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Review

Chronic Cerebrovascular Dysfunction After Traumatic Brain Injury

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Traumatic brain injuries (TBI) often involve vascular dysfunction that leads to long-term alterations in physiological and cognitive functions of the brain. Indeed, all the cells that form blood vessels and that are involved in maintaining their proper function can be altered by TBI. This Review focuses on the different types of cerebrovascular dysfunction that occur after TBI, including cerebral blood flow alterations, autoregulation impairments, subarachnoid hemorrhage, vasospasms, blood–brain barrier disruption, and edema formation. We also discuss the mechanisms that mediate these dysfunctions, focusing on the cellular components of cerebral blood vessels (endothelial cells, smooth muscle cells, astrocytes, pericytes, perivascular nerves) and their known and potential roles in the secondary injury cascade.

Key words: traumatic brain injury; cerebrovascular dysfunction; neurovascular dysfunction

During the last decades, researchers have focused on neurocentric dysfunctions after acute brain injuries, with an emphasis on the molecular mechanisms involved in early cell death. Traumatic brain injury (TBI) research has moved from acute vascular dysfunction to an increasing focus on neuronal death. As noted in various review articles (Zhang et al., 2012; Jullienne and Badaut, 2013), this strategy has failed to transfer new therapeutic compounds from research tools to clinical therapies. It is within this context that in 2002 the NIH and NINDS hosted a workshop that suggested that the neurovascular unit (NVU) should be considered, as well as a larger microsystem comprising vessels and the associated glial cells, as the functional target of injury (Grotta et al., 2002; Zhang et al., 2012). A dysfunctional NVU has recently been proposed to be involved in the mechanisms underlying neurodegenerative diseases, including Alzheimer's disease (AD; Iadecola, 2004; Zlokovic, 2011). Interestingly, TBI is frequently associated with higher long-term risk for AD, and vascular dysfunction has been suggested to be involved in the development of AD (Johnson et al., 2010). Therefore, the NVU and vascular malfunction could be involved in poor cognitive outcomes after TBI. This Review emphasizes the importance of the cerebrovascular dysfunction and related molecular mechanisms post-TBI.

TBI: CLINICAL DEFINITION

TBI contributes to more than 30% of all injury-related deaths in the United States (Faul et al., 2010) and represents in excess of 75,000 deaths each year in Europe

SIGNIFICANCE:

Traumatic brain injury (TBI) is a major health burden, and researchers have been focusing extensively on the neurocentric aspect of the disorder. Early changes in cerebral blood vessels after TBI have been known for a long time. However, it is now becoming clear that the different types of neurovascular dysfunction play major roles in TBI pathogenesis. We review and outline the various cerebrovascular dysfunctions occurring after TBI, such as cerebral blood flow and autoregulation impairment, subarachnoid hemorrhage, vasospasm, blood–brain barrier disruption, and edema formation.

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(Maas et al., 2015). TBI is defined as a brain lesion caused by a direct or indirect external mechanical impact such as the penetration of a projectile, or by blast waves, inducing the disruption of the normal structure and function of the brain. The most frequent causes of TBI among the general population are falls (35%), motor vehicle and traffic-related accidents (17%), being struck by or against an object (16%), and assaults (10%; Faul et al., 2010). Although TBI affects all ages, pediatric and elderly populations are more vulnerable than adults (Faul et al., 2010). Some populations, including military personnel and rescue workers, are more likely to endure blast waves, resulting in a higher risk for TBI. Finally, sports-related TBI is a public health concern because of the repetitive nature of these injuries and the fact that they are often unreported.

Three main levels of TBI severity can be defined clinically, based on the Glasgow coma scale (a three- to 15-point scale used to assess the patient's level of consciousness and neurologic function) or on the duration of the loss of consciousness. Most TBI (75%) is mild, and this is also known as concussion. There is no skull fracture and few or minor changes are observed on CT scan and/or standard MRI (Ashwal et al., 2014). For moderate and severe TBI, the presence of bleeding is frequently observed, especially in the case of blast injuries (Taber et al., 2006; Maas et al., 2008).

There are two distinct injury phases in TBI. The primary acute event is often followed by a secondary injury cascade that includes glutamatergic excitotoxicity, calcium overload, and vascular dysfunction. These secondary injuries usually last for several months or even years, resulting in a pattern of "chronic brain disease" (Johnson et al., 2010; Pop and Badaut, 2011; Smith et al., 2013). Several clinical studies have shown that after TBI and the acute period, there are long-lasting behavioral dysfunctions, including cognitive decline or emergence of psychiatric disorders remote from the initial injury (Smith et al., 2013; for a more complete review of these deficits see Obenaus, 2015). For example, even if patients recover well from physical problems, 30% of adults report altered cognitive function, such as memory and concentration deficits, up to 3 months after a mild TBI (Ponsford et al., 2011). It has also been shown that a TBI occurring early in life can lead to a higher risk of mortality, independently of its severity (McMillan and Teasdale, 2007; Himanen et al., 2011). Repeated TBIs are known as a risk factor for dementia, particularly when related to sport injuries. Indeed, repeated TBI is associated with long-term cognitive impairment, as reported for retired athletes (Guskiewicz et al., 2005; Lakhan and Kirchgessner, 2012).

