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Cerebrovascular inflammation: A critical trigger for neurovascular injury?

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ABSTRACT

The cerebrovascular system is not only inert bystandard that support the metabolic demands of the brain but also elicit the barrier functions against risk factors mediated neurovascular injury. The onsets of cerebrovascular inflammation are considered as stimuli that can provoke the host defense system and trigger the development of neurological disorders. Homeostasis of the brain function is regulated by the movement of endothelial, glial, and neuronal cells within the neurovascular unit (NVU), which acts as a "platform" for the coordinated action of anti- and pro-inflammatory mechanisms. The cerebrovascular system plays an integral role in the inflammatory response by either producing or expressing a variety of cytokines, adhesion molecules, metalloproteinases, and serine proteases. Excessive inflammatory cytokine production can further be affecting the blood-brain barrier (BBB) integrity and lead to brain tissue damage. In this review, we summarize the more recent evidence highlighting the importance of cerebrovascular injury in terms of risk prediction, and the mechanisms mediating the upregulation of inflammatory mediators in cerebrovascular dysfunction and neurodegeneration.

1. Introduction

The mammalian brain has a highly evolved and intricate network of the vasculature that effectively meets the high metabolic demand of neural tissue. The brain consumes round about 1/5 of the body's nutrients and energy. The neurovascular unit (NVU) comprises of a diverse set of interactions among endothelial cells, pericytes, neuronal and glial cells (Sá-Pereira et al., 2012), and is not only a passive entity that solely provides nutrients and oxygen to the underlying nervous tissue but also a dynamic structure that responds to model brain function (Iadecola, 2017; Listed, 2011). The idea of the NVU, authorized at the 2001 Stroke Progress Review Group (PRG) meeting of the National Institute of Neurological Disorders and Stroke (NINDS), highlights the close relationship between the vessels and brain. The deviations occurring in the cerebral vasculature may influence the permeability of BBB and eventually brain functioning.

Neurovascular abnormalities involve either structural or functional alterations of the cerebrovascular system. Structurally, altered vascular size and density, increased twisting of the vasculature, increased permeability or thickness of the vascular walls and even hemorrhage are likely changes in the neurovasculature. Functionally, the neurovascular deviations can be associated with altered vascular perfusion in cerebral blood volume (CBV), cerebral blood flow (CBF), blood pressure and oxygen consumption (Brown and Thore, 2011; Kalaria, 2010). The vascular risk factors such as infections, toxins, traumas, and systemic pro-inflammatory cytokines are capable of evoking a short-lived and immediate activation of the innate defense system within the CNS (Frank-Cannon et al., 2009; Popovich and Longbrake, 2008b). Cerebrovascular inflammation is an essential and fast host defense system to tissue injury, infectious agents and autoimmune reactions. In the peripheral tissues, typical inflammatory signs are the pain, swelling, and loss of function. The 'immune privilege' of the CNS is now evident that peripheral reaction access to the CNS is limited and tightly controlled and capable of mounting active inflammatory and immunologic responses to a variety of insults (Frank-Cannon et al., 2009; Galea et al., 2007). This acute neurovascular inflammatory process comprises movement of microglia resulting in their phenotypical and morphological changes and the release of inflammatory mediators such as chemokines and cytokines by these cells (Rivest, 2009). Under physiological conditions, microglia shows a passive phenotype (Streit, 2002) while activated microglia exhibits inflammatory process that acts to engage the defense system further and initiates tissue repair (Glass et al., 2010b). This reaction is ordinarily self-limiting; however, the persistence of the inflammatory process, by endogenous or exogenous factors, caused by devastating inflammatory cycles, result in pathological consequences (Glass et al., 2010b).

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Even though cerebrovascular inflammation may not usually represent an initiating factor in neurodegenerative disorders but a balance between pro- and anti-inflammatory cytokines determining sustained inflammatory responses in the CNS is significant in the disease progression (Glass et al., 2010a). Activated microglial cells exhibit a variety of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1, as well as nitric oxide (NO) and superoxide, which are neurotoxic and may intensify underlying disease states (Hanisch, 2002). Although the causes of several neurological disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) are multifaceted and may involve many factors, an active role of the early cerebrovascular inflammation has been clearly established (Pablo et al., 2005; Sweeney and Kisler, 2018). Activation of innate immune responses can be mediated by the involvement of pattern-recognition receptors (PRRs), such as TLRs, to initiate pro-inflammatory responses and activation of adaptive immunity. The final consequence of the brain diseases will rely on the role of inflammation and alteration of the inflammatory status driven by vascular risk factors.

This review highlights the role of cerebrovascular inflammation and affecting the function of the NVU, changes in BBB integrity and modulation of various pathophysiological factors and neurodegeneration. In particular, we focused on the role of cerebrovascular inflammation for initiating neurovascular injury and neurodegeneration.

2. Neurovascular injury

Almost all components of the NVU, including endothelial cells, pericytes, neurons, and glial cells, are involved in the development of neurovascular injury (Fig. 1) (Heye et al., 2014). Neurovascular injury relates to the damages of major blood vessels supplying the brainstem, brain, and upper spinal cord, including the basilar, vertebral, and carotid arteries. Endothelial cells form a dynamic interface between the BBB and peripheral tissues, which are critical for the maintenance of neurovascular homeostasis. Accordingly, injury in endothelial cells is considered one of the earliest symptoms of impaired vasoregulation mechanisms (Koizumi et al., 2016). Pericytes initially were recognized as a type of contractile cell in neurovascular tone regulation and later discovered that they respond to stress-related injury upon brain diseases dynamically. Loss of normal glial cells function in neurovascular injury may contribute to reduced support for neurons and dysfunction of the NVU (Garwood et al., 2017). Astrocytes and microglia are the primary cells responsible for the innate immune system in the CNS for the control of pathogen colonization and invasion (Iribarren et al., 2002). This neuroglia also produces signals for activation and recruitment of cells that contribute to adaptive immunity to finally eliminate the infection (Iribarren et al., 2002). Aging is also a significant factor that affects the integrity of the NVU. The age-related pathophysiological changes in the cellular mechanisms of the NVU have been shown to enhance the vulnerability of the NVU to neurodegeneration or reperfusion/ischemic injury and to result in aggravated brain injury (Sohrabji et al., 2013).

