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Astrocyte dysfunction and neurovascular impairment in neurological disorders: Correlation or causation?

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ABSTRACT

The neurovascular unit, consisting of neurons, astrocytes, and vascular cells, has become the focus of much discussion in the last two decades and emerging literature now suggests an association between neurovascular dysfunction and neurological disorders. In this review, we synthesize the known and suspected contributions of astrocytes to neurovascular dysfunction in disease. Throughout the brain, astrocytes are centrally positioned to dynamically mediate interactions between neurons and the cerebral vasculature, and play key roles in blood-brain barrier maintenance and neurovascular coupling. It is increasingly apparent that the changes in astrocytes in response to a variety of insults to brain tissue –collectively referred to as "reactive astrogliosis" – are not just an epiphenomenon restricted to morphological alterations, but comprise functional changes in astrocytes that contribute to the phenotype of neurological diseases with both beneficial and detrimental effects. In the context of the neurovascular unit, astrocyte dysfunction accompanies, and may contribute to, blood-brain barrier impairment and neurovascular dysregulation, highlighting the need to determine the exact nature of the relationship between astrocyte dysfunction and neurovascular impairments. Targeting astrocytes may represent a new strategy in combinatorial therapeutics for preventing the mismatch of energy supply and demand that often accompanies neurological disorders.

1. Introduction

Astrocytes play a pivotal role in the generation, maturation, and regulation of the neurovascular unit (NVU). Astrocytes are also extremely well-tuned to their microenvironment and respond to any disruptions therein, as occurs in disease and injury, with morphological and functional changes referred to as reactive astrogliosis. The question then arises: does reactive astrogliosis functionally alter the NVU in disease? A summary review of the literature suggests a close relationship between astrogliosis, changes in blood-brain barrier (BBB) permeability, and neurovascular dysfunction in several disorders. Indeed, astrogliosis is often prominent around blood vessels, and numerous disorders of the central nervous system (CNS) that exhibit astrogliosis – e.g. traumatic brain injury (TBI), ischemic stroke, Alzheimer's disease (AD) and related dementias, subarachnoid hemorrhage (SAH), etc. – are also accompanied by neurovascular dysregulation. Such dysregulation can include impairment of autoregulation, resting tone, neurovascular coupling (NVC) and/or BBB function: all processes that are regulated, to some extent, by astrocytes. From a purely economic viewpoint, when there is a decrease in blood flow to the brain, particularly under pathological stress when cells need even more energy to repair and recover, not all neurons and/or glial cells are likely to survive, or survive undamaged. Further, the extremely limited neurogenic capacity of the adult brain would then ensure that such degeneration will have a lasting impact on brain function. In other words, impairment of neurovascular regulation could cause neurodegeneration by producing a state of malnourishment of the brain (Fig. 1). This is the basic premise of the 'vascular' hypothesis of AD (Zlokovic, 2002), but might such dysregulation also contribute to a broader range of neuropathologies? Here, we attempt to summarize evidence gleaned from animal and

Abbreviations: 20-HETE, 20-hydroxyeicosatetraenoic acid; AD, Alzheimer's disease; ARTAG, aging-related tau astrogliopathy; BBB, blood-brain barrier; CBF, cerebral blood flow; CSD, cortical spreading depolarization; CTE, chronic traumatic encephalopathy; DCI, delayed cerebral ischemia; EETs, epoxyeicosatrienoic acids; FTLD, frontotemporal lobar degeneration; GFAP, glial fibrillary acidic protein; IF, intermediate filament; LPS, lipopolysaccharide; NVC, neurovascular coupling; NVU, neurovascular unit; PGE2, prostaglandin E2; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; TGFβ1, transforming growth factor β1

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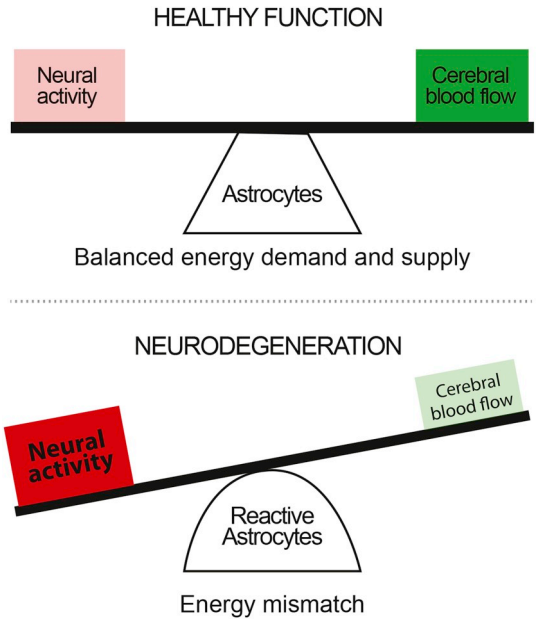

Fig. 1. Pathological implications of an imbalance in energy supply and demand. Under healthy physiological conditions, the energy demands of an active brain are supplied by nutrients delivered by the cerebral vasculature. The flow of blood and nutrients within this vasculature is fine-tuned by astrocytes via resting tone regulation and neurovascular coupling (NVC) pathways. Under pathological conditions, neurons and glial cells still require energy and this requirement may even be increased to allow the cells to cope with, and recover from, the pathological environment. However, during pathology, cerebral blood flow is often reduced and NVC is disrupted, which we hypothesize is due to altered signaling from reactive astrocytes. The resulting energy mismatch leads to the gradual development of a hypoxic condition, which is expected to contribute to progressive neuronal and astrocyte degeneration over time.

human studies to put forth the hypothesis that reactive astrogliosis may be the causative factor producing neurovascular dysfunction, which then exacerbates or perhaps, in some instances, even initiates neurodegeneration. This understudied topic has remarkable potential to help us understand the basic biology of neurological disorders and suggest new therapeutic interventions in the treatment and care of such conditions.

1.1. Astrocytes

Astrocytes were first identified in the mid-nineteenth century as a population of non-neuronal cells in the CNS that lacked axons and dendrites but bore short, highly ramified processes. They were initially identified as neuroglia by the pathologist Andriezen (1893), and later named astrocytes – the star cells – by Cajal (1995). Historically, astrocytes were divided into two subtypes: protoplasmic astrocytes, which are found in the grey matter and possess a dense cloud of fine processes that fill the interstitial space in the neuropil, and fibrous astrocytes, which are found in the white matter and possess fewer but thicker, longer processes. This basic nomenclature maintains a stronghold in the glial literature even today, despite accumulating evidence suggesting there are numerous subpopulations with striking heterogeneity, both between and within brain regions (Bayraktar et al., 2015; Farmer and Murai, 2017). Most of what we know about astrocyte functions today are based on investigations of grey matter protoplasmic astrocytes, and our understanding of white matter astrocytes, especially as it pertains to vascular regulation, is relatively limited. White matter astrocytes contact axons at the nodes of Ranvier (Butt et al., 1994), express excitatory neurotransmitter transporters, and may function to protect both oligodendroglia and axons from excitotoxicity (Baltan et al., 2011). They also facilitate myelination in the developing and mature brain via secretion of enzymes and other soluble factors, ion buffering, and metabolic substrate delivery (Lundgaard et al., 2014). Therefore, although the hypotheses forwarded in this review are largely based on findings from protoplasmic astrocytes of the grey matter, they are likely also relevant to the gliovascular structure and function in white matter.