TBI is a massive health burden worldwide, not only because of the cognitive and psychological impairments but also because of the economic costs that include medical expenses as well as indirect expenses such as losses of productivity (Corso et al., 2006; Gustavsson et al., 2011). Despite recent advances, comprehensive research on TBI pathophysiology is marginal compared with other acute injuries, such as stroke, or other neurodegenerative diseases. The numerous veterans from the Iraq and Afghanistan wars and the increased public awareness regarding sports-related concussion injuries have led to an increase in research to understand the pathophysiology of this heterogeneous disorder to develop better treatments. Various animal models, from rodents to larger animals, have been developed in order to obtain a better understanding of the cellular and molecular mechanisms (Prins and Hovda, 2003; Obenaus, 2012; Petraglia et al., 2014). The variety of preclinical models reflects the variety of severity and heterogeneity of clinical TBI. However, the definition of degree of TBI severity in different animal models is controversial and remains poorly defined. This is a critical point because the cellular and molecular responses to the injury depend not only on its severity but also on the location of the impact. Moreover, the age of the animals is important because the outcome is more severe for younger patients (McMillan and Teasdale, 2007; Himanen et al., 2011; Pop and Badaut, 2011). However, this is not the focus of our Review, and we refer the reader to other reviews addressing this question (Prins and Hovda, 2003; Obenaus, 2012; Petraglia et al., 2014). It is crucial to keep in mind that most preclinical TBI models exhibit vascular dysfunction ranging from blood–brain barrier (BBB) disruption to hemorrhage (Golding, 2002; DeWitt and Prough, 2003; Pop and Badaut, 2011). A recent review article illustrates the importance of the vascular responses and changes in morphology and perfusion after TBI (Kenney et al., 2015). The early vascular dysfunction has been known for almost 2 decades, and the long-term changes could be associated with premature aging of the brain or emergence of brain dysfunction after TBI.

TBI AS A CEREBROVASCULAR INJURY: CLINICAL EVIDENCE

Characteristics of the Brain Vasculature

Cerebral vessel morphology is composed of three distinct layers, each having unique roles. The innermost layer is called the *tunica intima* and is composed of a single layer of endothelial cells surrounded by a basement membrane. In the case of capillaries, the basement membrane encloses pericytes (Fig. 1). The layer around this first layer is called the *tunica media*, which is the muscular portion of the vessel. This medial layer is composed of vascular smooth muscle cells (SMC), surrounded by a basement membrane. The thickness of the smooth muscle layer is dependent on the size of the vessel. Pial arteries generally have two or three SMC layers, whereas penetrating arteries have only one or two SMC per circumference. The penetrating arteries give rise to arterioles that are composed of a single layer of SMC. Then, in the capillaries, pericytes can replace SMC, even though their density and distribution remain controversial. Finally, the outermost layer of the cerebral blood vessels is called the *tunica adventitia*. It is a strong layer composed of connective tissue allowing the blood vessel to resist forces acting on the vessel wall. The tunica adventitia contains mostly collagen fibers, fibroblasts, and associated cells, including terminal nerve fibers in pial arteries. However, after the end of the Virchow-Robin space, the *tunica adventitia* is almost absent, and the intraparenchymal

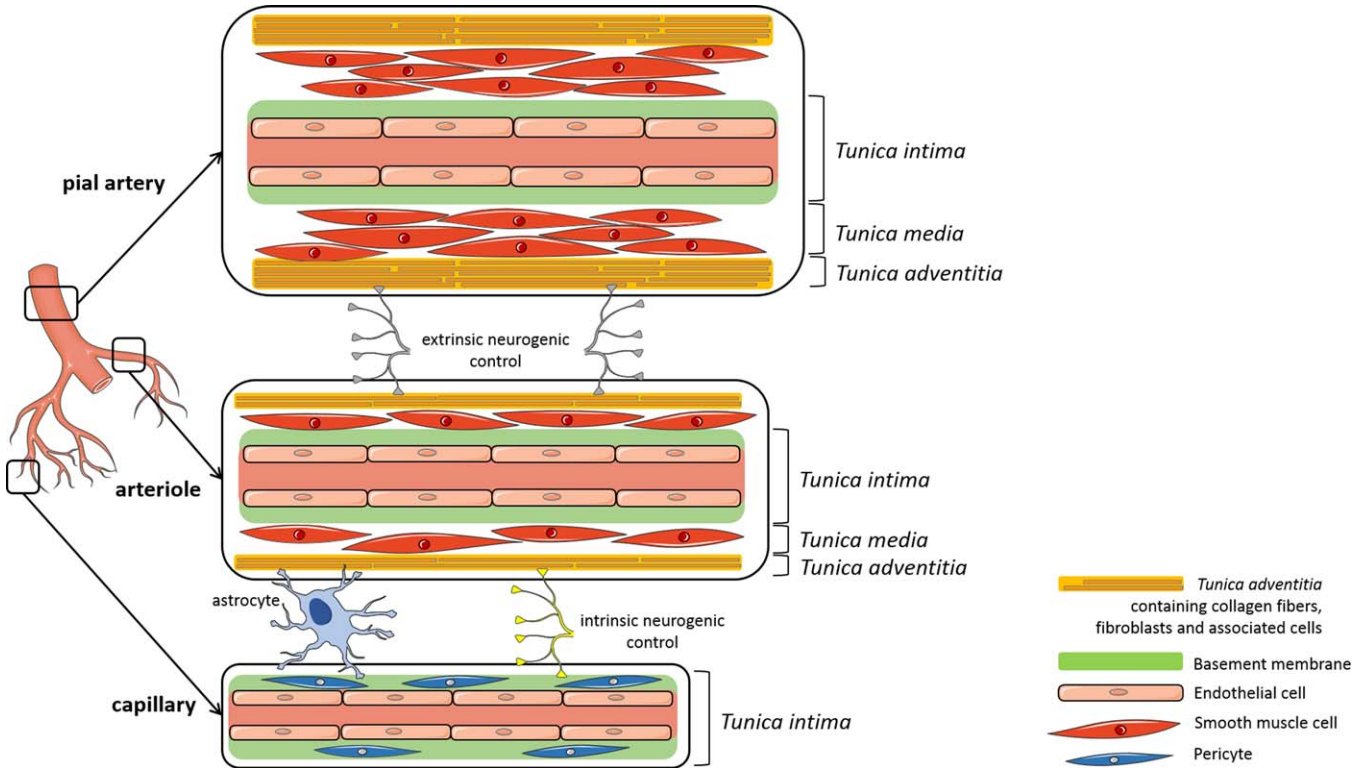

Fig. 1. Morphology and characteristics of cerebral blood vessels. Cerebral blood vessels are formed by three distinct layers, the tunica intima with endothelial cells and a basement membrane; the tunica media with smooth muscle cells; and the tunica adventitia with collagen fibers, fibroblasts and associated cells such as nerve fibers and astrocytes. Capillaries are formed with only a tunica intima with a basement membrane enclosing pericytes. This figure was produced using Servier Medical Art (www.servier.com). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

arterioles are in direct contact with astrocyte endfeet (Golding, 2002; Cipolla et al., 2004; Fig. 1).