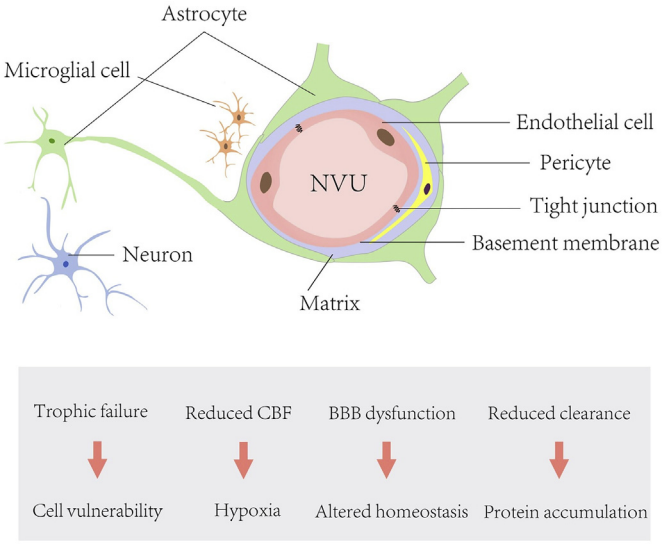

Fig. 1. Potential pathogenic mechanisms by which neurovascular dysfunction can cause brain injury. In the NUV, BBB is formed by endothelial cells that line up brain capillaries and are sealed by tight junctions (TJs). Glial cells (astrocytes, microglia), pericytes, and basement membranes interact with the endothelium of the BBB, providing structural and functional support. Variations of the NVU may lead to a decrease in CBF below the threshold necessary for normal brain function leading to hypoxia. BBB dysfunction may alter the homeostasis of the internal brain environment by limiting the delivery of nutrients and impairing the clearance of unwanted metabolites through efflux transporters. Reduction in trophic factor production by NVU cells may increase glial and neuronal vulnerability and susceptibility to disease. Variations of clearance pathways may promote the accumulation of molecules, such as tau and Aβ, leading to proteopathies.

3. Mechanisms of NVU dysfunction

The role of neurovascular dysfunction remains elusive but overwhelming evidence is linked to structural and functional variations of the NVU in neurodegenerative diseases (Janelidze et al., 2017; Kisler et al., 2017). The present understanding on the mechanisms of neurovascular dysfunction and neurodegeneration highlights an admiration of multicellular communications within the NVU, which comprise the progression of BBB damage, glial reaction, immune cell infiltration, and neuronal degeneration or cell death (Cai et al., 2017).

3.1. BBB and endothelium

The BBB is formed by endothelial cells lining the cerebral microvasculature and is an essential mechanism for protecting the brain from variations in plasma composition, xenobiotics, and neurotransmitters. The brain endothelium lies at the interface among the circulating peripheral cells, brain parenchyma, and critical mediators. Under normal physiological conditions, endothelial cells play a vital role (J. Abbott, 2002), confines the brain entry of critical mediators and circulating cells. However, commencement of the cerebral endothelium is fundamental in the brain's response to express inflammatory mediators including chemokines and cytokines, and upregulate their expression of CAM including E-selectin, VCAM-1, and ICAM-1 which leads to the recruitment of peripheral blood cells, including monocytes/macrophages, platelets, lymphocytes and neutrophils (Denes et al., 2010) (Fig. 2). The components of brain endothelial basal lamina (collagen IV) are degraded in response to cerebral ischemia in humans (Rosell et al., 2008), and astrocyte-basal lamina associations are lost in a murine model of cerebral ischemia (Milner et al., 2008). Vasoactive proteins, primarily VEGF increases the BBB integrity in a mouse model of intracerebral hemorrhage via MMP-9 expression (Wenlan et al., 2010) and can be aggravated by systemic inflammatory locations (Mccoll et al., 2008). VEGF expression associates with a reduction in the levels of the tight junction (TJ) proteins claudin-5 and occludin during inflammatory brain diseases (Azeb Tadesse et al., 2009). ET-1 released by activated endothelial cells has been shown to stimulate IL-1β and astrocytic expression (Didier et al., 2003). Endothelium-derived Sema3G regulates the hippocampal structure, and synaptic plasticity via Nrp-2/plexinA4 signaling cascade that activates intracellular Rac1 to promote excitatory glutamatergic synapse density and synaptic function (Tan et al., 2019). CRP has also been shown to aggravate the BBB permeability in guinea pigs by activating the contractile machinery and increasing ROS in cerebral endothelial cells (Kuhlmann et al., 2009). Brain endothelial cells are responding rapidly to co-morbidities,

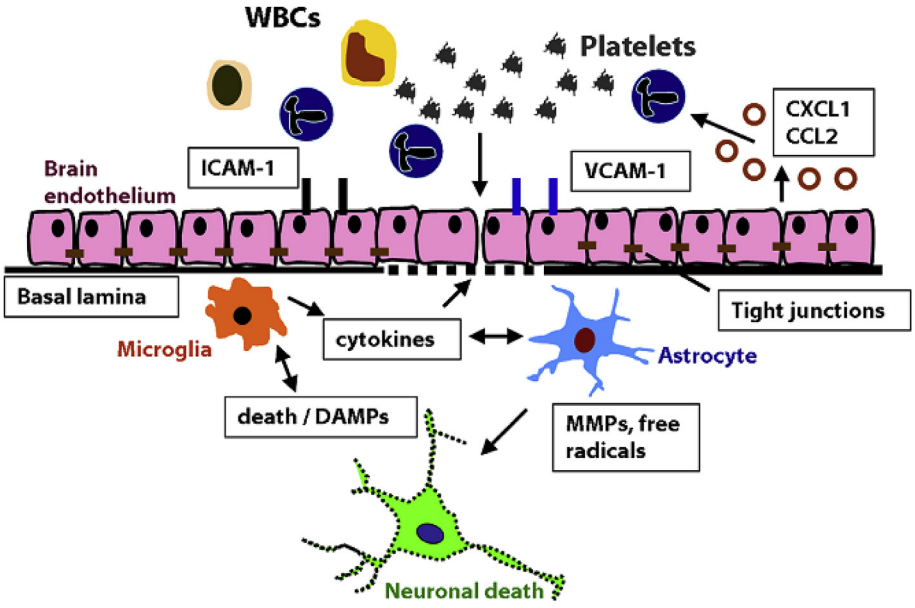

Fig. 2. Schematic representation of mechanisms of cerebral ischemia at the brain level (Denes et al., 2010). Endothelial and glial activation escort neurovascular injury in response to cerebral ischemia. Activated brain endothelial cells express CAMs such as ICAM-1, VCAM-1, which, together with chemokines (CXCL1, CCL2), recruit circulating platelets and WBCs. Damage-associated molecular patterns (DAMPs) and cytokines drive endothelial and glial activation, inducing the release of inflammatory molecules including the MMPs and free radicals, resulting in neuronal degradation.

elevated circulating inflammatory mediators and cerebral ischemia. Recent research aims to explore the underlying molecular mechanisms, in which brain endothelial cells are likely to be critical components.