In the grey matter, the fine processes of astrocytes permeate the neuropil to contact neuronal cell bodies, dendrites, synapses, nodes of Ranvier, ependymal cells, and the pia mater. A single astrocyte can interact with several neurons and > 100,000 synapses (Ventura and Harris, 1999; Bushong et al., 2004), forming the morphological basis of the tripartite synapse. At the other end, the endfoot processes of astrocytes almost completely encapsulate the parenchymal vasculature (Simard et al., 2003; Mathiisen et al., 2010). Astrocytes express several ion channels, transporters, and receptors, which facilitate their critical roles in modulating synaptic activity via potassium buffering, pH regulation, neurotransmitter uptake and gliotransmitter release, and general maintenance of neuronal homeostasis (Verkhratsky and Nedergaard, 2018). Mature astrocytes form a highly organized, gap junctionally-coupled network that tiles the brain, with each astrocyte occupying a unique spatial domain (Bushong et al., 2002). This spatially segregated yet intercellularly connected astrocyte syncytium allows astrocytes to discriminate and integrate neuronal signals, earning them recognition as partners in information processing (Araque et al., 2014). This syncytium may also enable astrocytes to supply energy substrates to neurons (Pellerin and Magistretti, 1994) and oligodendrocytes (Niu et al., 2016), although this is still debated (DiNuzzo et al., 2010; Diaz-Garcia et al., 2017; Dienel, 2017). Central to the argument presented in this review, astrocytes are also key players in cerebral blood flow (CBF) regulation. Based on their morphological characteristics, the visionary Cajal first hypothesized that astrocytes might control vascular diameter, and much evidence now supports their integral role in maintaining resting vascular tone as well as regulating NVC (Zonta et al., 2003; Mulligan and Macvicar, 2004; Metea and Newman, 2006; Takano et al., 2006; Kim et al., 2015; Rosenegger et al., 2015; Mishra et al., 2016).

1.2. Cerebral blood flow

The enhanced cognitive power with which the brain endows mammals and especially humans comes at a high price – both the size (Aiello, 1995) and metabolic rate (Karbowski, 2007) of the mammalian brain have evolved to be larger than that predicted by body size alone. Indeed, increased cerebral metabolic rate is considered one of the main factors driving higher cognitive development. This increase in metabolic activity results in a correspondingly large energy demand (Howarth et al., 2012), which is supplied by the extensive cerebrovascular network originating largely from the internal carotid arteries. Evolutionary changes in skull structure show that the carotid foramen, through which the internal carotid artery passes into the skull, is enlarged in the human skull compared to other hominids and may have been the initial evolutionary step that permitted the human brain to attain its current complexity (Seymour et al., 2016), stressing the importance of cerebral blood supply for higher cognitive function.

CBF is regulated via several mechanisms. Autoregulation ensures that the brain receives a relatively constant supply of blood and nutrients despite changes in systemic blood pressure (Tzeng and Ainslie, 2014; Filosa et al., 2016). Neurogenic signals from the basal forebrain and brain stem nuclei on penetrating arterioles and from peripheral trigeminal ganglionic innervation of pial blood vessels also contribute to the toneof cerebral vasculature and, therefore, CBF (Hamel, 2006; Cauli and Hamel, 2010). However, as the brain lacks energy stores and is reliant upon blood glucose-dependent aerobic respiration (Holmes and Holmes, 1926), CBF is also regulated locally in response to increased neuronal activity via NVC, thereby giving rise to functional hyperemia. NVC is regulated by signaling between neurons, astrocytes,

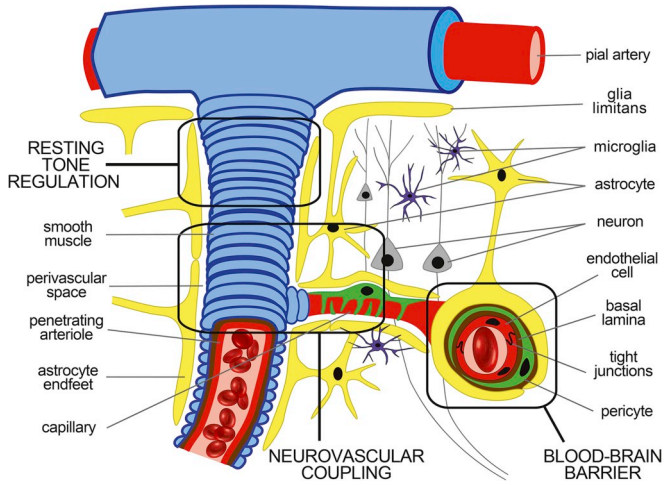

Fig. 2. Organization of the neurovascular unit. Pial arteries give rise to penetrating arterioles that dive into the brain parenchyma where they branch into smaller arterioles and capillaries. These arterioles receive intrinsic and extrinsic innervation perivascularly to facilitate resting tone regulation via their smooth muscle cell layer. The capillary microvessels lose this smooth muscle cell layer completely and are instead ensconced by astrocyte endfeet and contractile pericytes, which contact the capillary endothelial wall directly. The cerebral capillary microvessels are further distinguished by their endothelial cells, which are held together by tight junction proteins that form the innermost component of the blood-brain barrier. The endothelial cells, pericytes, and astrocytes, along with the neurons and microglia within a particular vascular domain, together comprise the neurovascular unit. These neuronal, glial and vascular components interact with each other to ensure precise spatiotemporal delivery of oxygen and nutrients from the blood to metabolically active regions of the brain via neurovascular coupling. Astrocytes are particularly important for this interaction, as they are centrally located between the metabolically active neurons and the cerebral vessels that are poised to respond to such activity.

and vascular cells (endothelial cells, vascular smooth muscle cells, and pericytes), which collectively make up the NVU (Iadecola, 2017; McConnell et al., 2017) (Fig. 2). The NVU is thus the epicenter of several tightly controlled, dynamic intercellular interactions orchestrated to maintain optimal global and local CBF (Filosa et al., 2016; Mishra, 2016). It is also the structural basis of the BBB, which isolates the brain from most circulating factors, antigens and, under healthy conditions, immune cells (Daneman and Barres, 2005; Iadecola, 2017).

1.3. Astrocytes as mediators of neurovascular coupling

Historically, NVC was believed to be a feedback system produced by metabolic demand: active neurons produce an energy deficit that triggers an increase in blood supply. When neuronal activity returns to normal, the energy deficit is no longer present and so blood supply returns to resting levels (Koehler et al., 2006; Attwell et al., 2010). Evidence from the past couple of decades, however, suggests that NVC is instead a feed-forward mechanism (Vaucher et al., 1997; Koehler et al., 2006; Attwell et al., 2010): neuronal activity stimulates a complex intercellular signaling cascade, resulting in the production and release of several vasoactive compounds that produce vascular dilation and an increase in blood flow. This feed-forward signaling is triggered regardless of local oxygen level (Lindauer et al., 2010). An emerging hypothesis suggests that a combination of both of these scenarios may be at play: the feed-forward system may regulate the rapid phase of the neurovascular response, whereas the feedback signaling may contribute to the slower, tonic phase (Baslow and Guilfoyle, 2017).

The role of astrocytes in conveying neurovascular signals to parenchymal arterioles has been extensively studied and reviewed (Howarth, 2014; Mishra, 2016; Iadecola, 2017). Astrocytes respond to neurotransmitters released during synaptic activity, such as glutamate (Alkayed et al., 1997; Zonta et al., 2003; Takano et al., 2006; Gordon et al., 2008) and ATP (Wells et al., 2015; Mishra et al., 2016), with an increase in their intracellular Ca^{2+} concentration (Mishra et al., 2016). This increased Ca^{2+} prompts astrocytes to synthesize and release an assortment of vasoactive substances that act on vascular smooth muscle cells to elicit vessel dilation and increase blood flow. Such vasoactive substances include ions such as K^+ (Filosa et al., 2006), metabolites of arachidonic acid such as prostaglandin E2 (PGE_2) (Zonta et al., 2003; Takano et al., 2006; Gordon et al., 2008; Mishra et al., 2011; Hall et al., 2014) and epoxyeicosatrienoic acids (EETs) (Alkayed et al., 1997; Metea and Newman, 2006), metabolic by-products such as lactate (Gordon et al., 2008), and products of ATP breakdown such as adenosine (Xu and Pelligrino, 2007; Vetri et al., 2011). Astrocyte-derived arachidonic acid can also be metabolized downstream in vascular smooth muscle cells to produce 20-hydroxyeicosatetraenoic acid (20-HETE) to induce vessel constriction (Mulligan and Macvicar, 2004; Metea and Newman, 2006; Mishra et al., 2011; Hall et al., 2014). Interestingly, astrocytic Ca^{2+}-dependent NVC is bidirectional – moderate increases in Ca^{2+} produce dilations, while large increases produce constrictions (Girouard et al., 2010). It must also be noted that NVC can also be triggered by direct signaling from neurons (Attwell et al., 2010; Cauli and Hamel, 2010) and is not dependent on any single signaling mechanism; rather, it appears to be product of several parallel and redundant pathways (Liu et al., 2012; Hosford and Gourine, 2019), underscoring the significance of NVC in maintaining healthy brain function. Further, not all factors involved in this parallel signaling have yet been identified: simultaneous blockade of almost all the above-described pathways is not enough to completely inhibit NVC.