Extra- and Intraparenchymal Blood Vessels

Pial vessels are located on the surface of the brain and give rise to smaller arteries that penetrate into the brain parenchyma with the Virchow-Robin space filled by cerebrospinal fluid (CSF). These penetrating arteries become intraparenchymal arterioles once the Virchow-Robin space disappears and are almost completely surrounded by astrocyte endfeet (Cipolla et al., 2004). Pial and penetrating arteries present mostly an "extrinsic" neurogenic control of the perfusion via a perivascular innervation from the peripheral nervous system (Rennels and Nelson, 1975).

Even though the myogenic regulation and the role of vascular SMCs and endothelial cells in maintaining cerebral perfusion are involved in the vascular tone, the control of perfusion in intraparenchymal arterioles is also influenced by "intrinsic" innervation coming from the surrounding brain neuropil, including interneurons and astrocytes (Cohen et al., 1996; Fig. 1). In fact, intraparenchymal arterioles have only one layer of vascular SMCs and are completely covered by astrocytes endfeet on their abluminal side. It has recently been well documented that astrocytes have an important role in the regulation of cerebral blood flow (CBF; Attwell et al., 2010; Howarth, 2014; Filosa et al., 2015). Indeed, astrocytes have a unique position within the NVU, where they contact synapses with their processes as well as 99% of the blood vessel surface (Filosa et al., 2015; Fig. 1). Therefore, by responding to neuronal activity (buffering neurotransmitters and ions, e.g., potassium), astrocytes can subsequently relay information to blood vessels to ensure adequate blood supply to areas with increased neuronal activity. This is blood flow–metabolism coupling, a physiological response also termed *neurovascular coupling*. Several studies, both in vitro (Mulligan and MacVicar, 2004; Blanco et al., 2008; Gordon et al., 2008) and in vivo (Winship et al., 2007; Lind et al., 2013; Otsu et al., 2015) have shown that in response to neuronal activation there is an increase in the intracellular calcium concentration in astrocytes and a subsequent release of vasoactive substances such as prostaglandin E2 and epoxyeicosatrienoic acids that induce vasodilation of the blood vessels. Moreover, increases in astrocytic calcium contribute to the production of other vasoactive substances such as nitric oxide (NO), glutamate, adenosine, and adenosine triphosphate (ATP; Filosa et al., 2015). In addition to the vasoactive substances, arachidonic acid is

produced and released by astrocytes and can also diffuse to the arteriole's SMC, where it is metabolized to the vasoconstrictor 20-hydroxyeicosatetraenoic acid (20-HETE; Gebremedhin et al., 2000). Indeed, studies have shown that, in addition to vasodilation, vasoconstriction of blood vessels can be induced by astrocytic activation (Mulligan and MacVicar, 2004; Metea and Newman, 2006; Blanco et al., 2008; Gordon et al., 2008).

The ability of astrocytes to induce vasoconstriction and vasodilation suggests that the balance of both vasodilatory and vasoconstrictive substances might contribute to the regulation of resting vascular tone and CBF, in addition to their role in neurovascular coupling (Filosa et al., 2015). Indeed, recent studies have shown that astrocytes are also involved in the regulation of parenchymal arteriole's vascular tone and cerebral autoregulation (Kim et al., 2015; Rosenegger et al., 2015). It is well known that astrocytes respond to an injury in the central nervous system by changing their phenotype and transform into reactive astrocytes with a change in their morphology and the level of expression of different proteins, such as glial fibrillary acidic protein (GFAP) and extracellular matrix proteins (laminin, perlecan, etc.). The differences in the evoked vascular responses (vasoconstriction vs. vasodilation) after astrocyte activation might also contribute to the differences observed in experimental approaches (i.e., nonphysiological stimulations, species of animals, different developmental stages; for review see Filosa et al., 2015). Regardless of the controversy surrounding the polarity of the evoked vascular response upon astrocyte stimulation, these studies firmly demonstrate an important role of astrocytes in the regulation of CBF under physiological conditions. This also suggests that astrocyte phenotype changes (quiescent vs. reactive astrocyte) should not be overlooked when studying pathologies that involve vascular dysfunction.

Clinical Observations

Decreased CBF and impaired cerebrovascular autoregulation. CBF has been studied in humans via computed tomography using different compounds such as ^{113}Xe, stable Xe, or $^{15}O_2$. Investigations showed that, early after a TBI (within the first 6 hr), significant numbers of patients present with depressed CBF values going as low as 22.5 ml/100 g/min when a normal CBF in adult humans should be approximately 45–50 ml/100 g/min (Bouma et al., 1991; DeWitt and Prough, 2003). It has been shown that the values can even reach 15 ml/100 g/min in patients with severe TBI (Bouma et al., 1992). For children, it has been shown that low CBF (<20 ml/100 g/min) and younger age (<5 years) were predictive of unfavorable outcomes, such as severe disability or vegetative state (Adelson et al., 2011).

This decreased CBF and its evolution during the first few weeks after a head injury are related to the recovery. Indeed, the reduction in CBF improves as recovery occurs (Langfitt et al., 1977). Moreover, when the CBF returns to normal within 3 weeks, the neurological outcome is significantly better than for the patients who still have a subnormal CBF after this time (Inoue et al., 2005).

Cerebrovascular autoregulation is an essential mechanism aimed at maintaining adequate blood perfusion in the brain by changes of cerebrovascular resistance. CBF is therefore maintained so that there is a constant local perfusion over a pressure range of 60–160 mmHg (Golding, 2002). After a brain injury, cerebrovascular autoregulation is impaired or abolished in many patients (Enevoldsen and Jensen, 1978; Rangel-Castilla et al., 2008). In summary, changes of CBF have been shown in patients after TBI, with a possible correlation with the outcomes.