3.2. Pericytes

Pericytes are surrounding endothelium (linked via Cx 43, N-cadherins and integrins) and are located in the perivascular space of the blood-brain barrier. Normally, pericytes contribute to BBB anatomy and physiology, providing vasculature stability and adapting diameter and smooth blood flow (Marchi and Lernernatoli, 2013). Pericytes modulate the contractile proteins (e.g., α-SMA) and BBB integrity (Vandenhaute and Elodie, 2011; Zlokovic, 2008), contribute to the regulation of capillary blood flow. It has also been established that pericytes deficit escort to leaking the BBB (Armulik et al., 2011). Pericytes in co-culture with endothelial/glial cells stabilize the configuration of capillary-like structures (Ramsauer et al., 2002), and can persuade integral plasma-membrane protein (occludin) expression in endothelial cells (Satoko et al., 2010). Both pericytes and astrocytes notably suppress endothelial proliferation which induce lumen polarization, proper localization of barrier proteins, and functional movement of transporters (Al Ahmad et al., 2011). *In vitro* pericytes and endothelial cells crosstalk enhances MMP-9 activity at the BBB (Zozulya and Weidenfeller, 2008). Dysfunction of pericytes triggers breakdown of the BBB and nitration of TRPM2 which induces autophagy (Jiang et al., 2017). Recently, pericytes have been considered as potential players in NVU remodeling in neurological disorders.

3.3. Reactive astrocytes

Astrocytes play critical roles in the brain and are involved in neuroinflammatory diseases. They become reactive in all pathological conditions in the brain such as infection, ischemia, inflammation, axotomy, and neurodegenerative disorders. Neuroinflammation-induced A1 reactive astrocytes upregulate many complement cascade genes that are devastating to synapses, suggesting that A1s might have destructive functions. In contrast, ischemia-induced A2 reactive astrocytes increased many neurotrophic factors as well as thrombospondins (TSPs). This upregulation advocates that A2s might have essential roles (Liddelow and Barres, 2017). Moreover, microglial activation, either by systemic LPS injection or by acute CNS injury, induces A1s reactive astrocytes by releasing the complement component subunit 1q (C1q), IL1α, and TNFα, which together are sufficient both *in vitro* and *in vivo* to persuade A1 reactive astrocytes (Liddelow et al., 2017). Studies strongly suggest that A1 reactive astrocytes might be influenced by NF-kB signaling. The NFκB pathway regulates cytokine production and is strongly associated with neuroinflammatory reactivity in astrocytes during neurodegenerative disease (Han-Yun et al., 2013; Migheli et al., 1997). Many pro-inflammatory mediators, such as cytokines, viral or bacterial antigens, stress, free radicals, amyloid, and many other factors activate the NFκB pathway (Barbara and Christian, 2009). Studies of NFκB activation of astrocytes in rodent models of neurodegenerative diseases provide evidence that NFκB activation in astrocytes might play an essential role in the progression of neurodegenerative diseases (Han-Yun et al., 2013; Hong et al., 2015). Commencement of astrocytes via NFκB pathway in the spinal cord of ALS patients is seen (Migheli et al., 1997). By contrast, the latest studies advocate that the JAK-STAT3 pathway is possibly mediating the commencement of A2 ischemic reactive astrocytes. This pathway regulates multiple cell functions, including cell differentiation, proliferation, and growth, and some inflammatory tasks (Ceyzériat et al., 2016). Numerous studies have comprised JAK-STAT3 in ischemic astrocyte reactivity after acute damage (Anderson et al., 2016; Ceyzériat et al., 2016). Indeed, A1 reactive astrocytes are present in brain regions implicated in neurodegeneration in a variety of human diseases, including AD, MS, ALS, PD, and HD (Liddelow et al., 2017). Also, the activation of PLA2 in reactive astrocytes has been shown to occur in some neurodegenerative diseases (Sun et al., 2014), including stroke (Sun et al., 2005) and AD (Gentile et al., 2012). Astrocytic PLA2 inhibitors reduced the glutamate toxicity in pre-treated astrocytes and increased neuronal sensitivity to chronic glutamate exposure in astrocyte-neuron co-cultures (Ha et al., 2014). Stated that, A1s release numerous complement cascade genes that can increase synaptic degeneration (Hong et al., 2016; Stevens et al., 2007) as well as a neurotoxin that provokes the death of oligodendrocytes and neurons, which brings renewed focus to the potential significance of reactive astrocytes in chronic neurodegenerative diseases.

3.4. Activated microglia

Increasing evidence indicates that resident immune cells (microglia) activation in the CNS is heterogeneous. Their varied functional phenotypes range from pro-inflammatory M1 phenotypes distinguished by upregulation of inflammatory mediators such as IL1β, TNF, and ROS (Block et al., 2007) to immunosuppressive M2 phenotypes

distinguished by upregulation of frizzled class receptor 1 (Fzd1), chitinase-like 3 (Chil3), and arginase 1 (Arg1) (Boche et al., 2013). One of the incredible hallmarks shared by various neurodegenerative diseases is microglia-mediated neuroinflammation (Tang and Le, 2016b). In general, M1 microglia predominates at the end stage of disease at the lesion site, when the repair process and immunoresolution of M2 microglia are hampered (Tang and Le, 2016a). In mechanical injuries like spinal cord and TBI or I/R injury induce the innate immune response to produce ROS and inflammatory mediators (Fleming et al., 2006; Moskowitz et al., 2010). The initial pro-inflammatory response is shifted (Oliver and Lennart, 2010) to an anti-inflammatory state where angiogenesis is promoted (Varin and Gordon, 2009). Consequently, when there is a proper transition from the M1 to M2 phenotype, the damage can be adequately repaired. The lack of M2 microglia not only means could fail to control neuroinflammation; but also mean lower levels of neuroprotective factors like IGF1 or BDNF, which microglia produces (Cherry et al., 2014). However, when the pro-inflammatory response did not give up and continued the production of inflammatory mediators, and ROS can escort to cell death and further tissue damage (Kigerl et al., 2009). Resolvin D1 and IL-10 were reduced in AD patients, suggesting that the lack of elements to induce M2 polarization has possible functional consequence in human diseases (Mantovani et al., 2004; Wang et al., 2015d). Thus, the changes of microglial phenotypes rely on the severity and disease stages and mastering the stage-specific controlling of M1/M2 phenotypes within proper time windows may provide better therapeutic outcomes.

Many other factors are involved in the mechanism of neurovascular dysfunctions such as immunocytes, e.g., monocytes, T cells, and leukocyte-endothelial cell adhesion; key mediators e.g., TLRs, ion channels, matrix metalloproteinase, cytokines, and inflammasomes; risk factors e.g., ER stress, oxidative/nitrosative stress, and mitochondrial stress, *etc.* (Fig. 3).

