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Authors

Prakash, Roshini
Carmichael, S Thomas

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Blood–brain barrier breakdown and neovascularization processes after stroke and traumatic brain injury

Roshini Prakash and **S. Thomas Carmichael**

Department of Neurology, David Geffen School of Medicine, UCLA, Los Angeles, California, USA

Abstract

Purpose of review—Angiogenesis or vascular reorganization plays a role in recovery after stroke and traumatic brain injury (TBI). In this review, we have focused on two major events that occur during stroke and TBI from a vascular perspective – what is the process and time course of blood–brain barrier (BBB) breakdown? and how does the surrounding vasculature recover and facilitate repair?

Recent findings—Despite differences in the primary injury, the BBB changes overlap between stroke and TBI. Disruption of BBB involves a series of events: formation of caveolae, trans and paracellular disruption, tight junction breakdown and vascular disruption. Confounding factors that need careful assessment and standardization are the severity, duration and extent of the stroke and TBI that influences BBB disruption. Vascular repair proceeds through long-term neovascularization processes: angiogenesis, arteriogenesis and vasculogenesis. Enhancing each of these processes may impart beneficial effects in endogenous recovery.

Summary—Our understanding of BBB breakdown acutely after the cerebrovascular injury has come a long way; however, we lack a clear understanding of the course of BBB disruption and BBB recovery and the evolution of individual cellular events associated with BBB change. Neovascularization responses have been widely studied in stroke for their role in functional recovery but the role of vascular reorganization after TBI in recovery is much less defined.

Keywords

blood–brain barrier; neovascularization; stroke; traumatic brain injury

INTRODUCTION

Both ischemic and traumatic brain injury (TBI) pose a significant burden on global health. An estimated 1.7 million people sustain TBI and about 0.8 million people suffer from stroke annually in the United States [1▪▪,2] http://www.cdc.gov/stroke/facts.htm, http://www.cdc.gov/traumaticbraininjury/pdf/BlueBook_factsheet-a.pdf. Stroke is primarily a disease of the elderly population, whereas TBI occurs in all age groups including children

Correspondence to Roshini Prakash, BPharm, PhD, Department of Neurology, David Geffen School of Medicine, UCLA, Los Angeles, CA 90095, USA. Tel: +1 706 288 6037; roshiniprakash@g.ucla.edu.

Conflicts of interest

There are no conflicts of interest.

and young adults. Despite substantial research in these two diseases, there is no definite pharmacological therapy for TBI. Therapies for stroke cluster around the early treatment of the clot [1▪▪,3] with no therapies directed at the substantial disability in survivors.

PATHOPHYSIOLOGY OF STROKE AND TRAUMATIC BRAIN INJURY

The pathophysiology of stroke and TBI differs in its mode of primary injury and the sequelae of the secondary injury events [3]. Ischemic stroke comprises 85% of all human strokes and is primarily caused by a sudden local reduction of cerebral blood flow to the brain. Acutely after ischemic stroke, metabolic disturbances and energy imbalance propagate into secondary injury mechanisms at the cellular and subcellular levels such as inflammation, gliosis and oxidative stress leading to the cell death in neurons, glial cells and vascular cells. In both large and small animal models, ischemic cerebral infarctions are modeled most commonly by either permanent or transient occlusion of the middle cerebral artery. Several excellent reviews have detailed the pathophysiology of acute ischemic stroke [3–5] and animal models of stroke [6–8].

KEY POINTS

- Both stroke and TBI involve similar events in BBB disruption.
- Confounding factors, such as severity, duration and extent of damage, influence BBB breakdown.
- Vascular recovery occurs via neovascularization processes in both stroke and TBI.
- Neovascularization processes have been extensively studied after stroke, but we lack an understanding of these events after TBI.

TBI is caused by a force on the head that results in structural deformation and mechanical stress to neuropil and stretching of axonal connections, resulting in diffuse axonal injury [3,9▪,10,11]. Depending on the severity of the TBI (mild, moderate and severe), vascular disruption occurs and may result in hemorrhage. TBI has a heterogeneous pathogenesis and is classified into: contusion, diffuse or petechial hemorrhage, white and gray matter injury [12]. Depending on the presence or absence of a lesion, TBI can be classified as focal or diffuse. Despite high reproducibility in preclinical models, the human conditions have greater variability in the distribution and localization of brain damage. Several review articles discuss animal models of TBI [13▪,14–16].