Subarachnoid hemorrhage and vasospasms. Moderate and severe TBI may induce intracranial bleeding that can be associated with skull fracture or parenchymal contusions. Hematomas can increase intracranial pressure through the distortion of the injured brain tissue and ischemic lesions from the compression of the surrounding vasculature. Several types of bleeding can occur between the skull and the brain, epidural hematoma (between the skull and the dura mater), subdural hematoma (between the dura and the arachnoid mater), and subarachnoid hemorrhage (SAH; between the arachnoid and the pia mater).

SAH is a common feature of severe TBI. Approximately 40% of the patients with a severe head trauma present with SAH, which is associated with poor functional outcomes (Eisenberg et al., 1990; Servadei et al., 2002). Severe SAH can lead to death or severe disability even if it is detected and treated early, although treatment options are limited.

Cerebral vasospasms have been shown to correlate with severe SAH. They are characterized by contractions of the cerebral vasculature and usually predict a poor outcome. Indeed, 30–50% of the patients with SAH will develop vasospasms, increasing the risk of ischemic injuries (Armin et al., 2006). The onset occurs between days 2 and 15 after injury (Martin et al., 1997) and is accompanied by hypoperfusion in 50% of patients. With regard to the type of injury, it has been shown that blast injury patients are more likely to develop vasospasms than patients with other types of TBI (Zubkov et al., 2000). Moreover, vasospasms in blast-induced TBI have been shown to last for up to 30 days (Armonda et al., 2006), although they tend to resolve completely after 14 days in closed-head TBI without blast (Oertel et al., 2005).

Bleeding after severe and moderate TBI is a landmark of the acute vascular dysfunction. However, even without major bleeding, the BBB can still be injured in all TBI severities, from mild to severe, and can be associated with edema formation.

Edema formation and BBB disruption. Decreased CBF induces hypoxic/ischemic conditions, further contributing to the evolution of secondary injuries as well as the presence of microbleeding or hemorrhagic components. After a brain injury, edema formation can have dramatic consequences for morbidity and mortality because it induces intracranial hypertension and contributes to the vicious cycle of the secondary injury cascade (Unterberg et al., 2004). Classically, two types of brain edema have been described, cytotoxic and vasogenic. Cytotoxic edema is defined by cell swelling, without an

initial BBB alteration, whereas vasogenic edema is caused by an initial BBB disruption and an increased permeability of endothelial cells. However, this concept has recently been revised, suggesting that, during the phase of edema build-up following an acute brain injury, *anoxic* and *ionic* edema precede vasogenic edema (Badaut et al., 2013). Anoxic edema occurs within a few minutes after the initial injury; it is characterized by the swelling of astrocytes and neuronal dendrites, resulting from the lack of energy induced by oxygen and nutrient deprivation. Without sufficient energy, control of the ionic gradients is affected, resulting in water entry into the cells. Anoxic edema is quickly followed by ionic edema, in which the absence of oxygen and nutrients leads to the alteration of the ionic gradients within endothelial cells, with transcapillary flux of Na^+ ions and tissue swelling (Badaut et al., 2013). Finally, vasogenic edema appears because of the increased permeability of endothelial cells.

In patients, BBB disruption allows diffusion of molecules of over 500 kDa in the peripheral circulation and can therefore be measured by serum markers. Typically, the assessment of BBB status is made through the measurement of the CSF–serum albumin quotient (Andersson et al., 1994). A study has shown that serum levels of S100-β, an astrocytic protein, could also indicate BBB dysfunction 12 hr after severe TBI; this is a less invasive technique (Blyth et al., 2009). However, a recent meta-analysis suggests that this measurement would be more useful in evaluating the TBI severity and in determining the long-term prognosis in patients with moderate to severe brain injury (Mercier et al., 2013). In a clinical study involving patients with severe nonpenetrating brain injuries, 44% of the patients had significant BBB disruption, which was associated with more severe TBI and worse outcomes after 18 months (Ho et al., 2014). Moreover, another study suggests that patients with severe TBI and BBB disruption had a higher risk for intracranial pressure as well as a trend toward increased mortality (Saw et al., 2014).

In general there is better knowledge on molecular changes in BBB dysfunction in rodent models than in human (see below). After a TBI, the upregulation of different matrix metalloproteases (MMPs) is known to alter proteins of the extracellular matrix and participate in the degradation of the BBB. Despite limited information on MMP expression in the human brain after TBI, a recent clinical study involving eight patients with severe TBI investigated the temporal response of several MMPs from cerebral microdialysates and in CSF over 6 days following the injury. MMP8 and MMP9 are increased in the brain and in the arterial plasma immediately following trauma. They progressively decrease, whereas MMP7 starts rising slowly after 4 days. Interestingly, MMP8 levels are associated with mortality (Roberts et al., 2013). A very recent study involving 100 patients with severe TBI did not show any difference in serum MMP9 levels between survivors and nonsurviving patients at 30 days. However, the authors showed significantly higher serum TIMP-1 (tissue inhibitor of MMP1) levels among nonsurviving patients compared with survivors, suggesting that TIMP-1 could be used as a prognostic biomarker of mortality in TBI patients (Lorente et al., 2014).

Vascular dysfunction is present after TBI, from BBB alteration (capillary level) to modification of the brain perfusion (large blood vessels). Altogether these clinical findings strongly suggest alterations at different levels of the vascular tree.

PRECLINICAL OBSERVATIONS

Preclinical TBI models have the advantage of advancing our knowledge of the cerebrovascular and NVU changes that may occur after TBI.