Astrocytes have been shown to play an essential role in NVC at the microvascular capillary level (Biesecker et al., 2016; Mishra et al., 2016). In the cortex, ATP released by active neurons causes a Ca^{2+} influx in astrocytes via ionotropic P2X1 channels, which stimulates arachidonic acid production and its downstream metabolism to vasodilatory PGE_2. PGE_2 then acts on EP_4 receptors on pericytes, the contractile cells on capillaries, thereby dilating capillaries (Mishra et al., 2016). In contrast to previous findings, these and other studies also reported that interfering with astrocyte Ca^{2+} is not sufficient to block arteriolar NVC, calling the importance of Ca^{2+}-dependent astrocyte mechanisms in arteriole regulation into question (Nizar et al., 2013; Takata et al., 2013; Bonder and McCarthy, 2014; Jego et al., 2014; Biesecker et al., 2016; Mishra et al., 2016). Some of these studies only evaluated the role of astrocytic Ca^{2+} signals within the soma or inositol trisphosphate (IP3) dependent release of Ca^{2+} from internal stores in mediating vascular responses, and thus may not be representative of the role played by IP3-independent astrocyte Ca^{2+} signals (Srinivasan et al., 2015), particularly in process microdomains or vascular endfeet (Otsu et al., 2015). In a recent report (Mishra et al., 2016), we showed that chelating fast astrocyte Ca^{2+} does not change arteriole NVC but significantly reduces capillary NVC. It has also been proposed that astrocytes may only regulate arteriole NVC under conditions of high or persistent neuronal activity (Institoris et al., 2015). Taken together, these data support the notion that astrocytes regulate NVC at the microvascular capillary level and, under some circumstances, also at the arteriole level (Iadecola, 2017).

1.4. Astrocytes as modulators of cerebral blood flow

Recent evidence highlights the role of the local NVU and astrocytes in maintaining resting vascular tone (Filosa et al., 2016) via the release of both constrictive and dilatory factors. Though pressure-evoked vascular constriction of parenchymal arterioles is *initiated* by myogenic factors, it is now demonstrably *maintained* by astrocyte-dependent signaling (Kim et al., 2015). Specifically, an increase in intravascular pressure activates mechanosensitive, Ca^{2+}-permeable TRPV4 channels on astrocytes, resulting in a rise in astrocyte Ca^{2+}. This in turn causes

astrocytes to release purinergic signals that are necessary to maintain the pressure-evoked constriction (Kim et al., 2015). Similarly, the resting vascular tone of retinal arterioles is dependent on purinergic signaling from Müller glial cells (Kur and Newman, 2014), the retinal approximate of astrocytes. Another study reported that Ca^{2+}-dependent cyclooxygenase metabolites released from astrocytes dilates cortical arterioles at rest, and that arresting astrocyte Ca^{2+} results in arteriole constriction (Rosenegger et al., 2015). Further, cortical vasodilation induced by basal forebrain stimulation, a response previously thought to be entirely neurogenic, was recently shown to be, in part, dependent on astrocytic release of epoxyeicosanoids (Lecrux et al., 2012). A healthy balance between such dilatory and constrictive signals is likely important for regulating vascular tone and maintaining resting blood flow at physiologically desirable levels.

1.5. Astrocytes and the blood-brain barrier

The microvasculature in most organ systems is fenestrated, lacks endothelial tight junctions and is readily permeable to substances in the blood. The brain vasculature, in contrast, is endowed with the BBB, which regulates permeability across the vascular wall in order to maintain homeostasis of the CNS microenvironment and, under healthy conditions, to protect the brain from the peripheral immune system. Tight junctions form a physical barrier at the BBB: they exist between overlapping processes of endothelial cells and prevent substances in the blood from leaking into the CNS extracellular space (Reese and Karnovsky, 1967; Coomber and Stewart, 1985). Thus, passage of substances from the blood to the brain requires either a transporter-mediated or a transcytosis-dependent pathway.

Intricate crosstalk between NVU components, including astrocytes, pericytes and endothelial cells, generates and maintains the BBB. During development, pericytes help establish the BBB by inhibiting the expression of endothelial genes that enhance vascular permeability (Daneman et al., 2010) and inducing polarization of the astrocyte endfeet abutting the vasculature (Armulik et al., 2010). The BBB is often impaired in neurologic disease, suggesting that continued maintenance is required during adult life to preserve normal barrier function (Daneman and Barres, 2005; Abbott et al., 2006). Astrocytes play a key role in this maintenance by secreting trophic factors such as transforming growth factor β1 (TGFβ1), glial-derived neurotrophic factor, fibroblast growth factor and angiopoietin-1 that preserve the BBB phenotype in endothelial cells (Abbott et al., 2006; Daneman and Prat, 2015).

2. Reactive astrogliosis and astrocyte dysfunction

Astrocytes respond to CNS disease and injury via an overt process known as reactive astrogliosis. Astrogliosis encompasses a host of morphological, transcriptomic, epigenetic, and proliferative changes in astrocytes (Anderson et al., 2014) and often occurs in a graded manner (Sofroniew, 2009). Mild to moderate astrogliosis (e.g. mild trauma, diffuse immune activation), comprises a small and reversible increase in astrocytic expression of cytoskeletal intermediate filament (IF) proteins such as glial fibrillary acidic protein (GFAP) and vimentin (Brenner, 2014) (Fig. 3A–C) together with cellular hypertrophy. Severe astrogliosis (e.g. major infection, chronic neurodegeneration) produces an irreversible, lasting change in the cytoarchitecture and functional properties of astrocytes. In extreme cases, this leads to the formation of a glial scar wherein astrocytes proliferate and form dense intertwined webs to fill in and wall off the empty spaces left by dead or dying cells (Fig. 3D), thereby protecting normal CNS tissue by suppressing the spread of infectious agents, inflammatory cells (and the cytokines and metabolites they release), and cell death. Chronic glial scarring from this kind of astrogliosis was, until recently, thought to detrimentally and physically prevent axon regrowth and thus functional recovery in spinal cord injury (Davies et al., 1999). This prevailing dogma is challenged by a recent study demonstrating that molecular signals expressed by the glial scar tissue support axon growth and, indeed, allow nerve fibers to regrow across spinal lesions (Anderson et al., 2016). Importantly, the exact cellular changes underlying astrogliosis are likely context-dependent (Zamanian et al., 2012), defined by the specific disease and/or injury (Sofroniew, 2014; Liddelow and Barres, 2017), and perhaps even the stage of the disease. Notably, increases in IF proteins and astrogliosis are not only induced by injury, but also in aging (Sabbatini et al., 1999; Clarke et al., 2018). An emerging area of research centers on the question of whether senescence or degenerative changes that affect astrocytes, rather than neurons, promote aging and age-related disease in humans.

Transcriptomic analysis of reactive astrocytes has highlighted the striking heterogeneity of these cells and led to the idea of 'good' verses 'bad' astrogliosis (Liddelow and Barres, 2017). Insults that mimic infection, such as injections of the bacterial toxin lipopolysaccharide (LPS) *in vivo* or treatment with inflammatory cytokines *ex vivo*, induce expression of cytokines that are likely to aggravate pathology, while insults that cause ischemia induce the expression of proteins involved in tissue repair and neuroprotection (Zamanian et al., 2012). These indications are partly borne out by mechanistic studies: astrocytes responding to LPS stimulation actively phagocytose neurons and negatively impact recovery (Liddelow et al., 2017), while astrocytes responding to ischemia (Liu et al., 2014; Becerra-Calixto and Cardona-Gomez, 2017; Tachibana et al., 2017), spinal cord injury (Faulkner et al., 2004; Anderson et al., 2016), or TBI (Shinozaki et al., 2017) can enhance recovery. This is not entirely unexpected as astrocytes are very adaptable cells that continuously tune in to their environment and respond to it accordingly to establish and maintain homeostasis. In this sense, reactive astrogliosis is a response that aims to re-establish homeostasis after injury and attenuate damage to the nervous tissue. However, similar to peripheral inflammatory responses, astrogliosis may become injurious under specific conditions and exacerbate damage (Barres, 2008; Anderson et al., 2014). It is also likely that a spatial and temporal heterogeneity of astrocyte reactivity exists relative to the site of injury. Future research should focus on identifying and categorizing the disease-ameliorating and disease-exacerbating aspects of astrocyte reactivity. Results from such studies may facilitate therapeutic fine-tuning of astrogliosis to skew the process towards neuroprotection and functional recovery.