3.5. Role of immunocytes

3.5.1. Leukocyte-endothelial cells adhesion

The relocation of leukocytes from blood vessels into the CNS is a key factor in the pathogenesis of neurological disorders involving acute and chronic inflammation (Langer and Chavakis, 2009). The adhesion of leukocytes to vascular endothelium is a hallmark of the inflammatory process (Granger and Kubes, 1994). The endothelial cells adhesion contribute to the pathogenesis of seizures and inhibition of leukocyte-endothelial interactions in a mouse model of debilitating disease (Fabene et al., 2008). Han and co-workers analyzed that leukocyte-endothelial cell adhesion, $P2RX_7$-dependent microglial activation and neurovascular damage in septic mice using multiple approaches (Wang et al., 2015a). Cathepsin B inhibition ameliorates leukocyte-endothelial cell adhesion in the BTBR mouse model of autism spectrum disorder (ASD) (Wang et al., 2018). Casein kinase II is implicated in the regulation of leukocyte-endothelial cell adhesions during stroke by mediating the expression of ICAM-1 and E-selectin (Ampofo et al., 2016). Targeting FPR2/ALX activity reduces leukocyte-endothelial cell adhesions in an animal model of cerebral ischemia-reperfusion (I/R) injury (Smith et al., 2015). The categorization of molecular mechanisms controlling leukocyte trafficking and vascular inflammation could, therefore, lead to establishing the basis of BBB dysfunction during neurodegenerative disorders and may help to the development of new therapeutic approaches (Zenaro et al., 2017). We still find a huge need for research to explore the exact role of leukocyte-endothelial cells adhesion in the regulation of neurovascular injury and neurodegeneration.

3.5.2. Monocytes

Recently research exposed the participation of monocytes in the commencement of brain inflammation suggest their critical role in the neurovascular injury (Jones et al., 2017). The infiltration of blood

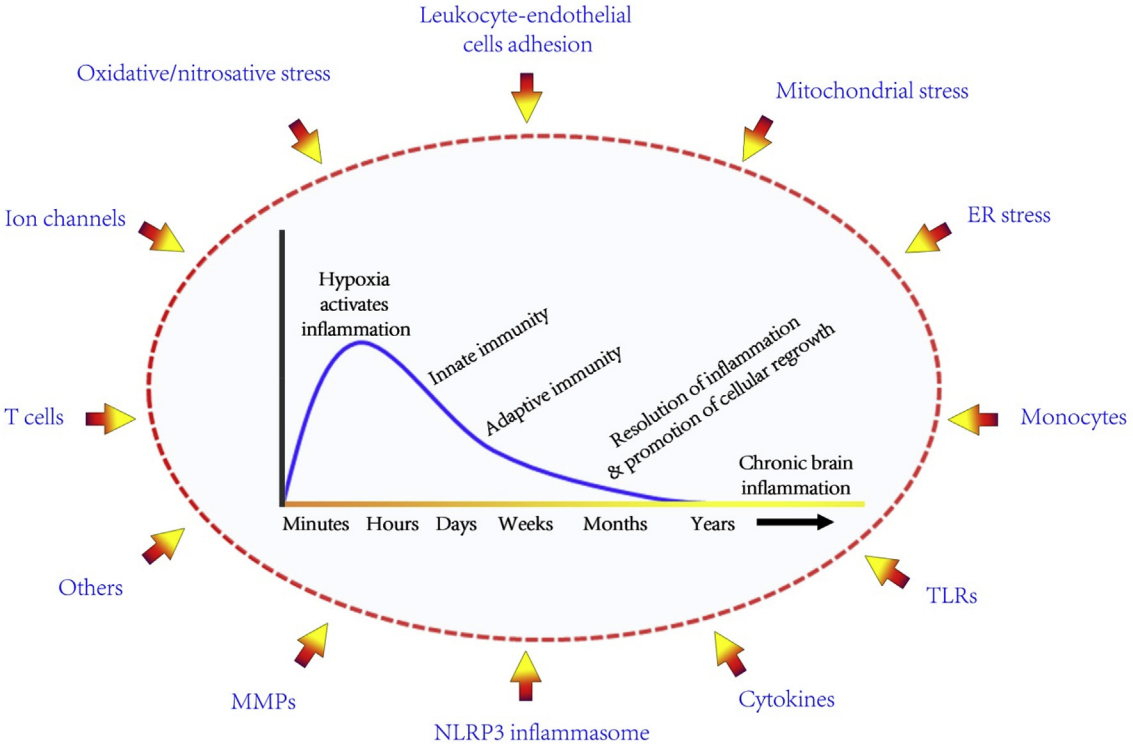

Fig. 3. The development of cerebrovascular inflammation and immune response in the progression of neurovascular injury. Chronic inflammation from autoimmune disease, atherosclerosis, and physiological stress results in progressive cerebrovascular injury. Acute occlusion of the cerebral vasculature produces intravascular hypoxia that triggers a rapid inflammatory response. As tissue damage proceeds, cellular components activate the innate immune system and set the stage for the engagement of adaptive immunity.

monocytes into the brain were observed in the murine model of PD (Harms et al., 2018) and stroke (Williams et al., 2012). It is also revealed that neurodegenerative actions activate primary peripheral immune cells response in the forebrain of mice (Scheld et al., 2016). Monocytes also secrete HGF, a neuroprotective and neuroinflammation-suppressive mediator, in IFN-α-treated patients with MS (M et al., 2012). This fact was further supported by partial depletion of the pro-inflammatory monocyte population is neuroprotective in the myenteric plexus but not in the basal ganglia in an MPTP mouse model of PD (Côté et al., 2015). Monocytes contribute in the process of Aβ or SOD1 clearance by the innate immune system may be important for preventing/controlling disease onset in an AD and ALS (Cashman et al., 2012) and phagocytic activity and engulf some unwanted proteins (Kadiu et al., 2005). Brain perivascular macrophages (PVM) are essential for the neurovascular dysfunction mediated by Aβ peptides in a mouse model of AD (Park et al., 2017). Brain PVM also mediates neurovascular dysfunction and cognitive impairment in a mouse model of hypertension (Faraco et al., 2016). Another study also recognized that brain leukocyte infiltration initiated by EAE or peripheral inflammation occured through pathways linked to the CSF-filled compartments of the midbrain and forebrain (Schmitt et al., 2012). Some mediators of inflammation such as saturated fatty acid palmitate induce human monocytic cell toxicity toward neuronal cells and exploring a possible link between neuroinflammation and obesity-related metabolic impairments (Little et al., 2012). Constitutive activity of myeloid cells derived NF-κB compel pathogenicity of macrophages and monocytes during autoimmune neuroinflammation (Ellrichmann et al., 2012). These mechanisms mentioned above demonstrate a clear association of monocytes in the process of neurovascular dysfunction, which consequently causes neurodegeneration.