CBF and Energy Metabolism

As in clinical settings (Bouma et al., 1991, 1992), changes in the CBF have been observed in animal models of TBI. Reduction of CBF after injury has been observed in animal models of severe controlled cortical impact (CCI; Bryan et al., 1995; Kochanek et al., 1995; Plesnila et al., 2003). In a severe CCI model, and using MRI with iron as a contrast agent, a marked drop in the cerebral blood volume has been shown after injury in adult rats, which had not recovered at the lesion site 2 weeks post-TBI (Immonen et al., 2010). In a lateral fluid percussion (LFP) injury model, which induces a more diffuse type of brain injury, decreased CBF in the perilesional cortex and hippocampus has been observed up to 8 months after injury in adult rats (Hayward et al., 2010). Importantly, a reduction of CBF has also been observed in mild TBI models (Villapol et al., 2014; Long et al., 2015). In a mild CCI model with adult rats, a decrease in CBF at the lesion site was observed acutely after the injury with recovery to near-normal values after 2 weeks (Long et al., 2015). In a mild/moderate CCI model, the reduction of CBF was delayed, with restoration at 30 days post-TBI in young adult mice (Villapol et al., 2015).

Altered CBF is likely to contribute to secondary injuries after TBI by decreasing glucose and oxygen delivery. The brain does not have sufficient energy stores and is therefore highly dependent on continuous CBF. Moreover, it has been shown that, during the first 6 hr after concussion in rats, cells in the injured brain show evidence of hypermetabolism (Yoshino et al., 1991). Consequently, the decreased CBF and the hypermetabolism occurring early after TBI result in a mismatch between demand and supply, known as uncoupling of CBF and glucose metabolism. After this hypermetabolic phase, glucose metabolism has been shown to be decreased in an age-dependent manner. In young adult rodent models (P35), it lasts for 5–10 days (Hovda et al., 1991; Yoshino et al., 1991), whereas it only lasts for 3 days in juvenile rats (P17; Thomas et al., 2000). In human studies, it can last for up to 1 month (Bergsneider et al., 2001; Glenn et al., 2015). Aerobic metabolism is decreased and anaerobic glycolysis is increased, resulting in production of lactate (Verweij et al., 2007). Even though lactate has long been considered a waste product of impaired metabolism,

it is now clear that it has a key role in energy metabolism after head injury. Not only can it be used by neurons to produce energy (Pellerin, 2003), it is now suggested that it is a preferential fuel for the brain (Bartnik et al., 2007). In a study of TBI patients using isotope tracers, Glenn and colleagues (2015) showed that approximately 70% of the carbohydrate consumed by the injured brain comes from the peripheral lactate production. On the other hand, it has been shown that increased lactate in the cerebral parenchyma is associated with poor neurological outcomes in pediatric populations (Ashwal et al., 2000). To explain this difference, Glenn and colleagues suggest that lactate accumulation in the brain is in the first case a result of high production complicated by limited disposal and in the second case a result of metabolic stasis leading to acidosis (Glenn et al., 2015).

Intravenous lactate therapy has been used in rats after fluid percussion injury and has been shown to have beneficial effects on cognition (Holloway et al., 2007). Lauritzen and colleagues (2014) suggest that these beneficial effects could be due not only to an increased metabolism of lactate but also to its binding to the receptor hydrocarboxylic acid receptor 1 (HCA1). Indeed, the authors suggest that, when lactate concentration rises, HCA1 inhibits cAMP generation, thereby slowing glycolysis rates (Lauritzen et al., 2014).

Several studies have investigated the expression of lactate transporters, monocarboxylate transporters (MCTs), after TBI. MCTs in brain lysates are increased during the first week post-CCI in young adult rats at P35 and P75 (Prins and Giza, 2006). The same research group performed a study in which they used a ketogenic diet in the rats for 1 week after the injury. This diet increased MCT levels, improved the behavioral outcomes, and reduced the cortical lesion volumes but only in younger rats (Appelberg et al., 2009).

It is also interesting to note that another study by Prins and collaborators (2013) showed that the metabolic depression occurring after a single head injury reflects the time course of vulnerability of the brain. The authors suggest that glucose metabolism could serve as a biomarker to determine the duration of cerebral vulnerability. This concept would be very important to consider, especially for repeated brain injuries within the context of sports injuries.

Early BBB Opening

The effect of TBI on the BBB differs according to age and the type and severity of the injury. The changes of the BBB have been studied mainly at early time points, and they can range from simple alterations to complete rupture of the biochemical and functional properties. Opening of the BBB happens immediately after a TBI and contributes to vasogenic edema. In a concussion model in cats, the opening has been shown as early as 3 min after injury (Povlishock et al., 1978).

Several components of the BBB can be affected after a TBI. First, the endothelium itself has been shown to sustain morphological lesions. In a cat model of moderate to severe fluid percussion injury, electron microscopy revealed the presence of two types of lesions on the luminal surface of pial arterioles, crater-shaped indentations and dome-shaped projections of the endothelial cell surface, typically corresponding to necrotic cells (Wei et al., 1980). In a cortical cold injury model in rats, microvessels in the lesion area (from the pial surface to the fourth cortical layer) have been found to be necrotic early after the impact (Nag et al., 2007). Interestingly, the smooth muscle layer of the vessels was not morphologically altered by the impact (Wei et al., 1980).

Moreover, the tight junction complex has been shown to be affected after different experimental models of TBI. Early after the injury, pial and intracerebral vessels show decreased claudin-5 (at 2 days) and occludin (at 2 and 4 days) levels in a model of cortical cold injury in rats (Nag et al., 2007). In a model of mild closed-head injury, tight junction complexes appear intact under electron microscopy during the first hours after injury (Rafols et al., 2007). However, it has been shown that, in models of mild TBI induced by blast shock waves, there is a loss of tight junction proteins (occludin, claudin-5, and zonula occludens protein-1) at 6 and 24 hr postinjury (Abdul-Muneer et al., 2013) and increased immunoglobulin G extravasation 5 min, 24 hr, and 48 hr postinjury (Yeoh et al., 2013; for review see Shetty et al., 2014). In a juvenile CCI model, immunoglobulin G extravasation levels are high near the injury site and surrounding tissue at 1 and 3 days and are lower by 7 days (Pop and Badaut, 2011).

After a TBI, the upregulation of different MMPs is known to participate in the degradation of the BBB. MMP9 and MMP2 increase acutely after TBI in rodents (Wang et al., 2000; Zhang et al., 2010). MMP3 activity, however, is increased chronically after TBI in rats and may play a role in synapse restoration (Zhang et al., 2010). After TBI in a P7 rat, MMP2 and MMP9 mRNA and protein levels are elevated in the injured tissue (Sifringer et al., 2007).