Features that characterize astrogliosis include decreased expression of inwardly rectifying K^+ (K_{ir}) channels (Ji et al., 2012), the glutamate transporters GLT-1 and GLAST (Piao et al., 2015; Hubbard et al., 2016), the purinergic receptor P2Y1 (Shinozaki et al., 2017) and adenosine kinase (Gouder et al., 2004; Aronica et al., 2013). Loss of perivascular localization of the water transporter AQP4 (Eid et al., 2005; Alvestad et al., 2013) and an increase in the expression or activation of metabotropic glutamate receptors (Aronica et al., 2000; Anneser et al., 2004; Zamanian et al., 2012; Rusnakova et al., 2013) have also been reported. Such changes can produce glutamate and potassium imbalances in the neuropil, leading to excitotoxicity or epileptiform activity. However, they do not always occur concurrently and, instead, are remarkably context-dependent. It is also important to note that overt astrogliosis, as defined by upregulation of IF proteins and/or hypertrophy, is not obligatory for astrocytes to dysfunction and disrupt neuronal function. For example, in Huntington's disease, dysregulation of astrocytic K_{ir} channels and Ca^{2+} signaling occurs in the absence of IF protein upregulation (Jiang et al., 2016) and, in diabetic retinopathy, glial-dependent neurovascular uncoupling can occur before gliosis is pronounced (Mishra and Newman, 2010). Another example is presented by multiple sulfatase deficiency, a lysosomal storage disorder caused by mutations in the sulfatase modifying factor 1 gene – transgenic mice with this mutation only in astrocytes display no overt astrogliosis, despite exhibiting degeneration of cortical neurons and anxiety behavior (Di Malta et al., 2012). These findings stress the need for a more nuanced sub-classification of astrocyte dysfunction states. For the purposes of this review,

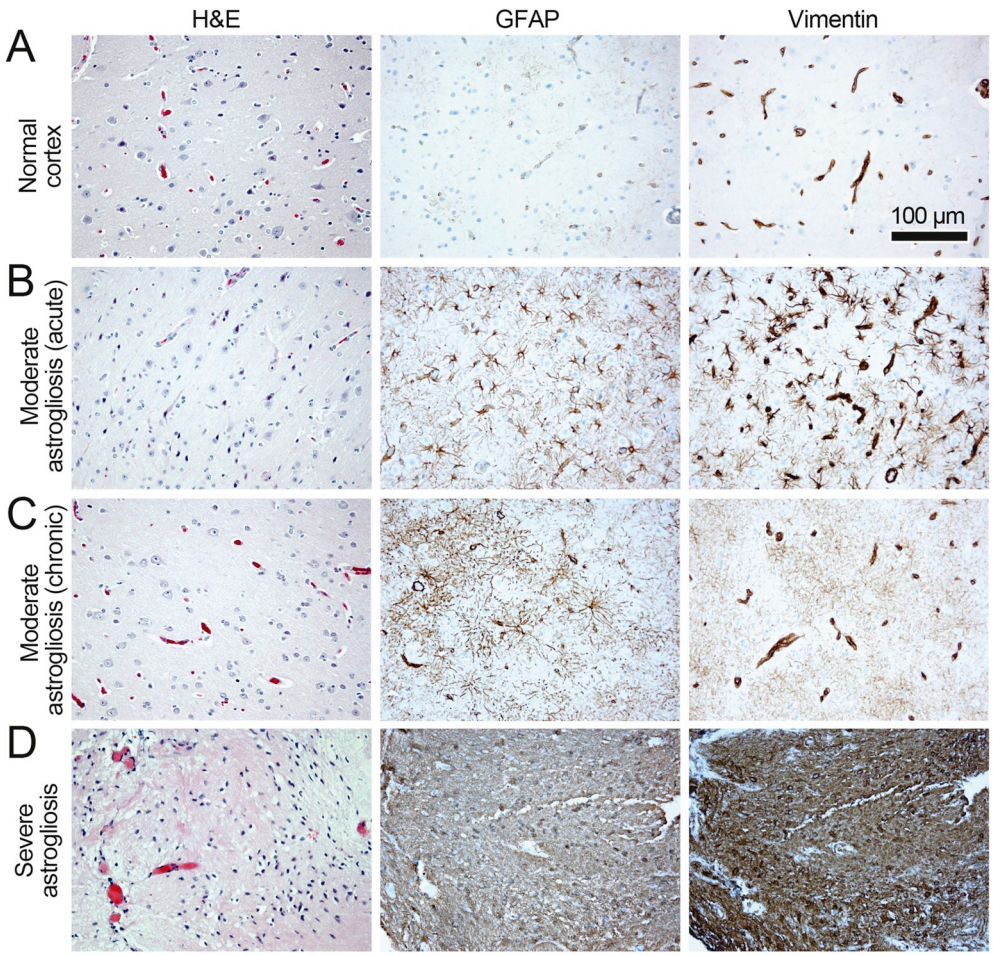

Fig. 3. Conventional immunohistochemical markers demonstrate astrogliosis grading in tissue from epilepsy patients. Cytoskeletal changes in reactive astrocytes as manifested in intermediate filament expression. All subjects were patients with epilepsy who underwent temporal lobectomy for resection of seizure focus. Images of hematoxylin- and eosin-stained sections are depicted in the first column, and corresponding brain regions immunostained for the intermediate filament proteins GFAP and vimentin are shown in the second and third columns, respectively. **A**: A relatively normal-appearing cortex. GFAP is minimally expressed and vimentin expression is restricted to vascular endothelial and smooth muscle cells. **B**: A subacute phase of relatively moderate astrogliosis with increased astrocyte GFAP in proximal cell processes and a similar pattern of more striking vimentin expression. **C**: A moderate astrogliosis that is more long-standing, with GFAP and vimentin expression distributed widely throughout the dense cloud of astrocyte fine processes. With moderate gliosis, morphologic changes detected by histologic assessment of hematoxylin- and eosin-stained sections are subtle. Neuronal loss may be inconspicuous. Vimentin expression is still more pronounced in the vascular cells than astrocytes. **D**: A severe chronic gliosis associated with a cortical penetrating injury that was the cause of epilepsy. Hematoxylin- and eosin-staining shows complete loss of neurons and dense eosinophilic astrocyte cytoplasm. Astrocyte GFAP and vimentin are highly expressed to the degree that vascular structures are present but obscured on vimentin immunohistochemistry; this tissue appears to have completely converted to a glial scar.

we use the terms ‘astrogliosis’ and ‘reactive astrocytes’ to encompass both morphologically overt astrogliosis and astrocyte dysfunction.

3. Astrocyte-mediated neuropathologies

Defects that primarily affect astrocytes are relatively rare but highlight some important aspects of the roles of astrocytes in health and disease. These defects tend to fall into two categories: young-onset inherited disease due to mutations in genes that are expressed in astrocytes and contribute to important astrocyte functions, and older-onset disease with morphologic or biochemical features that implicate astrocytes more than other cells as contributors to disease etiology.