BLOOD–BRAIN BARRIER DISRUPTION AFTER STROKE AND TRAUMATIC BRAIN INJURY

What is the blood–brain barrier?

The blood–brain barrier (BBB) is a unique and integral feature of the central nervous system, earlier known to be regulated only by the microcapillary endothelial cells that form an interface between the blood and the neuronal tissue [17▪▪]. This structure is now known

to encompass astrocytic processes, pericytes and the adjacent neurons in addition to capillaries. This coordinated network of cells is pivotal in maintaining not only barrier homeostasis but also control over the influx and efflux of substances for proper neuronal functioning in both health and disease conditions [17▪▪,18]. Brain endothelial cells are distinct from those in the peripheral vasculature and are characterized by – abundant mitochondria, absence of fenestrations and fewer caveolae (specialized lipid rafts) that restrict pinocytosis; specialized tight junction proteins (claudins, occludins and adherens) found in the basement membrane that control paracellular (transfer of substances between cells) transport. Capillary endothelium is covered by pericytes on the abluminal surface, forming a physical barrier that stabilizes the vasculature, regulates blood flow and limits transcellular (transfer of substances across the cell) activity that is specific to the central nervous system [19,20]. Additionally, astrocytes ensheath vascular cells and promote barrier-specific properties. Astrocytic end feet are highly polarized and rich in the water channel aquaporin-4 that regulates electrolyte and water balance [21,22]. More recently, neuronal cells have been documented to induce BBB properties in endothelial cells and astrocytes in coculture models [23,24▪]. Thus, BBB properties are a combined effect of protein complexes, cellular features and interactions among the resident cells themselves [25,26].

Clinical and experimental findings indicate that BBB damage and dysfunction is a common and prominent pathological feature in stroke and TBI. Several underlying events are involved, such as disruption of the tight junction seals, alterations in endothelial transport properties and extracellular matrix degradation. Understanding the time course and events involved in BBB disruption is important to determine – the rate and extent to which it leads to secondary injury events, the extent and the level of barrier disruption that allows free mobility of toxic substances and identify the window of opportunity to deliver therapeutics. In the next section, we review the spatial and temporal changes in BBB breakdown.

Blood–brain barrier breakdown in stroke

Extensive research in animal models suggests that BBB compromise after stroke occurs in two phases – an immediate early phase of enhanced permeability seen 4–6 h after ischemia followed by a delayed opening of the BBB seen 2–3 days after stroke. Leakage kinetics assessed from animal models suggests that BBB opening can either be continuous and monophasic [27,28] or biphasic [29–31] depending upon the animal species, method of detection, occlusion methods, degree and duration of occlusion. These findings suggest that BBB opening is heterogeneous and depends upon the nature of stroke. Furthermore, the size of the extravasating dyes used to assess BBB opening may contribute to the detection of a differential response [32]. Depending on the method of reperfusion (mechanical – using filament model vs. thrombolytic – using tPA), BBB disruption and perfusion spatially differs between the two methods [33]. Mechanical disruption leads to enhanced reperfusion with a distinct BBB damage in the ischemic core at acute time points compared with thrombolysis, which leads to poor reperfusion, associated with diffuse and nonuniform BBB damage. The response to mechanical reperfusion may be because of a rapid flow of blood and free radical generation, unlike thrombolysis, which is gradual. Furthermore, microemboli due to partial thromobolysis can lead to microvascular obstruction resulting in nonuniform BBB opening.

BBB opening correlates with matrix metalloprotei-nase-9 (MMP-9) expression in both experimental and clinical studies [33,34]. Activation of MMPs is seen both in the acute and delayed phases of the BBB breakdown. Understanding BBB dysfunction in the context of reperfusion remains a challenge and is highly debatable.