Finally, astrocytes, which are a key component of the BBB (Abbott et al., 2006), have been shown to be decreased in number after LFP injury in the adult rat hippocampus (Hill-Felberg et al., 1999; Zhao et al., 2003), contributing to BBB alteration. Astrocyte loss starts as early as 30 min postinjury and continues until 24 hr (Zhao et al., 2003). Another study focused on later time points and showed that the astrocyte population in the injured hippocampus at 7 days was reduced by 64% of the total population compared with uninjured rats. After 1 month, the astrocyte population is restored to 85%, showing compensation for the earlier cell loss (Hill-Felberg et al., 1999).

SMC Changes

As described earlier, the cerebral blood vessels contain a smooth muscle layer called the *tunica media* in the vascular wall, in cortical arterioles consisting of one to

three layers of SMCs (Fig. 1; Rafols et al., 2007). During vascular development, SMCs present mostly a synthetic phenotype, with high growth and synthetic rates, contributing to the secretion of extracellular matrix proteins such as collagen and elastin, which are important for the stability of the blood vessels (Wagenseil and Mecham, 2009). In adult blood vessels, SMCs acquire a contractile phenotype, with a low proliferation rate and a low synthetic activity. They express a number of contractile proteins such as alpha smooth muscle actin (αSMA), smooth muscle-myosin heavy chain (SM-MHC), smoothelin-A/B, and calponin, as well as ion channels and signaling molecules required for the contractile function of the cell (Owens et al., 2004; Rensen et al., 2007). Nonmuscle MHC isoform-B and cellular retinol binding protein (CRBP)-1 have been described as suitable markers for synthetic SMCs. They are upregulated when MHC is decreased in the proliferating SMCs (Rensen et al., 2007). Both synthetic and contractile phenotypes exist in the smooth muscle layer, but it should be noted that they represent two ends of a wide spectrum of SMCs with intermediate phenotypes. The ratio of synthetic and contractile markers changes depending on the developmental age, the vascular environment, and the physio-/pathological situation (Rensen et al., 2007).

SMCs have been shown to exhibit long-term changes after a TBI and are therefore involved in different types of secondary injuries. Endothelin-1 is a peptide released mainly from the vascular endothelium and induced after TBI (Inoue et al., 1989). It contributes to increased αSMA in SMC and pericyte during the first hours postinjury, resulting in a decreased diameter of arterioles (Dore-Duffy et al., 2011). Molecular changes have been observed in other potential contractile proteins such as calponin in rodent models of TBI. Calponin expression is significantly increased during the first 48h, in association with enhanced vasoreactivity. This modification is also under the influence of the endothelin pathway (Kreipke and Rafols, 2009). Inhibition of calponin phosphorylation reduces changes in vasoreactivity post-TBI and is associated with improved CBF (Kreipke and Rafols, 2009). Similar phenotypic switching has been observed in an in vitro model of SMCs exposed to blast injury showing a mRNA decrease of the contractile protein smoothelin and an absence of SM-MHC in relation to vasospasm after blast-TBI (Alford et al., 2011).

Together with autoregulation, myogenic regulation is one of the mechanisms regulating the constancy of the blood flow during changes in perfusion pressure. The myogenic response is initiated by the vascular smooth muscle itself. For example, when the smooth muscle stretches, SMCs contract. After head trauma, the myogenic response can be impaired by responding abnormally to pressure changes due to various molecular mechanisms, including elevated protein kinase C activity and altered transient receptor potential channels (Golding et al., 1998; Mathew et al., 1999).

Nitric oxide (NO) signaling has been shown to be involved in the regulation of cerebrovascular tone (Hamel, 2006). The effects of NO are balanced between favorable, due to NO-mediated stimulation of cGMP and vasodilation at low concentrations, and unfavorable due to free radical-related proinflammatory effects at high concentrations. The activity of endothelial NOS (eNOS) exhibits a bimodal change after TBI with an initial increase spanning a few minutes followed by a ∼50% decrease relative to baseline levels for 7 days before normalizing (Wada et al., 1998; Cherian et al., 2004). This decrease of constitutive NOS activity may contribute to altered CBF and cerebral autoregulation, in combination with changes in the myogenic response of the SMCs. Inducible NOS (iNOS) expression and activity have been shown to be increased not only in SMCs but also in neurons, macrophages, neutrophils, astrocytes, and oligodendrocytes, reaching peak levels between 4 and 48 hr after injury (Clark et al., 1996; Cherian et al., 2004; Steiner et al., 2004). Unfortunately, upregulation of iNOS results in a harmful increase of tissue NO levels (Cherian et al., 2004) that are well known to contribute to the secondary injury cascade including neuroinflammation, apoptosis, excitotoxicity, energy depletion, and production of reactive oxygen species (Guix et al., 2005).

Changes in perivascular innervation. Along with the changes observed in endothelial and SMCs, it has been suggested that the perivascular innervation could be altered after TBI and thereby involved in the cerebrovascular dysfunction. The perivascular nerve plexus is part of the neurogenic regulation of the vascular tone of the pial and larger arteries and several studies have shown that the cerebrovascular response to vasoactive substances is impaired after TBI (Wei et al., 1980; Armstead, 1997; Fujita et al., 2012). Significant changes are observed in the perivascular nerves of cerebral arteries during the first week after severe diffuse TBI induced by impact acceleration (Ueda et al., 2006). A decrease in the number of perivascular nerve fibers peaking at 24 hr after injury have been described, and in some instances a decrease in perivascular nerve fibers up to 7 days postinjury (Ueda et al., 2006). This decrease in the number of fibers could be due to erythrocyte toxicity after SAH because blood is known to cause the denervation of cerebral arteries 3–7 days after exposure (Duff et al., 1986; Sercombe et al., 2002). It is associated with a decrease in the concentration of vasoactive substances like acetylcholine, vasoactive intestinal peptide, substance P, and calcitonin gene-related peptide (Sercombe et al., 2002). Therefore, the neurogenic control of the vascular tone is affected by a TBI, due to the decreased number of nerve fibers in the perivascular area.