Of the inherited diseases, Alexander disease is a clear example, caused by mutations in the GFAP gene. It features not only morphological changes and functional losses in astrocytes, but prominent secondary effects on other glial cells (e.g. microglial activation and oligodendrocyte loss that produce noticeable demyelination), BBB disruption, and variable neuronal loss (Mignot et al., 2004; Sosunov et al., 2018). Another example is hereditary spastic paraplegia, in which mutations in EAAT2 (GLT-1), the astrocyte glutamate transporter, produce loss of upper motor neurons (Meyer et al., 1998; Parodi et al., 2017). Amyotrophic lateral sclerosis is yet another case, where SOD1 mutations are thought to produce motor neuron degeneration through a non-cell autonomous mechanism that involves astrocyte stimulation of neuronal excitability (Papadeas et al., 2011; Fritz et al., 2013; Hayashi et al., 2016).

Some diseases produce neuronal or axonal loss through an acquired immune-mediated attack that targets astrocytes. Immune-mediated attacks on astrocyte AQP4 was recently shown to be the basis of most cases of neuromyelitis optica (Jarius and Wildemann, 2010), with astrocyte dysfunction leading to NVU disruption, oligodendroglial death, and demyelination (Ratelade and Verkman, 2012). Another similar autoimmune condition, GFAP astrocytopathy, was described in 2016, wherein patients’ immune systems generate antibodies against GFAP with associated subventricular and perivascular damage (Fang et al., 2016), ultimately resulting in encephalopathy, inflammatory myelitis, tremor, and ataxia. The primary astrocyte insult appears to begin around the pial, ventricular, or perivascular regions, perhaps because these are regions where the peripheral immune system can first interact with brain tissue. The pathophysiology underlying this condition is not fully understood but it is suggested that antigen-specific cytotoxic T-cells (rather than the anti-GFAP antibody itself) may play a role in some cases, or that an immune attack triggered by occult neoplasm expressing astrocyte antigens may be responsible in others (Zekeridou et al., 2018). It could also be downstream of other astrocyte dysfunctions, a question currently under investigation (Zekeridou et al., 2018).

Several late-onset conditions associated with astrocyte dysfunction have also recently gained scientific attention. Age-related neuropathologies associated with protein aggregation within astrocytes, especially hyperphosphorylated tau, have been described in frontotemporal lobar degeneration (FTLD), Pick's disease, progressive supranuclear palsy, cortico-basal degeneration, and aging-related tau astrogliopathy (ARTAG) (Komori, 1999; Kovacs et al., 2017). Astrocytic tauopathy tends to be the dominant pathologic feature in some tau mutation-associated FTLD as well as the pathologic lesion of ARTAG (Kovacs et al., 2017). All of these diseases feature prominent neuronal

loss and/or demyelination. Key roles for astrocytes have been proposed in additional diseases that feature neuronal loss, including epilepsy, Huntington's disease, and Parkinson's disease, and often involve blood-brain barrier dysfunction and altered astrocyte metabolism (Weissberg et al., 2015; Booth et al., 2017; Khakh et al., 2017; Boison and Steinhauser, 2018; Skotte et al., 2018; Yan et al., 2018).

The distinction between astrogliosis and astrocytopathy in disease is noteworthy: astrogliosis is defined as the active response of astrocytes to an injury (neuronal death, ischemia or TBI etc.) and involves aberrant loss or gain of astrocyte function, while astrocytopathy is defined as astrocyte degeneration characterized by swollen cell bodies, retracted short processes, and loss of fine processes and endfeet (Pekny et al., 2016; Kim et al., 2017). Particularly in conditions where astrocytopathy is observed, the disease is likely to be secondary to unhealthy astrocytes. Is astrocytopathy a separate independent phenomenon, or is it the end-product of prolonged astrogliosis and functional disruption? We do not know. However, evidence provided above supports the concept of astrocytopathy or 'astrodegeneration' as another important contributor to the pathogenesis of disease, including those that have been considered primarily or exclusively neuronal in nature, and should be considered a possible etiological factor in neurodegenerative diseases.

4. Astrogliosis and neurovascular unit impairment in neurodegenerative disorders

Many CNS diseases feature NVU abnormalities. Some are readily attributable to NVU abnormalities, such as stroke and vasculitis. In many others – including AD, TBI, chronic traumatic encephalopathy (CTE), etc. – NVU abnormalities are rampant, but the reason for these abnormalities and their contribution to disease etiology is unclear (reviewed in McConnell et al., 2017 and Liebner et al., 2018). Given the central positioning of astrocytes between neurons and vascular cells within the NVU, it is plausible that they aberrantly influence the NVU, thus disrupting the BBB and NVC, and contribute to neurological disorders. Here we focus our attention on three disorders - AD, TBI, and stroke – and discuss the evidence implying a possible causal relationship between astrogliosis and NVU dysfunction. Although TBI and stroke are acute-onset conditions, they have chronic impacts on neurological health, including increased incidence and rate of cognitive decline (Savva et al., 2010; Levine et al., 2015; Ozen et al., 2015). Further, accumulating evidence that AD patients have a history of evident or silent infarcts further stresses the interaction of such acute injuries with chronic conditions (Vermeer et al., 2003; Yang et al., 2015). These chronic consequences of acute injuries may partially originate from impairments in astrocyte-vascular signaling. We also briefly discuss the association between astrogliosis and vascular dysfunction in white matter diseases.

4.1. Alzheimer's disease and related dementias

AD is the leading neurodegenerative cause of cognitive decline and dementia. AD diagnosis is based on neurological evaluation and neuroimaging data, and is confirmed port-mortem by histological presence of extracellular plaques of amyloid β protein (Aβ) and intracellular neurofibrillary tangles of hyperphosphorylated tau protein within neurons. In many cases, Aβ deposition also occurs around the vasculature in the form of cerebral amyloid angiopathy (CAA). However, aside from a few mutations responsible for familial cases, the actual cause of AD remains unknown. While much of the past work on AD has predominantly focused on neurogenic mechanisms and neuroprotection (Kuruva and Reddy, 2017), epidemiological data suggest that vascular pathology is also a key contributing factor. Although the vascular hypothesis of AD and dementia was proposed over two decades ago (de la Torre and Mussivand, 1993; de la Torre, 1997; Farkas and Luiten, 2001; Zlokovic, 2002), only recently has it become the focus of renewed attention (Kalaria, 2010; Snyder et al., 2015; Montagne et al., 2016). Indeed, the National Institute of Neurological Disorders and Stroke has now focused a new research framework for investigations specifically into vascular contributions to cognitive impairment and dementia (Corriveau et al., 2016).

BBB dysfunction and cerebral hypoperfusion both occur early in AD (Kelleher and Soiza, 2013; Iturria-Medina et al., 2016), and decreased tissue oxygenation is observed even in patients with mild cognitive impairment (Tarumi et al., 2014), suggesting disruption of CBF regulation. Indeed, impairment of NVC occurs in AD patients (Rosengarten et al., 2009; Nicolakakis and Hamel, 2011; Kotliar et al., 2017), with regions of amyloid deposition being characterized by large reductions in CBF (Mattsson et al., 2014). A recent analysis of the patient data deposited in the multicenter AD Neuroimaging Initiative showed that cerebrovascular dysregulation was not only the strongest and earliest detectable event during the development of cognitive impairment, but was correlated with disease progression even before amyloid β (Aβ) accumulation and functional/metabolic changes (Iturria-Medina et al., 2016). Animal models of AD are also characterized by impaired NVC (Rancillac et al., 2012; Kimbrough et al., 2015; Joo et al., 2017; Tarantini et al., 2017; Gutierrez-Jimenez et al., 2018), lower resting CBF (Niwa et al., 2002) and lower oxygen extraction fraction (Gutierrez-Jimenez et al., 2018), often preceding plaque deposition (Niwa et al., 2002). In an animal model of CAA, cerebral hypoperfusion accelerated the rate of CAA burden and the appearance of cortical microinfarcts (Okamoto et al., 2012). CAA can interrupt NVC signals (Kimbrough et al., 2015), likely producing local hypoxia, which can, in turn, induce Aβ generation (Zhang et al., 2007). Thus, a vicious feedback loop is initiated wherein Aβ and hypoxia exacerbate each other. Consistent with this, a study of demented patients experiencing hypoperfusion due to a unilateral carotid artery stenosis were found to have a much higher Aβ load preferentially in the stenosed hemisphere (Huang et al., 2012). These findings extend strong support for the hypothesis that neurovascular dysfunction may be causative in AD rather than purely correlative.