3.5.3. T cells

A greater understanding of the T-cell-mediated regulation of neuroinflammation involved in devastating neurodegenerative disorders (González and Pacheco, 2014). It was demonstrated that cutaneous manipulation of VEGF leads to alterations in blood vessels, immunocytes, and nerves (Ward et al., 2011). Immune cells trafficking involved across the BBB of the CNS in stroke and MS (Lopes Pinheiro et al., 2016). Curcumin decreases the expression of VCAM-1, IFN-γ, IL-17 and T cells infiltrating in the mice model of intracerebral hemorrhage (Liu et al., 2016). It was revealed that $CD4^+$ T cells are cytotoxic in a murine model of PD and contributed to neuronal cell death by the Fas/FasL pathway (Appel, 2009). Recently, it was also demonstrated that T cells penetrate to the site of secondary neurodegeneration after ischemic stroke (Jones et al., 2017). The suppression of NK/$CD8^+$ T cells significantly reduces astrogliosis but induces shorter lifespan and cerebellar dysfunction in a mouse model of Sandhoff disease (White et al., 2017). T cells may damage motor neurons by cells crosstalk or cytokines secretion, or contribute indirectly to motor neuron damage through activation of macrophages and microglia (Holmøy, 2010). Recently, Th17 cell-mediated neuroinflammation critically regulates Aβ1-42-induced neurodegenerative actions in a murine model of AD (Zhang et al., 2013). Interleukin-17 KO mice showed considerably reduced infiltration of macrophages and T cells into the injured sciatic nerves and reduced the activation of astrocytes and microglia in the L3-5 ventral and dorsal horns of the spinal cord (Saresella et al., 2011). Interleukin-17 administration considerably increased in the numbers of stimulated dendritic cells and infiltrating neutrophils in the injected sciatic nerves and hind paws (CF and G, 2011). Together, it is hypothesized that a better understanding of the complexity of T cells in neurovascular dysfunction can assist the researchers to explore novel therapeutic targets.

3.6. Role of key mediators

3.6.1. TLRs

Pattern recognition receptors (PRRs), such as TLRs and NLRs, not only expressed in cells of the host defense system but also cells of the NVU and cerebrovascular form the BBB. Different types of TLRs are expressed in the brain in murine models and human cells (Carty and Bowie, 2011). The most important damage-associated molecular PRRs in the NUV are TLR2, TLR4, and NLR family PYDCP1 and PYDCP3, which are stimulated during physiopathology in neurons, astrocytes, microglia, and possibly pericytes and endothelial cells (Wilhelm et al., 2017). The innate immune response is activated by TLRs in the brain (Arroyo et al., 2011) and expression is modulated by multiple factors, including pro-inflammatory cytokines in several aspects of neurodegenerative diseases (Keqiang et al., 2006; Olson and Miller, 2004). The expression can also be up-regulated by any foreign particle, inflammation, infection (Mckimmie et al., 2005; Zekki et al., 2010), consequently amplifying the innate immune response. Therefore, the role for TLRs in several aspects of brain disorders has been projected, for example, in AD where persistent glial activation without acute inflammation is observed and in MS where an adaptive immune system is elicited following inflammation and glial activation (Popovich and Longbrake, 2008a). Stress-responsive HO-1 isoenzyme participates in TLR-4-induced inflammation during ischemic brain injury and vascular dementia (Wang et al., 2016a). The absence of TLR4 decreases NVU and secondary inflammatory reactions after TBI in TLR4 KO mice. Furthermore, the movements of expression of IκB-α, NF-κB, and p-JNK pathway were also lesser in the brains of mice (Ahmad et al., 2013). Salvianolic acid B and glycyrrhizin ameliorate cerebral I/R injury in a rodent model by attenuating TLR-2, -4/MyD88/TRAF6 signaling pathway (Chang et al., 2014; Wang et al., 2016b). TLR-4 antagonists protect the brain in a rodent model of I/R injury and a potential target for ischemic stroke (Hua et al., 2015; Kawakita et al., 2017). Curcumin inhibits TLR-2, -4 and downstream NF-κB signaling pathway attenuates brain damage in a murine model of focal cerebral ischemia (Tu et al., 2014). Specific TLRs and co-receptors can indirectly/directly be activated to stimulate Aβ uptake, depending on the disease phase. Fibrillar Aβ can directly communicate with TLR2, TLR4, and CD14 to motivate microglial's phagocytosis in the start, and inflammatory reactions in the late stages (Gambuzza et al., 2014).

3.6.2. Ion channels

The growing body of evidence reveals the mutation or altered ion channels function in neurological diseases such as PD, AD, HD, MS, ALS, and age-related disorders (Kumar et al., 2016). The new development in the acid-sensing ion channels (ASICs), voltage-gated sodium ion channels, and ion channels on microglia smooth the way of their association in the process of neurovascular dysfunction and neurodegeneration (Hossain et al., 2016; Ortega-Ramírez et al., 2017; Skaper, 2011). Cannabinoids ion channels are widely studied and imperative for neurodegenerative diseases and attenuate the effects of aging during neurogenesis and neuroinflammation (Fernándezruiz et al., 2013; Marchalant et al., 2009). ATP-gated $P2X_7$ ion channels are expressed predominantly on cells of monocytes and macrophages in the periphery and astrocytes and microglia in the CNS. One of the hallmark features of $P2X_7$ activation is release of the pro-inflammatory cytokines IL-18, IL-1β, IL-6, TNF-α, and chemokines (Shiratori et al., 2010; W et al., 2001), cathepsins (Clark et al., 2010), glutamate (Andó and Sperlágh, 2013) and NO (Codocedo et al., 2013). $P2X_7$-mediated signaling has been most extensively studied in IL-1β regulation in the periphery (Choi et al., 2007; Monif et al., 2010) and thought to contribute neuroinflammatory tone in the CNS leading to neurodegenerative and neuropsychiatric disorders (Iwata et al., 2013). While the role of ATP-induced $P2X_7$ activation in CNS pathology is clinically untested, emerging pre-clinical research supports the hypothesis. $P2X_7$ signaling also promotes microsphere embolism-triggered microglia activation by

maintaining the elevation of FasL in brain inflammatory lesion (Lu et al., 2012). We still need huge research to explore the exact role of these ion channels in the regulation of neurovascular dysfunction and neurodegeneration.

3.6.3. MMPs

Proteolytic enzymes are involved in ECM remodeling under normal conditions, but in pathologic states can attack the BBB (Wang et al., 2007). A large body of evidence in both preclinical, as well as clinical studies, suggests that MMPs may interrupt BBB integrity and play a critical role in the physiopathology of neurodegenerative disorders (Seo et al., 2012; Vafadari et al., 2016; Weekman and Wilcock, 2016). The activation of MMPs may persuade the degradations of a matrix, as well as TJs between endothelial cells and undesired outcomes, have been implicated in BBB permeability in neurodegenerative diseases such as vascular cognitive impairment (Candelariojalil et al., 2011; Shen and Gu, 2014). The inhibition of MMP-3, -9 suppresses the expression of iNOS and pro-inflammatory molecules in LPS-induced microglia, supporting the role of MMPs in the neurovascular dysfunction and neurodegeneration (Woo et al., 2010). Notably, MMP-9 released by the monocytes raises as a function of differentiation and is implicated in neurodegeneration related neuroinflammation (Vos et al., 2000). In the EAE mouse model, MMPs also play a significant role in the commencement of peripheral immune cells and mediate neuroinflammation (Schiffmann et al., 2014). Thus, it can be supposed that MMPs are widely involved in the pathogenesis of neurovascular dysfunction and neurodegeneration.