BBB dysfunction begins with the disruption of tight junction proteins and opening of the barrier junctions due to oxidative stress induced by free radical generation after ischemia. The tight junction protein Claudin-5 expression is decreased after BBB opening in both stroke and TBI and is later elevated when BBB permeability is restored [35,36]. More recently, subcellular events of active tight junction remodeling and endothelial paracellular and transcellular processes have been reinvestigated suggesting that endothelial caveolae are increased in acute early opening, whereas tight junction remodeling begins later at delayed time points of ischemic reperfusion injury [37▪▪]. Caveolin-1 mediates this initial BBB opening [38,39]. A comparative analysis of three different models of stroke reveals four stages in acute BBB breakdown: endothelial swelling, endothelial membrane disruption, disruption of tight junction seals between vascular cells and adjacent glia, and complete vascular disruption [40▪].

Spatiotemporal assessment of barrier changes suggests that the onset of BBB dysfunction corresponds to the severity of ischemia [41]. Prolonged ischemia increases the severity and extent of BBB opening, assessed using extravasation of a high molecular weight fluorescent dye in a rat model of stroke [42]. The time course of BBB opening differs between different models of permanent occlusion from 12 to 48 h. These earlier studies, however, show an irreversible opening of the BBB with prolonged duration of ischemia [43,44].

Blood–brain barrier breakdown in traumatic brain injury

Analogous to the ischemic stroke, TBI also elicits a biphasic BBB disruption. Acutely after TBI, shear forces lead to mechanical injury of the microvascular supply, compromising the BBB. Imaging studies reveal that the initial impact from TBI results in disruption of the tight junction complexes, widening of the intercellular spaces, flattening and compression of the vasculature and reduction of the vascular lumen followed by cellular swelling [45,46]. A recent study showed that although BBB regulation is centered on brain capillaries, acutely after the injury all vessel types (capillaries, arterioles and venules) equally contribute to BBB leakage [47,48]. BBB breakdown in the acute early phase is rapid and leads to heightened BBB permeability that lasts for a few hours and declines immediately. A delayed second phase of BBB disruption occurs 3–7 days after TBI [25]. BBB breakdown results in increased endothelial caveolae and transcytotic activity, mediated by caveolin-1 h after TBI followed by decreased expression of claudin-5 and occlusion that can last for days [38,39,49]. Disruption of BBB in general leads to dysregulation of vascular autoregulatory capacity, an inflammatory response mediated by glial cells and reduced neurovascular coupling [50].

Although a biphasic activity in BBB disruption is seen in animal models and human TBI that subsides within a few days, clinical data for some patients have also shown long-term BBB disruptions that can last for months to years. The consequence of BBB breakdown can be diverse depending upon the severity and duration of the response. It is likely that long-

lasting BBB disruptions are causally linked to chronic neuroinflammation, neuronal loss and Aβ diseases that can lead to the development of neurodegenerative process (cognitive impairment and dementia) and continues at a steady state after the primary injury [51,52■■, 53–55]. Prolonged BBB breakdown also contributes to early or delayed onset of epilepsy. This is in part due to altered neurotransmission, reduced astrocytic uptake of potassium and neuronal hypersynchronization [56■,57]. Severe BBB disruption also leads to cytotoxic edema and cell death, whereas subtle BBB disruption can favor and promote tissue repair (described in the subsequent section). This indicates that neuroprotective agents can be an appropriate strategy to reduce BBB breakdown in severe and prolonged conditions, whereas repair promoting/accelerating agents can be beneficial during mild BBB breakdown.

Interest in understanding the extent of BBB opening to large and small molecules in both phases of BBB breakdown suggests that the acute phase allows transport of both small and large molecules, while barrier restriction to large molecules is restored after 4–5 h after TBI [58]. Permeability to large molecules has been observed again 2–3 days after TBI [59–61]. Electron microscopic experiments reveal a hierarchical damage of BBB: milder disruptions are associated with transcellular pathways and allow the movement of small molecules; severe disruptions are mediated by paracellular disruption of tight junction seals, allowing the movement of larger molecules. However, a recent study suggests that transport of small molecules through the interstitial space is independent of the extravasation of large molecules [62]. These studies indicate that depending upon the imaging methods and extravasating dyes used, the severity and extent of BBB disruption is differential depending upon the size of the molecule. This calls for a standardization and optimization of detection parameters and techniques [63].