Astrogliosis and Consequences on Blood Perfusion and BBB

In cases of severe injury, astrocytes become reactive and proliferate to form a glial scar (Burda and Sofroniew, 2014). The role of astrogliosis is still debated; it can be both beneficial and detrimental to the surrounding tissues, depending on the timeline of the pathological processes (Sofroniew, 2009). Regardless of this controversy, the process of astrogliosis can have a profound impact on the

events following a brain injury because astrocytes have numerous functions in the healthy central nervous system, such as providing energy for neurons, regulating ion and neurotransmitter homeostasis, participating in synapse development and function, and regulating CBF (Sofroniew and Vinters, 2010).

Astrocytes are among the first cells to respond to TBI and the mechanical forces of TBI trigger astrogliosis (Burda et al., 2015). It seems that astrocytes are especially vulnerable to mechanical injury, and, even though it is still not clear how this response is mediated, it could involve the activation of astrocytic mechanoreceptive channels (Burda et al., 2015). The activation of astrocytes with stretch injury or shear stress involves a rapid calcium influx (Rzigalinski et al., 1998; Maneshi et al., 2015). Moreover, TBI induces activation of signaling pathways in astrocytes, including inositol triphosphate (IP3) signaling, with IP3 concentration being increased up to 48 hr postinjury (Floyd et al., 2001). The induction of IP3 signaling increases intracellular calcium concentration, which in turn activates phospholipase A2 (among many other calcium-sensitive enzymes such as protein kinase C and calpain) and can influence the release of vasoactive substances (Howarth, 2014). Therefore, any changes in the intracellular calcium concentration within astrocytes postinjury could influence the release of vasoactive substances, and as a consequence the regulation of CBF and perfusion, and contribute to the cerebrovascular dysfunction post-TBI.

It has been demonstrated that several vasoactive substances can be released from astrocytes after trauma. Stretch injury to primary astrocyte cultures induced a release of isoprostanes (Hoffman et al., 2000), shown to be vasoconstrictors of cerebral arterioles (Hoffman et al., 1997). Interestingly, increased levels of isoprostanes in CSF have been observed in adult and pediatric patients after moderate and severe TBI (Bayir et al., 2002; Varma et al., 2003; Yen et al., 2015). Therefore, increased secretion of isoprostanes from astrocytes could contribute to the decreased cerebral perfusion after TBI. Similarly, a stretch injury on primary astrocyte cultures provoked endothelin 1 release from astrocytes associated with calcium influx (Ostrow et al., 2000). Endothelin 1 is another powerful vasoconstrictor, and its levels are increased after TBI in multiple animal models (Petrov and Rafols, 2001; Armstead and Kreipke, 2011; Armstead and Raghupathi, 2011). Increases in endothelin 1 have been associated with unfavorable outcomes in children after severe TBI (Salonia et al., 2010). In addition, an increase in the expression of endothelin 1 receptors has been observed after TBI in several animal models (Kallakuri et al., 2010).

In addition to the role of astrocytes in vascular tone, the cells play a key role in the integrity of the BBB (Abbott et al., 2006). In fact, they can release various factors such as cytokines and inflammatory mediators that can affect the BBB after brain injury (Chodobski et al., 2011; Sofroniew, 2014). For example, astrocytic secretion of chemokines (Chodobski et al., 2011) and three isoforms of transforming growth factor-β (TGF-β; Constam et al., 1992) have been shown to contribute to the BBB leakage after brain injury (Shen et al., 2011). In patients, increased TGF-β expression has been observed in patients with severe TBI, in whom it parallels BBB function (Morganti-Kossmann et al., 1999). As discussed above, MMPs affect the structure of the BBB after TBI, and they are extensively produced by reactive astrocytes (Chen and Swanson, 2003).

The expression of the water channel aquaporin 4, expressed mainly on astrocyte endfeet in proximity to blood vessels in the cortex, is also altered after TBI, which is related to the formation of cerebral edema (Badaut et al., 2013). There is a correlation between the level of aquaporin 4 expression and disruption of the BBB (Fukuda and Badaut, 2012). In addition to the secretion of different molecules that can affect the BBB integrity and cerebral perfusion, the physical interaction between astrocytes and the vasculature can also be changed after TBI (Villapol et al., 2014), which all can contribute to the vascular dysfunction after TBI.

Altogether, astrocytes change their phenotype and can contribute to the vascular pathology observed after TBI. The neurodegeneration observed after TBI could be a result of chronic neuroinflammation and astrocyte activation (Faden and Loane, 2015). Therefore, it may be important to consider the contribution of reactive astrocytes to the long-term consequences of vascular dysfunction.

LONG-TERM PATHOLOGICAL MECHANISMS BEHIND VASCULAR DYSFUNCTIONS

BBB Dysfunctions and Long-Term Degeneration

As discussed above, there is a wide range of alterations to the brain vasculature at early time points after TBI. These changes support the hypothesis that TBI is a cerebrovascular injury with major dysfunction of the NVU after the primary impact. Most studies have so far focused on neuronal cell death and long-term recovery after TBI. However, little is known about the long-lasting changes in the brain vasculature and their involvement in functional outcome.

For a long time, the opening of the BBB was considered a short-term event that normalized within 1 week, as we observed in our rodent TBI model (Pop and Badaut, 2011). However, the BBB remains opened as late as 30 days after an insult in a stroke model (Strbian et al., 2008), suggesting long-lasting changes of the endothelial properties. At 2 months postinjury in our juvenile TBI model, the BBB function seems to be restored because IgG staining was not detected around the lesion site (Pop et al., 2013). Moreover, claudin-5 expression in the penetrating arteries is significantly increased 2 months postinjury (Pop et al., 2013) as well as 2 weeks after moderate compression of rat somatosensory cortex in a different study (Lin et al., 2010). These observations suggest that the long-term phenotypic transformations of the endothelial cells compensate for the early BBB alteration (Pop et al., 2013).