What, if any, is the role of astrocytes in this dysfunction? Reactive astrogliosis is a common and widespread histologic feature of AD (Rodriguez-Arellano et al., 2015; Taipa et al., 2017). In both patients and animals models, reactive astrocytes associate strongly with senile plaques (Mandybur and Chuirazzi, 1990; Cullen, 1997; Rodriguez-Arellano et al., 2015) where they play an important role in Aβ degradation and clearance (Wyss-Coray et al., 2003). These astrocytes exhibit not only local, but global, network-wide increases in Ca^{2+} signaling (Kuchibhotla et al., 2009) and clear presynaptic dystrophic neurites by engulfing and degrading them (Gomez-Arboledas et al., 2018). Thus, generally speaking, astrocytes appear to take on a phagocytic role in AD, conferring neuroprotection. However, there is also ample evidence for detrimental roles of astrocytes; they exhibit decreased expression and activity of glutamine synthetase (Olabarria et al., 2011), overexpress inducible nitric oxide synthase (Akama and Van Eldik, 2000), and can inhibit neuronal function by synthesizing and releasing GABA (Jo et al., 2014). At the NVU, astrocytes exhibit several changes that may alter their ability to maintain the BBB and regulate NVC. Reactive astrocytes surrounding Aβ plaques exhibit Ca^{2+} hyperactivity driven by metabotropic purinergic signaling (Delekate et al., 2014) and, in models of CAA, the vascular coverage by astrocyte endfeet is reduced with concurrent downregulation of K^+ and AQP4 channels (Wilcock et al., 2009). As Ca^{2+}-dependent K^+ release from astrocytes is one of the established pathways regulating NVC, dysfunction of these signals in reactive astrocytes could have an immediate and strong effect on local blood flow. Further, dysfunction of the glymphatic clearance system, which relies on astrocytic AQP4 channels, was also recently suggested to increase Aβ accumulation in an AD model (Peng et al., 2016). Further research needs to directly address whether reactive astrogliosis, via these or other mechanisms (AA metabolites, adenosine, lactate etc.), attenuates NVC or alters perivascular

Aβ clearance in AD.

Astrocyte dysfunction has been demonstrated to directly induce AD-like vascular and amyloid pathology in one interesting case. In mice overexpressing astrocyte-specific TGFβ1, astrogliosis develops at a young age and is followed by a reduction in CBF, an increase in perivascular Aβ accumulation (even in the absence of an Aβ-overexpressing mutant genotype), and finally cerebral hemorrhage – similar to the progression of AD pathology in human disease (Wyss-Coray et al., 2000a, 2000b; Gaertner et al., 2005). TGFβ receptor-dependent signaling produces astrogliosis in response to blood-borne proteins that leak into the brain in the event of BBB failure (Heinemann et al., 2012). It is therefore possible to imagine a scenario whereby an early disruption of the BBB (perhaps induced by peripheral inflammation (Cattaneo et al., 2017)) and induction of astrogliosis initiates a molecular and cellular domino effect that, under repeated stress or in the right genetic background, dysregulates the NVU and overwhelms Aβ clearance systems, thus leading to AD pathology. Indeed, loss of BBB integrity is common in animal models of AD (Montagne et al., 2017), and blood constituents such as albumin, fibrinogen, and immunoglobulins accumulate in aging human brains (Goodall et al., 2017), particularly in astrocytes. Even more compellingly, TGFβ1 levels are increased in the brains (Wyss-Coray et al., 1997) and cerebrospinal fluid of AD patients (Zetterberg et al., 2004). These findings lend credence to the general hypothesis that an initial BBB failure event leads to astrogliosis (and also microglial activation (Heppner et al., 2015; Sarlus and Heneka, 2017), not discussed in this review), which induces neurovascular dysregulation and hypoperfusion, which then increase microinfarcts and Aβ formation. Upon prolonged and repeated insults, or within the right genetic background, such astrocyte-directed NVU dysregulation could lead to increased Aβ deposition and, ultimately, increased neuronal injury to result in the typical “sporadic” cases of AD. Now that we are beginning to understand the connections between astrocytes, neurovascular regulation, and BBB maintenance in physiology and their impairment in AD pathology, it is time to revise our strategy to one that aims to preserve not only neurons but also astrocytes, other glial cells and vascular cells: indeed, the whole community must survive for cognitive function to be saved (Barres, 2008).

4.2. Traumatic brain injury

TBI occurs when the brain sustains physical trauma due to impact, penetration, or rapid movement (vibrations) within the skull. Because TBI can result from multiple injury paradigms, and affect all genders and ages, the exact pathophysiology underlying the disorder is unique to each patient in both region and extent. Age and injury severity can both strongly influence pathological outcomes (Reuler and Gardner, 1987). In general, pathophysiological changes are characterized as either primary (occurring immediately as a result of the trauma) or secondary (occurring later as a result of neuroinflammation and altered cellular signaling). Among these changes, disequilibrated ionic flux and glucose metabolism are neurochemical hallmarks of the disorder. The latter causes what is referred to as a post-TBI energy crisis: vulnerable brain cells need a relatively increased glucose supply to repair and recover, but a pathological decrease in glucose uptake into the brain due to decreased CBF (Golding et al., 1999; Selwyn et al., 2013), impaired glucose transport (Cornford et al., 1996) and/or metabolic processing (Bartnik et al., 2005) results in an energy mismatch between the energy demands and supply. Further, hypoperfusion and reduced autoregulation are observed in both TBI patients (Soustiel and Sviri, 2007; Newsome et al., 2012; Hinzman et al., 2014; Sours et al., 2015) and animal models (Yuan et al., 1988) with attendant astrogliosis (Burda et al., 2015).

TBI can initiate a host of secondary injury cascades that lead to widespread dysfunction of the NVU, neurovascular uncoupling, and changes in microvascular ultrastructure (Logsdon et al., 2015; Kenney et al., 2016; Toth et al., 2016). Specifically, trauma can result in vascular endothelial cell injury, leading to vasospasm, vasoconstriction, micro-thrombosis and oxidative stress, all of which exacerbate the inflammatory response (Lenzlinger et al., 2002; Veenith et al., 2016). TBI is also strongly associated with induction of cortical spreading depolarizations (CSD), which produce severe alterations in resting and reactive CBF, including NVC (Hartings et al., 2009; Lauritzen et al., 2011; Hinzman et al., 2014) (see section 4.3 on *Stroke* for further discussion of CSD and cerebrovascular dysregulation). Mechanical vascular injury can also directly result in ischemia and, in some cases, hemorrhage, allowing iron and blood components to be released into the parenchyma where they can induce neuronal toxicity (Wagner et al., 2003) and neurovascular uncoupling and vasospasm (Balbi et al., 2017). Microvascular injury is also a feature of CTE, which has become the topic of intense study in recent years (Kenney et al., 2016). A NINDS/NIBIB consensus group recently defined CTE to be neuropathologically identified by tau accumulation in neurons and astrocytes specifically in perivascular locations (McKee et al., 2016). The relationship between this perivascular tau accumulation and vascular dysfunction is particularly interesting and future studies are required to address whether perivascular astrogliosis produces or hastens the later cognitive manifestations of both TBI and CTE.

Both immediate and long-term loss of BBB properties have been reported following experimental TBI (Baskaya et al., 1997). BBB loss causes edema and increased expression of matrix metalloproteinase 9 (Suehiro et al., 2004), which results in a positive feedback cycle inducing further damage to blood vessels (Underly et al., 2017). Post-mortem studies in humans show that BBB loss persists for decades after a traumatic incident (Hay et al., 2015). Given that TBI can mechanically impair the BBB and that blood-borne substances like albumin, thrombin, and fibrinogen can activate astrogliosis via TGFβ receptors (Schachtrup et al., 2010; Heinemann et al., 2012; Piao et al., 2017), this chronic loss of BBB may contribute to lasting astrocyte dysfunction and alter the neuronal environment. There is contrasting evidence for the downstream effects of astrogliosis and astrocyte dysfunction – while some studies find that astrogliosis exacerbates tissue loss and behavioral deficits after TBI (Chen et al., 2017; Menzel et al., 2017), others have found that astrogliosis enhances neuroprotection (Shinozaki et al., 2017), helps stabilize the NVU, and normalizes CBF after TBI (Villapol et al., 2014). Such divergent findings suggest that the consequences of astrogliosis after TBI are multifaceted and complex (Burda et al., 2015). How does the long-lasting failure of the BBB affect the evolution of astrogliosis over time? And how do these two events together impact the NVU, blood flow regulation, and neuronal survival? These are questions that have yet to be answered (Fig. 4).