3.6.4. NLRP3 inflammasomes

Recently, several studies have demonstrated the role of NLRP3 inflammasome participates in cellular damage and mediating inflammatory responses to neurological disorders (Li et al., 2018). Activation of NLRP3 inflammasome in human brain endothelial cells may confer a yet unexplored role to the BBB in a neuroimmune system and inflammatory processes (Nagyoszi et al., 2015). NLRP3 inflammasomes link neurovascular dysfunction and neurodegeneration in preclinical and clinical studied (Lenart et al., 2016). Mitochondrial dysfunction provokes NLRP3 inflammasome activation at different stages in a rat model of cerebral I/R injury (Gong et al., 2018). Nrf2 acted as a protective regulator against NLRP3 inflammasome activation through regulating the Trx1/TXNIP complex in a rat model of cerebral I/R injury (Hou et al., 2018). IVIg suppressed NLRP1 and NLRP3 inflammasome-mediated neuronal death in a mice model of ischemic stroke. Similarly, NLRP1 and NLRP3 inflammasome proteins levels, IL-18 and IL-1β were also elevated in the brain tissues of stroke patients (Fann et al., 2013). Activation of NLRP3 inflammasome-mediated in an AD mouse model by chronic cerebral hypoperfusion (Shang et al., 2018). The NLRP3 inflammasome also implicated in the pathogenesis of PD and inhibiting the downstream pathway of the NLRP3/caspase-1/IL-1β axis can alleviate the incidence of PD symptoms (Mao et al., 2017). These findings suggest that NLRP3-inflammasomes play a critical role in neurodegenerative diseases and stroke, and further suggested potential clinical assistance of therapeutic interventions that target inflammasome activity.

3.6.5. Cytokines

The cytokines have been found to be key players in neurological disorders. A balance between pro- and anti-inflammatory cytokines is important in the physiopathology of neurovascular dysfunction and neurodegeneration. A number of studies have revealed that abnormally elevated levels of pro-inflammatory cytokines such as IL-1β (Amantea et al., 2016), IL-1 (Pradillo et al., 2017), IL-6, TNF-α (Zhu et al., 2016), and anti-inflammatory cytokine IL-33 (Korhonen et al., 2015), and inflammatory cytokine, for instance, IL-18 (Johnson et al., 2015), IL-23 (Wang et al., 2015c), IL-10 (Lagerstedt et al., 2018), mediated greater role in the neurodegenerative diseases. Protective effect of calpain inhibitor on NVU was due to downregulating NF-κB-related expression of MMP-9, inflammatory cascade, and supporting the permeability of TJ during TBI in mice (Tao et al., 2017). The IL-17 was also found to coordinate inflammatory reactions in a wide range of autoimmune and inflammatory diseases of the nervous system (Yao et al., 2010).

3.7. Role of risk factors induced cerebrovascular inflammation

3.7.1. Endoplasmic reticulum stress

The ER stress is an intricate mechanism that mediates many responses during brain injury, thus being vital to determine the fate of neurons (Su and Li, 2016). It is feasible that the timing of events for ER stress signaling regulation is significant for the balance of physiopathology such that ER stress is initially protective, aiming to restore ER homeostasis, whereas prolonged periods of ER stress can be harmful and damaging (Xin et al., 2014). The role of ER stress markers is well documented in arterial and venous stroke (Tiwari et al., 2015). The ER stress-induces secondary brain injury in intracerebral hemorrhage of rats (Duan et al., 2017). Remote ischemic postconditioning alleviates the brain injury by attenuating the ER stress markers such as CHOP, Bim, and caspase-3 and increase the Bcl-2 expression (Liu et al., 2014). Erythropoietin reduces ER stress signals such as ATF6α, CHOP, and caspase-3 in brain microvessels of cerebral I/R injury in a rat model (Zhao et al., 2015). Over-expression of Bax inhibitor-1 (BI-1) can attenuate the apoptosis of hippocampal neurons in rats with subarachnoid hemorrhage by inhibiting the activation of ER stress-mediated IRE1-JNK signaling pathway, thus attenuating the early brain injury (Liu et al., 2017). Mdivi-1 and melatonin ameliorate the brain injury by the suppression of inflammation-related BBB disruption and ER stress-based apoptosis (Carloni et al., 2014; Fan et al., 2017). Takashi et al., elegantly established that -SNO of PDI inhibits PDI function, leads to dysregulated protein folding within the ER, evokes ER stress, and begins neuronal cell death (Takashi et al., 2006). Although oxidative/nitrosative stress have been related to cerebrovascular disorders, at this point, it is not feasible to conclude that these processes are the primary cause of neuronal death. However, it is feasible that these stresses modify the severity and progression of these devastating diseases.

3.7.2. Oxidative/nitrosative stress

Oxidative stress induces brain injury at high levels by oxidizing biological molecules, such as proteins, DNA, and lipids (Lu et al., 2018). Oxidative stress occurs when there is an inability or impairment to antioxidant balance with reactive oxygen species (ROS) such as superoxide (O_2-) and reactive nitrogen species (RNS) such as peroxynitrite (ONOO-) (Velzen et al., 2017). ROS/RNS at modest levels also plays a vital role in the normal physiology of many processes like induction of mitogenic response, signaling pathways and in defense against contagious pathogens (Di et al., 2016). No is a second messenger, produced by brain cells and biological activities of NO depending on its sources (Santos et al., 2014). NO produced by neuronal/inducible NOS can be harmful and persuade cerebrovascular endothelial injury through inflammation and oxidative stress (Ulrich, 2006). When combined with O_2-, NO produces highly reactive oxidant ONOO-, which damages the cerebrovascular endothelium and disrupts BBB permeability (Pun et al., 2009; Stuehr et al., 2004). However, excessive generation of NO/ONOO- signaling is associated with complex neurovascular pathogenic cascades that lead to neurodegenerative diseases, including vascular dementia, ischemic stroke and AD (Rong-Rong et al., 2012; Torreilles et al., 1999). Multiple clinical and pre-clinical studies have established the relationship between oxidative stress and neuroinflammation on the NVU dysfunction, and BBB permeability is established mechanisms in neurological diseases with co-morbid neuropsychiatric disorders such as epilepsy, stroke, TBI, MS, and AD (Najjar et al., 2013a, 2013b). NVU dysfunction and BBB disruption contribute to neuropsychiatric disorders by oxidative stress and neuroinflammation (Najjar et al., 2017).

Curcumin ameliorates the oxidative stress in a murine model of brain, liver, and kidney (Samarghandian et al., 2017). Oxidative stress indirectly activates MMPs, directly decreases the TJs proteins, and in turn, contributes to BBB permeability. Oxidative stress loses the vasculature, and perivascular unit by activation of fluid channel proteins and MMPs assists cellular or vascular fluid edema, enhances BBB permeability, and leads to a progression of neuroinflammation. Similarly, oxidative stress stimulates directly the growth factors and inflammatory cytokines such as TNF-α, IL-1β, and TGF-β or indirectly by stimulating MMPs. In another pathway, MMPs degrade the endothelial VEGFR-2 and leads to a subsequent elevation of serum/cellular VEGF level. The decline in VEGFR-2 and subsequently incline in VEGF-A levels leads to neuroinflammation and apoptosis by the release of IL-1β and activation of caspase-1/3 (Abdul-Muneer et al., 2015).