TBI-induced long-term neurodegeneration is in part related to its effects on the BBB. Many studies have shown that TBI can accelerate brain aging and promote accumulation of aberrant proteins such as amyloid-β (Aβ; Johnson et al., 2010). Our recent studies suggest that when a TBI occurs early in life it can have long-term consequences. We previously reported for juvenile TBI an impairment of sensorimotor function and spatial memory deficits up to 6 months after the injury (Kamper et al., 2013). Some studies have suggested a link between vascular function and cognitive deficits (Alosco et al., 2013), and it is possible that the cognitive impairments that we observed could be due to phenotypic changes of the BBB, including a decrease of the efflux pump P-glycoprotein (P-gp) and an increase of the perivascular matrix proteins perlecan and fibronectin. These changes are observed at 2 and 6 months after injury (Jullienne et al., 2014), and the matrix changes have also been observed in AD patients (Lepelletier et al., 2015). Changes in the matrix properties possibly participate in neurodegenerative processes by leading to the accumulation of Aβ, decreasing its clearance and its perivascular drainage (Pop et al., 2013; Jullienne et al., 2014). P-gp has been suggested to be a key player in Aβ clearance from the brain parenchyma because its expression is decreased on endothelial cells in aged human and AD brains as well as in aged rodents (Silverberg et al., 2010). In addition, P-gp knockout models have increased Aβ deposition after injection of Aβ in the brain (Cirrito et al., 2005).

The caveolin protein family takes part in the caveolae formation, which is known to be involved in endocytosis, transcytosis, and exocytosis in endothelial cells (Jodoin et al., 2003; Predescu et al., 2007). Caveolin-1 (cav-1), is one of three isoforms that is expressed by brain endothelial cells (Lisanti et al., 1994; Virgintino et al., 2002). Cav-1 also modulates the activity of signaling molecules, including inhibition of endothelial NO synthase (eNOS; Bucci et al., 2000; Bauer et al., 2005). Its expression is increased in the endothelium during the first week after a cold injury model of TBI (Nag et al., 2007). In support of the phenotypic transformation of the endothelium after juvenile TBI, we observed an increase in cav-1 immunostaining in brain cortical vessels at 2 months post-injury (Badaut and Bix, 2014; Badaut et al., 2015). This observation also suggests that cav-1 could play a role in the altered claudin-5 and P-gp expression that occur after TBI. Interestingly, cav-1 has been associated with stabilization of claudin-5 within the caveolae (McCaffrey et al., 2007) and with a decrease of P-gp activity (McCaffrey et al., 2012). We believe that the changes in the BBB properties both short- and long-term after TBI will have direct and indirect consequences for the astrocytic properties and subsequently brain perfusion.

SMC Changes Long-Term After TBI

It is known that phenotypic changes of SMCs play a critical role in various major human diseases, including cancer, hypertension, asthma, and atherosclerosis. SMCs exhibit a high phenotypic plasticity, which allows them to switch from a contractile function (to regulate blood vessel diameter) to a secretive function (to produce extracellular matrix proteins; Alexander and Owens, 2012).

The decrease of CBF observed after TBI would generate chronic hypoxia throughout the vascular tree. In sheep, the SMCs of the carotid artery after chronic hypoxia differentiate from contractile to synthetic phenotype under a vascular endothelial growth factor (VEGF)-driven mechanism, leading to an altered arterial contractility (Hubbell et al., 2012). SMCs lose their contractile properties via a decrease of SM-MHC and an increase of nonmuscle MHC (Hubbell et al., 2012). Moreover, hypoxia induces an increase in contractile protein MLC-20 and a decrease of MLC-kinase by upregulating VEGF receptors Flk-1 and Flt-1 (Adeoye et al., 2013). VEGF levels change in TBI (Morgan et al., 2007; Mellergard et al., 2010), but so do levels of other growth factors and cytokines. SMC phenotypic modulation in the periphery is under the control of several molecular pathways that could be present after TBI, such as platelet-derived growth factor (PDGF)-BB, PDGF-DD, and interleukin-1β. All of these pathways can induce rapid downregulation in expression of multiple SMC differentiation marker genes, including αSMA, SM-MHC, and calponin (Alexander and Owens, 2012). A wide range of signaling pathways is involved in the responses to these molecular proteins, and it is highly possible that the early changes in the NVU environment can contribute to long-term changes in the SMC phenotype.

CONCLUSIONS AND FUTURE THERAPEUTIC STRATEGIES

TBI is a massive health burden for which basic science researchers and clinicians have shown that it is undeniably also a cerebrovascular injury. Each of the components of the NVU plays key roles in the pathogenesis of injury, during the short- and long-term periods after injury. Molecular and cellular mechanisms leading to long-term impairments are dependent on the type of injury and its severity and the age of the patient, and these parameters must to be considered in each case to improve recovery. This review highlights important targets regarding the management of secondary injuries as they relate to the cerebral vasculature. Indeed, endothelial cells, astrocytes, and SMCs are all involved in CBF regulation, edema formation, BBB disruption, vasospasms, and energy metabolism. The Review pinpoints the involvement of multiple players within the NVU. Therefore, future therapeutic strategies should reflect this complexity and combine different treatment at different time points. This strategy has recently been discussed by Margulies and colleagues (2016) in a review entitled Combination therapies for traumatic brain injury: retrospective considerations. This article provides an overview of six different projects aiming for multidrug testing, with insights, difficulties, and recommendations for development of future therapy for TBI. Our review of the literature suggests that intravenous injection of lactate

(Holloway et al., 2007), inhalation of NO (Terpolilli et al., 2013), injection of an inhibitor of c-Jun–N-terminal kinase (Borsello et al., 2003), and extracellular matrix proteins such as perlecan domain V (Jullienne et al., 2014) are promising targets and could be considered for combination with the aim of restoring vascular function. There is therefore an ongoing need to study the mechanisms by which these cellular constituents respond to TBI and how they modulate the cerebrovascular tone.

CONFLICT OF INTEREST STATEMENT

No author has a conflict of interest.

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