4.3. Stroke

Stroke is a common presentation of cerebrovascular disease in the brain. Ischemic stroke results from a thrombus or embolus blocking an artery supplying the brain, causing an immediate infarct in that artery's territory. In contrast, hemorrhagic stroke results from a ruptured vascular defect such as an aneurysm, often in the sub-arachnoid space, and has a very high rate of mortality; among surviving patients, delayed cerebral ischemia (DCI) is the leading cause of poor outcome (Xiao et al., 2017). Focal neurological deficits due to the insult are an initial physiological hallmark of stroke and vary based on the severity, duration and location of the injury. Pathological and cellular changes also develop in the surrounding brain regions, where neuronal, glial, and cerebrovascular injury all co-occur. Following ischemic stroke, the most pronounced among these is the glial response: phagocytic microglia within and around the infarct engulf debris from dying cells, proliferating reactive astrocytes generate a protective glial scar around the perimeter of the infarct, and astrocytes in the non-ischemic regions beyond the infarct perimeter become reactive in a spatial gradient.

The current standard of care for ischemic stroke is removal of the clot, achieved chemically by administering tissue plasminogen activator

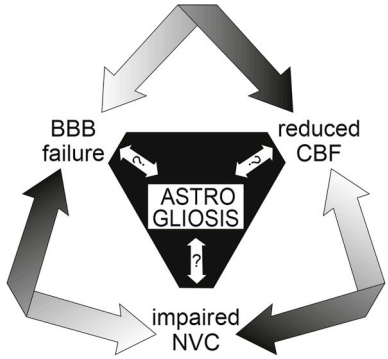

Fig. 4. Interrelationship between astrogliosis and cerebrovascular dysfunction. Do reactive astrocytes contribute to pathological cerebrovascular dysfunction in disease? With their central positioning between neurons and cerebral vessels and their multifaceted roles in homeostatic blood-brain barrier (BBB) maintenance, cerebral blood flow (CBF) regulation, and neurovascular coupling (NVC), astrocytes have the potential to adversely affect all of these processes when they are reactive and in a morphologically and functionally altered state. Although astrogliosis almost certainly contributes to and exacerbates the dysfunction of these processes, it is unclear whether it precedes them or results from them.

or mechanically by thrombectomy. Despite recanalization of the culprit artery, a state of microvascular hypoperfusion often continues to exist – the so-called 'no-reflow' phenomenon. Indeed, the level of capillary perfusion is more predictive of functional recovery in patients (Al-Ali et al., 2016) than recanalization of the blocked artery alone (Cho et al., 2015). This microvascular block was believed to be the result of platelet or leukocyte adhesion in small vessels (Abumiya et al., 2000), but evidence now suggests that active capillary constriction (Leffler et al., 1989; Hauck et al., 2004) due to pericyte contraction (Hall et al., 2014) also plays a significant role. Capillary hypoperfusion produced by pericyte contraction is also a feature of DCI following SAH (Johshita et al., 1990; Li et al., 2016). As astrocytes play a central role in regulating capillary level blood flow (Biesecker et al., 2016; Mishra et al., 2016), the possibility that astrocyte dysfunction is contributing to this hypoperfusion warrants further investigation.

Several studies also suggest a significant loss of NVC in stroke patients in the asymptomatic, non-ischemic brain tissue surrounding the infarct, either unilaterally within the stroke hemisphere (Krainik et al., 2005; Salinet et al., 2015) or bilaterally in both hemispheres (Lin et al., 2011; Salinet et al., 2018). This loss of local blood flow regulation, which likely results in hypoperfusion, is proposed to underlie the increased rate and incidence of dementia in stroke patients (Savva et al., 2010; Levine et al., 2015). However, mechanistic studies investigating the cause of NVC loss are still lacking (El Amki and Wegener, 2017). An even worse case occurs following SAH, where NVC is inverted - neuronal activity gives rise to vascular constriction and CBF reduction both *in vitro* (Koide et al., 2013; Pappas et al., 2015) and *in vivo* (Balbi et al., 2017). This extreme and evidently detrimental response likely contributes to the development of DCI after SAH.

Ischemia and injury can also trigger a continuum of CSDs, a phenomenon that is characterized by failure of neuronal ion homeostasis, mass depolarization of neurons and astrocytes, excitotoxicity and edema (Lauritzen et al., 2011; Dreier et al., 2018). After a stroke, CSDs in the ischemic region are often terminal and contribute to the neuronal damage and death in the infarct core. In the peri-infarct region, CSDs are shorter in duration and spread across the cortex at the rate of approximately 2–5 mm (Lauritzen et al., 2011). Importantly, CSDs are associated with large changes in CBF. In otherwise healthy tissue, CSDs evoke a large hyperemic response (Dreier, 2011) that does not cause tissue dysfunction or damage (Nedergaard and Hansen, 1988). However, in pathological contexts such as after ischemic stroke, SAH, or TBI, CSDs induce an inverse NVC response, resulting in vasoconstriction and decreased CBF (Dreier et al., 1998; Dreier, 2011; Hinzman et al., 2014). CSD can further induce a lack of vascular reactivity and loss of evoked NVC (Lauritzen et al., 2011). The combined effect of low CBF, lack of cerebrovascular reactivity and neurovascular uncoupling, in the face of the increased energy metabolism during pathological CSD, produces a condition of cortical spreading ischemia and results in widespread neuron death (Dreier et al., 2000). This is one of the rare cases where inverse NVC has been directly associated with tissue damage (Dreier et al., 2018).

A breakdown of the BBB also occurs in patients with ischemic stroke (Merali et al., 2017; Villringer et al., 2017) and SAH (Lampl et al., 2005), as well as in animal models (Cipolla et al., 2004; Pan et al., 2017). This breakdown results from the loss of tight junction proteins such as occludin (Pan et al., 2017) and an increase in pinocytic transcytosis across the endothelium (Cipolla et al., 2004). Loss of BBB precedes the reduction in CBF (Tamaki et al., 1984) and predicts long-term functional outcome in patients (Jiang et al., 2018), and thus, appears to be an early event after stroke.

Reactive astrogliosis is also prominent after stroke (Hayakawa et al., 2012; Abeysinghe et al., 2016; Becerra-Calixto and Cardona-Gomez, 2017; Sims and Yew, 2017). The transcriptomic profile of astrocytes after ischemic injury shows that they take on a beneficial anti-inflammatory phenotype (Zamanian et al., 2012; Rusnakova et al., 2013), which may function to stabilize and resolve the injury. Astrogliosis is correlated with CNS remodeling and motor recovery (Liu et al., 2014), and with enhanced survival of neuronal and vascular cells following early reperfusion (Tachibana et al., 2017). However, not all aspects of the astrocyte response are positive: morphologically, swelling of astrocyte endfeet can compress brain microvessels and thereby decreases microvascular perfusion (Ito et al., 2011). As cerebral vessels lose BBB properties after stroke, this vessel compression may be an astrocytic response to limit the extravasation of blood-borne solutes into the brain or a response to blood-borne solutes that have already extravasated (Xiang et al., 2016). Further, although astrogliosis and BBB breakdown are concurrently observed even in brain regions far from the site of ischemia (Garbuzova-Davis et al., 2013), the temporal relationship between them is still an open question. Does astrogliosis cause BBB breakdown, or is BBB breakdown (via leakage of blood proteins such as albumin, thrombin, and fibrinogen) producing astrogliosis? It is likely that these factors feed into each other bidirectionally, thereby exacerbating the damage caused by ischemia.