Furthermore, *in vitro* studies demonstrated that endothelial NO could increase CBF by enhancing vasodilation, inhibiting platelet aggregation by increasing endothelial cGMP levels (Pun et al., 2009), and downregulating the production of vasoconstrictors such as 20-HETE acid (David et al., 2010). Endothelial NO can also ameliorate cerebrovascular endothelial oxidative injury by scavenging cellular free radicals. Reduced eNOS activity can reduce endothelial NO levels resulting in (a) reduced CBF, (b) increased platelet aggregation, which may contribute to an increased risk of cerebrovascular disease, and (c) decreased cerebrovascular reactivity due to an oxidative injury of the cerebrovascular endothelium (Najjar et al., 2013b). Calmodulin antagonist (DY-9836) ameliorates cognitive dysfunction by inhibiting NLRP3 signaling and nitrosative stress in BCAS mice (Wang et al., 2017b). In a murine model of ischemic injury, the formation of ONOO- in the cerebral vasculature contributes to the progression of ischemic damage (Xin et al., 2015), while the underlying mechanism remains elusive. Han and co-workers also demonstrated that nitrosative stress initiates the ubiquitination of Prx1 and subsequent disturbance of redox homeostasis in endothelial cells both *in vivo* and *in vitro* during an ischemia-like injury (Rong-Rong et al., 2014). The induction of ROS and the loss of mitochondrial Omi/HtrA2 are related to GSNO-induced apoptosis in human endothelial cells (QB et al., 2010). Han and co-workers also demonstrated the potential vasoprotective effect of melatonin in ischemic injury promoted keap1 nitration in endothelial cells (Rong-Rong et al., 2013). Melatonin ameliorates hypoglycemic stress-induced brain endothelial TJ injury by inhibiting protein nitration of TIGAR and suggested that indole has a translational potential for severe hypoglycemia induced neurovascular damage (Wang et al., 2017a). In another study melatonin also ameliorates ischemic-like injury-evoked nitrosative stress in endothelial cells via HtrA2/PED pathways (Feng et al., 2011). Thus, these findings provide added evidence of a role for nitrosative/oxidative stress in neurodegenerative disorders and indicate that ER stress may serve as a critical common factor that couples NO-induced cellular stress to neurodegeneration.

3.7.3. Mitochondrial stress

Many pieces of evidence suggest that altered apoptosis and increased oxidative stress are responsible for the pathogenesis of several neurodegenerative diseases such as AD, PD, HD, and ALS. In various neurodegenerative disorders, mitochondrial stress has been considered as the leading cause in pathogenesis (Federico et al., 2012). The CNS also depends on mitochondrial function, as it has incredible energy demand. Because mitochondria supplying ATP to the cell by oxidative phosphorylation synthesizes key mediators and respond to apoptosis as well as in oxidative stress. Due to the environmental factors and generation of ROS mutations occurs in the mitochondrial DNA (Houten et al., 2006), which in turn escorts to energy failure and neurodegenerative diseases (Bhat et al., 2015). In the aging process, normal homeostasis in oxidative stress response is disturbed which leads to an intracellular increase in the levels of ROS generated by defective-mitochondria (Wang et al., 2013; Wei et al., 2001). Oxidative stress deranges the mitochondrial respiratory chain, leads to DNA mutations in mitochondria, affects membrane-permeability, influences calcium homeostasis, and mitochondrial defense systems. These changes lead to amplifying neuronal dysfunction or the development of neurodegenerative diseases and trigger neurodegeneration (Chunyan et al., 2013). Melatonin alleviates intracerebral hemorrhage-induced secondary brain injury in rats via suppressing oxidative stress, apoptosis, DNA damage, inflammation, and mitochondrial injury (Wang et al., 2018). Increased mitochondrial oxidative stress potentially exacerbates cerebrovascular inflammation and injury in aging mice (Springo et al., 2015). Mitochondrial-specific antioxidants such as R-alpha-lipoic acid and acetyl-L-carnitine seem to be potential treatments option for AD (Palacios et al., 2011). The induction of ROS and loss of mitochondrial Omi/HtrA2 are associated with GSNO-induced apoptosis in human endothelial cells (Liu et al., 2010). Thus, targeting the factors that damage mitochondria and reversing its effect by eliminating the imbalance seen in energy production can make powerful strategies for the treatment of neurodegenerative diseases.

3.8. Other mechanisms contributing to cerebrovascular inflammation

Besides the mechanisms mentioned above of neurovascular dysfunction, some other mechanisms also persuade neurovascular inflammation and neurodegeneration. The primary source of superoxide in the cerebral blood vessels is NADPH oxidase (NOX) (Dusting et al., 2005). Recently, increased expression of NOX4 in an animal model of focal permanent cerebral ischemia is established (Vallet et al., 2005). Increased levels of NOX4 have been reported within 24 h after the onset of ischemia and persist throughout a month of a follow-up period. Clinical studies also indicate that VEGF-induced angiogenesis and endothelial cell signaling are tightly controlled by the REDOX environment at the level of VEGF receptor and provide novel insights into the NOX as a potential therapeutic target for angiogenesis-dependent diseases (Masuko et al., 2002; Paravicini et al., 2004). MALAT1 is an lncRNA contributing to protecting the brain microvascular integrity and ameliorates stroke through C/EBPβ/MALAT1/CREB/PGC-1α/PPARγ pathway (Ruan et al., 2019). Postnatal ablation of CREB and CREM also results in progressive neuronal degeneration in the adult brain (Lonze and Ginty, 2002; Mayr and Montminy, 2001). Recently, miRNA-155 was originated to negatively regulate the BBB function in the process of neurovascular dysfunction and neurodegeneration (Lopezramirez et al., 2014). Similarly, NLRP3 (Yang et al., 2014), neuropeptide Y (Duarteneves et al., 2015), IL-18 and kinins (Wu et al., 2016), σ1R (Dong et al., 2016), ER agonist (Chakrabarti et al., 2014), CXCR3 (Koper et al., 2018), DPTP a synthetic clovamide derivative (Lim et al., 2015), and neurotransmitters (Gawali et al., 2016) are also responding towards the attenuation of neurovascular inflammation-mediated neurodegeneration. Glial cells in the brain react to the stimuli and surrounding milieu by epigenetic mechanisms and rapidly respond to a variety of molecules that signal changes in CNS homeostasis (Jimenezpacheco et al., 2017). In response to these signals, microglia influence neuronal connections, alter the functions of other glial cells and mediate inflammatory reactions to injury or disease (Kohman, 2012). It is also now become clear that iron besides oxidative stress plays a significant role in the pathogenesis of neuroinflammation (Medeiros et al., 2016). Many studies have described that autophagy plays a vital role in the process of neurovascular inflammation and neurodegeneration (Ji et al., 2018; Liang and Le, 2015). Elevated C-reactive protein (CRP) plasma concentrations is also observed with an increased risk of cerebrovascular as well as cardiovascular events in ischemic stroke patients (Di Napoli et al., 2005). Taking together, as suggested by above pieces of evidence, the mechanism of neurovascular dysfunction is a sequence of versatile molecular interactions that we are only initiating to understand.

