final infarct volume on CT/MRI scans [322]. F2-isoprostanes (F2-isoP) are widely considered accurate and reliable biomarkers of oxidative damage that can be measured in plasma, serum, urine, saliva, and cerebrospinal fluid [323]. F2-isoP are measured in nanomolar units and are accurately analyzed using analytical platforms such as high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), and light chromatography-mass spectrometry (LC-MS). F2-isoP have been studied among individuals with various neurological conditions such as acute ischemic stroke (AIS) and PD [324]. Elevated hyperacute plasma F2-isoP concentrations independently predict the occurrence of infarct growth and infarct growth volume in patients with AIS [325]. Measuring plasma F2-isoP might be helpful in the acute setting to stratify patients with AIS for relative severity of ischemic injury and expected progression.

6.2. Antioxidant Drugs. Edaravone, a new antioxidant and hydroxyl radical scavenger, is the novel scavenger for clinical use, mainly for nervous system diseases [327, 328]. In vitro and in vivo data of edaravone suggests that it may possess broad free radical scavenging activity and protect neurons, glia, and vascular endothelial cells against oxidative stress [329]. It was found that the neuroprotective effect of edaravone on hippocampal oxidative stress and cognitive impairment may be related to the enhancement of the antioxidant defense system through activation of the ERK/Nrf2/HO-1 signaling pathway [330]. Similarly, edaravone has been shown to exert a neuroprotective effect through its ability to suppress astrocyte activation and markedly decrease MDA levels and increase SOD levels in stroke events [331]. Edaravone was also found to ameliorate such an oxidative damage by t-PA with protecting outer layers of BBB (in vivo) and tight junctions (in vitro) [332].

NAC, a well-known antioxidant, is a prescription product for treating cystic fibrosis and acetaminophen overdose and is also widely available as a dietary supplement. It was found that the antioxidant defense mechanisms of NAC mainly include directly scavenging free radicals and enhancing the activation of Nrf2 [333]. Long-term oral administration of NAC in patients with PD substantially increased the levels of GSH and thus inhibits oxidative stress [334]. Brain cortex GSH, total antioxidant status (TAS), vitamin A, vitamin C, and vitamin E values were improved by NAC treatments in TBI-induced rats [335].

Minocycline is a semisynthetic derivative of the tetracycline group of antibiotics that is capable of crossing the BBB, which exerts the neuroprotective effect by anti-inflammatory and antioxidative stress. Patients with AIS who received oral minocycline combined with tPA had a significantly better thrombolytic effect by inhibiting the activity of MMP-9 [336]. Minocycline can downregulate the expression of iNOS and upregulate the expression of eNOS in vascular dementia, which restrains oxidative stress to protect neural function [337]. The present study showed that minocycline treatment can activate astrocytes and microglia, attenuate oxidative stress, increase GSH levels, decrease the content of MDA and nitrite, and reduce neuronal degeneration [338].

Other common drugs for the treatment of type 2 diabetes, such as metformin, a biguanide drug, may also benefit TBI, AD, and stroke patients [339–341]. Metformin can improve the neurological function and oxidative stress status of acute stroke patients with type 2 diabetes, and its mechanism may be related to the AMPK/mTOR signaling pathway and oxidative stress [342]. Pretreatment with metformin could activate Nrf2 antioxidant pathways and enhance the level of glutathione and catalase activities through induction of AMPK after transient global cerebral ischemia [343]. It has been reported that metformin plays a neuroprotective role by inhibiting the level of MDA and 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) induced by ICH [344].

In addition to the main antioxidants mentioned above, fingolimod, idebenone, and DMF have a better clinical value in neurological diseases. Fingolimod is an oral sphingosine-1-phosphate receptor analog used to treat relapsing-remitting MS (RRMS). The neuroprotective effect of flavonoids against focal cerebral I/R injury in rats may be associated with the decreased production of oxidative stress targets including NO, tNOS, iNOS, and cNOS [345]. Idebenone is a short-chain benzoquinone that is structurally related to coenzyme Q10 (ubiquinone) and is a potent antioxidant and electron carrier [346]. It was approved in Japan in

1986 for the treatment of AD and other cognitive disorders [347]. Pretreatment with idebenone on pilocarpine could induce changes in MDA, GSH, NO, and CAT content in rat hippocampus tissue [348]. DMF is the first line of disease-modifying therapies for patients who have got RRMS. Its antioxidant mechanism has been confirmed to attenuate ROS overproduction, promote Nrf2/HO-1 pathway activation, increase reactivity of astrocytes and microglia, increase the content of SOD and GSH, and decrease MDA level for the treatment of MS or other demyelinating diseases [349, 350]. Future studies should include more RCTs to confirm the clinical efficacy of these treatments.

7. Conclusion

In summary, substantial evidence exists that implicates the role of oxidative stress and BBB disruption in the pathogenesis of neurological diseases. A variety of pathological factors can cause BBB compromise, mainly increasing BBB permeability. Also, direct insults on endothelial cells and the BBB can affect other components of the neurovascular unit, namely, peripheral cells, astrocytes, and basement membrane, further aggravating BBB damage and dysfunction. In neurological diseases, disruption of the integrity of the BBB is usually the first pathological change that occurs before clinical symptoms appear. The tight connection, inflammation, and degradation of MMP caused by oxidative stress are often accompanied by the opening of the BBB, which eventually leads to neuronal dysfunction, neuroinflammation, and neurodegeneration. Studying the relevance of oxidative stress to the development and outcome of neurological diseases and protecting the BBB in the early stages of diseases will help limit disease progression and improve clinical prognosis. Future research could be directed to examine the importance of redox imbalances in the pathogenesis of neurological diseases to reveal chelating agents that can be used to curb the progression of neurological diseases.

Conflicts of Interest

The authors declare no conflict of interest.

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