Post-stroke astrogliosis is particularly noticeable in astrocyte endfeet around cerebral vessels (Fig. 5), indicating that CBF reduction and NVC impairment after stroke may be due to astrocyte dysfunction. After SAH, astrocytes display large amplitude Ca^{2+} oscillations, which result in K^+ efflux from their endfeet onto the vasculature, raising the extracellular K^+ concentration high enough to constrict vessels, and thus resulting in NVC inversion (Koide et al., 2012). Similarly large astrocyte Ca^{2+} signals are observed immediately following ischemic stroke (Ding et al., 2009; Rakers and Petzold, 2017) with a negative impact on neuronal recovery. Large astrocytic Ca^{2+} waves also occur during CSD (Chuquet et al., 2007), which are common after stroke, and both the vasoconstriction and NVC inversion observed following CSD depend on astrocyte Ca^{2+} (Chuquet et al., 2007; Major et al., 2017) and, to some extent, the vasoconstrictive arachidonic acid metabolite 20-HETE (Fordsmann et al., 2013). In addition, a recent study reported that the decrease in CBF associated with ischemic stroke was mitigated when astrogliosis was attenuated (Begum et al., 2018). These findings suggest a causal role for astrogliosis in blood flow impairment after stroke; however, more work is required before this relationship is sufficiently experimentally corroborated.

Although it is certain that early astrogliosis is an adaptive, neuroprotective response following ischemia (Zamanian et al., 2012), could it evolve past a threshold beyond which, perhaps depending on the extent and duration of injury, it becomes a detrimental process? Or perhaps the vascular effects of astrogliosis are maladaptive 'side effects'.

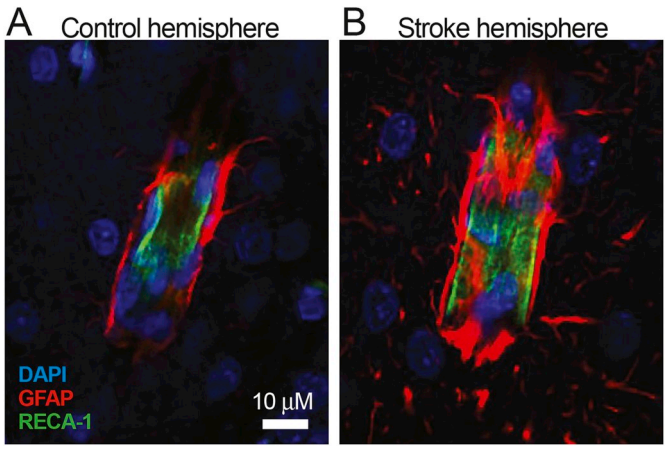

Fig. 5. Stroke-induced astrogliosis is prominent at astrocyte endfeet in rat cortex. A: GFAP immunolabeled astrocyte endfeet (red) terminating on a cortical vessel in the control hemisphere of a rat that underwent transient experimental stroke. **B**: Astrocyte endfeet terminating on a vessel in the peri-infarct intact cortical tissue of the stroke hemisphere. Note the increased expression of GFAP and hypertrophy of the endfeet processes, suggesting astrogliosis. DAPI is shown in blue and the rat endothelial cell marker (RECA-1) is shown in green. Images were obtained on a Zeiss LSM 780 3 days after middle cerebral artery occlusion in a 6 week-old Long Evans rat.

Resolving the temporal dynamics and the nature of the relationship between BBB failure, astrogliosis, and vascular regulation following stroke might provide insights into this evolution and suggest new targeted therapies aimed at modulating astrogliosis and/or restoring cerebral microvascular flow in a temporally fine-tuned manner to protect the stroke penumbra.

5. Possible roles of astrogliosis in white matter disorders

With advancing age, an increasing burden of cognitive impairment appears to be related to cerebral small vessel disease, the later stages of which are characterized by demyelination and axonal loss observed as regions of white matter hyperintensities (WMH) on T_2-weighted MRI images (Hase et al., 2017). WMH are observed in 90–95% of people over the age of 60 (de Leeuw et al., 2001) and are also prominent in younger patients with depression (Thomas et al., 2002) and post-stroke dementia (Chen et al., 2016). Despite their high incidence in the general population, very little is known about their underlying cause. Could astrogliosis or astrocytopathy of white matter astrocytes and the resultant cerebrovascular insufficiency be producing these WMH? Post mortem analyses show that regions of WMH often display enlarged perivascular spaces, lacunar infarcts, and changes in the NVU compartments. In particular, drastic reductions in astrocyte numbers (Zambenedetti et al., 2002) as well as structural changes and loss of perivascular endfeet are observed (Chen et al., 2016). Further, astrocytes in regions of WMH undergo clasmatodendrosis, a phenomenon that looks very much like an explosive astrocyte degeneration (Hulse et al., 2001). Whether, and how, astrogliosis, astrocytopathy and/or astrodegeneration contribute to white matter disease is not easily answered by clinical studies or a single-time point post-mortem analysis of human tissue. Therefore, there is an urgent need develop reliable animal models of WMH and other white matter pathologies to address these questions.

6. Conclusions

Essentially every approach to therapy for brain diseases due to any cause has largely been focused on prevention or reversal of pathologic alterations in neurons – witness the common use of the term "neuroprotection" to summarize these therapeutic strategies as a whole.

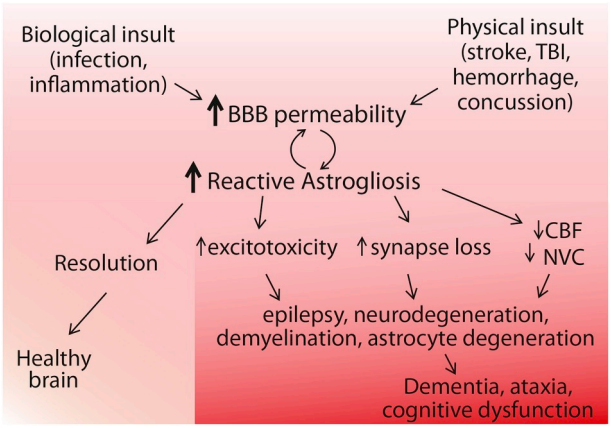

Fig. 6. A proposed model of astrogliosis progression and pathological manifestation. Biological insults such as peripheral infection or systemic inflammation and physical insults such as concussion, TBI, and stroke may result in BBB failure, allowing (normally blood-restricted) substances such as albumin and thrombin to leak into the brain. The presence of these blood-borne proteins in the neuronal microenvironment is detected by astrocytes and reactive astrogliosis ensues. This response is likely initiated in order to contain the damage and re-establish homeostasis. When the attempt is successful, the insult is resolved and healthy physiology prevails. Occasionally, this gliotic response might be too exaggerated and surpasses an as-yet unidentified threshold when it becomes damaging instead, resulting in excitotoxicity (lack of neurotransmitter uptake and/or K^+ buffering), synapse loss, and reduction of cerebral blood flow (CBF) and neurovascular coupling (NVC). Interactions between these neurotoxic end-effects may also occur; for example, a decrease in CBF and NVC might precede and cause synapse loss. Together, these effects of astrogliosis synergize to trigger degeneration of neurons and glia, ultimately precipitating the symptoms of many neurological disorders, including dementia, cognitive disorder, and ataxia.

Certainly, there is likely to be utility in this approach for many diseases. However, despite years of dedicated effort aimed at these approaches, successes have been limited for most diseases and thoroughly disappointing in others. With this in mind, we consider whether it might be helpful to modify the current paradigm for understanding brain disease to incorporate approaches that ask whether susceptibility to major brain diseases might not lie entirely or even primarily in neurons, but rather in astrocytes, the quintessential "neuroprotectant" cells, with effects on neurons as a secondary consequence (Fig. 6). If a castle is under siege, the survival of the royal family is best assured if the fort is strengthened, the front-line soldiers are well-armed, and the food and water supply are protected. Ultimately, the development of strategies for glio-protection and vasculo-protection may prove the most effective ways to achieve neuroprotection by harnessing the ability of astrocytes to support neuronal function and by providing the energy supply to fuel recovery and function. We anticipate that future research exploring these possibilities will open the door to new combinatorial therapeutics that have a renewed chance of success in human patients.

Conflicts of interest

None.

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