Table 1
Summarizes the major targets, possible pathways and implications of cerebrovascualr injury in neurological disorders.

Major targets	Pathways	Implications	References
Leukocyte-endothelial cells adhesion	- P2RX$_7$-dependent microglial activation, - inhibition of leukocyte-endothelial interactions, - casein kinase II mediating the expression of ICAM-1 and E-selectin, - FPR2/ALX activity,	- Neurovascular damage, - seizures - stroke, - septic encephalopathy,	(Ampofo et al., 2016; Fabene et al., 2008; Smith et al., 2015; Wang et al., 2015b)
Monocytes	- Infiltration of monocytes into the brain, - secrete HGF, - Aβ or SOD1 clearance, - brain PVM, - brain leucocytes infiltration	- Stroke and PD, - MS, - AD and ALS, - AD, - peripheral inflammation	(Cashman et al., 2012; Harms et al., 2018; Park et al., 2017; Schmitt et al., 2012)
T cells	- $CD4^+$ T cells contribute to neuronal death by the Fas/FasL pathway, - penetrate to the secondary neurodegeneration, - suppression of NK/CD8+ T cells, - crosstalk/cytokines secretion, - Th17 cell-mediated neuroinflammation,	- PD, - ischemic stroke, - Sandhoff disease, - damage motor neurons, - AD	(Appel, 2009; Holmøy, 2010; Jones et al., 2017; White et al., 2017; Zhang et al., 2013)
Toll-like receptors	- activate an innate immune response, - persistent glial activation, - inflammation and glial activation, - HO-1 isoenzyme	- neurodegenerative diseases, - AD - MS - brain and vascular dementia	(Arroyo et al., 2011; Popovich and Longbrake, 2008a; Wang et al., 2016a)
Ion channels	- Acid-sensing ion channels, voltage-gated sodium ion channels, ion channels on microglia, - cannabinoids ion channels, - P2X$_7$ activation	- Neurovascular dysfunction and neurodegenerative, - aging during neurogenesis and neuroinflammation, - neurodegenerative and neuropsychiatric,	(Fernándezruiz et al., 2013; Hossain et al., 2016; Iwata et al., 2013; Ortega-Ramírez et al., 2017; Skaper, 2011)
Matrix metalloproteinase	- interrupt BBB integrity, - degradation of matrix and TJ, - increase the function of differentiation, - PGE2/EP4 signaling in peripheral immune cells	- neurodegenerative disorders, - vascular cognitive impairment, - neurodegenerative, - promote EAE,	(Candelariojalil et al., 2011; Schiffmann et al., 2014; Vafadari et al., 2016; Vos et al., 2000; Weekman and Wilcock, 2016)
NLRP3 inflammasome	- participates in cellular damage, - mitochondrial dysfunction provokes NLRP3 inflammasome, - elevation of inflammasome proteins levels, IL-18 and IL-1β, - inhibiting the downstream pathway of the NLRP3/caspase-1/IL-1β axis, - calmodulin antagonist by inhibiting NLRP3/nitrosative stress	- inflammatory responses to neurological disorders, - cerebral I/R injury, - ischemic stroke, - PD - improve cognitive dysfunction,	(Fann et al., 2013; Gong et al., 2018; Li et al., 2018; Mao et al., 2017; Nagyoszi et al., 2015; Wang et al., 2017b)
Endoplasmic reticulum stress	- elevated ER stress markers, - BI-1 can attenuate the apoptosis by IRE1-JNK pathway, - erythropoietin reduces ATF6α, CHOP, and caspase-3 in microvessel, - dysregulated protein folding	- arterial and venous stroke, - brain injury, - cerebral I/R injury - neuronal death	(Liu et al., 2017; Takashi et al., 2006; Tiwari et al., 2015; Zhao et al., 2015)
Oxidative/nitrosative stress	- activates MMPs, - by e/i NOS, - $ONOO^-$ damages the cerebrovascular endothelium, - associated neurovascular pathogenic cascades, - BBB disruption, - melatonin by inhibiting protein nitration of TIGAR, - nitration of TRPM2 during pericytes injury,	- BBB permeability, - cerebrovascular endothelial injury, - disrupt BBB, - vascular dementia, ischemic stroke and AD, - neuropsychiatric disorders, - ameliorates stress-induced TJ injury, - autophagy	(Abdul-Muneer et al., 2015; Jiang et al., 2017; Najjar et al., 2017; Pun et al., 2009; Rong-Rong et al., 2012; Torreilles et al., 1999; Ulrich, 2006; Wang et al., 2017a)
Mitochondrial stress	- Increased mitochondrial oxidative stress, - mitochondrial DNA mutations, - by suppressing mitochondrial lesion - oxidative stress deranges the mitochondria,	- cerebrovascular inflammation, - neurodegenerative diseases, - Melatonin alleviates brain injury, - neurodegenerative disease,	(Bhat et al., 2015; Chunyan et al., 2013; Houten et al., 2006; Springo et al., 2015; Wang et al., 2018)
Cytokines	- elevated levels of IL-18, IL-23, IL-10, - IL-17, - P2X$_7$ signaling promotes microglia activation,	- Neurological disorders, - inflammatory disease, - maintaining the FasL in brain inflammatory lesion,	(Johnson et al., 2015; Lagerstedt et al., 2018; Lu et al., 2012; Wang et al., 2015c; Yao et al., 2010)
Other targets	- expression of NOX4, miRNA-155, - BBB microvascular integrity, - epigenetic mechanisms - Autophagy-related neurovascular inflammation	- focal permanent brain ischemia, - neurovascular dysfunction, - brain injury or disease - neurodegeneration,	(Lopezramirez et al., 2014; Vallet et al., 2005) Ruan et al. (2019) Jimenezpacheco et al. (2017) (Ji et al., 2018; Liang and Le, 2015)

4. Conclusions

This review has highlighted the role of neurovascular injury in the pathogenesis of neurological disorders and molecular and cellular inflammatory cascades triggered after inflammation (Table 1). The physiological and biochemical responses to neurovascular dysfunction have been discussed in this review. Normal functioning of the NVU is the critical factor for homeostasis and brain repair. Attenuation of neurovascular injury is a promising approach to control neuroinflammation. The development of innovative research designs with anti-inflammatory and other antioxidant agents would provide a better therapeutic strategy to treat the pathophysiology of neurological disorders. The therapeutic aspects by reducing neuroinflammation and attenuating neurological disorders are other scopes of future study.

Conflicts of interest

All authors declare that there is no conflict of interest regarding the content of this article.

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Appendix A. Supplementary data

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