Secondary events, such as edema, abnormal brain activity, microglial activation, astrogliosis and neuroinflammation, can reciprocally contribute to a further increase in BBB breakdown [26,64]. In some TBI situations, diffuse axonal injury and severe BBB disruptions can lead to metabolic disturbances, reduced cerebral blood flow and tissue hypoxia forming an ischemic zone that culminates into a focal lesion [65,66]. In addition to the BBB disruption, depending on the severity of the TBI, structural damage of the choroid plexus also opens up the blood cerebrospinal fluid barrier, augmenting immune trafficking [25,67].

In total, mechanisms observed during BBB breakdown – trans and paracellular disruption and enhanced permeability, tight junction disruption and leakage of solutes both large and small – are common to both stroke and TBI. Although the cerebrovascular injuries are heterogeneous, three key parameters influence BBB breakdown during stroke and TBI – severity of the BBB disruption, extent of BBB permeability and duration of the BBB opening. Thus, understanding and standardizing clinically relevant BBB studies during injury can further enhance our understanding to utilize rightly sized therapeutic agents (neuroprotective and restorative agents) during the right window (acute/delayed) of opportunity.

REPARATIVE NEOVASCULARIZATION AFTER STROKE AND TRAUMATIC BRAIN INJURY

What is neovascularization?

Neovascularization or formation and remodeling of vessels is a tissue response observed after injury and has been documented to occur both after stroke and TBI. Neovascularization encompasses three processes: angiogenesis – new vessel formation by proliferation, migration of vascular cells forming capillary sprouts from the pre-existing vasculature, arteriogenesis – also referred to as collateralization – positive outward remodeling of fully functional vessels to large caliber vessels that have the ability to bypass occlusion sites. This is mainly dependent on mechanical shear stress, compared with angiogenesis which is a hypoxia driven vasculogenesis – formation of new vessels from endothelial progenitor cells. Each of these neovascularization processes is different from the other. However, each occurs simultaneously after TBI and stroke and has the capability to repair tissue injury by promoting tissue perfusion and neurological functions.

In the central nervous system, neovascularization is a tightly regulated process that involves the participation of endothelial cells, extracellular matrix changes and migration and proliferation of vascular cells forming capillaries. This process requires an orchestrated interplay of many stimulators, inhibitors and matrix components [68,69]. In normal physiological conditions, the brain vasculature is quiescent and only contributes to the maintenance and growth of the tissue. The interrelationship between vascular and neuronal cells in the central nervous system is highly sophisticated and forms an intricate network termed as the ‘neurovascular niche’ along with BBB components, oligodendrocytes and microglia [17▪▪].

After stroke, neovascularization begins in the tissue in the peri-infarct region as a response to the injury-induced hypoxia/ischemic events (mitochondrial dysfunction and reduced oxygenation), reduction in blood supply and BBB disruption [70▪▪]. Two key parameters influence restoration of blood flow: presence of collaterals and a capacity to undergo vascular remodeling and produce angiogenic mediators. A majority of the research reveals that spontaneous vascular remodeling occurs after TBI and stroke [71,72▪,73] with exceptions that show the absence of vascular remodeling depending upon the region of assessment [74], impaired plasticity and remodeling associated with age [75–77] and comorbid conditions [78,79]. Vascular modeling is associated with improved neurological outcomes [73]. Enhanced neuronal remodeling (generation of new neurons-neurogenesis and axonal reorganization) occurs in the region of active neovascularization and is associated with the vasculature [80], thus indicating that angiogenesis is directly associated with aspects of tissue repair.

Angiogenesis after stroke and traumatic brain injury

As compared to stroke in which there is up to an 85% reduction in blood flow, cerebral blood flow (CBF) reductionisonlyupto50%inTBIatinitialtimepoints [57,81,82]. Alterations in CBF differ between mild and severe TBI. Severe TBI is associated with heightened reductions in CBF around the impact zones, whereas mild TBI results in either small

reductions in CBF or even hyperperfusion at acute timepoints [83–86]. Both stroke and TBI involve BBB disruption, hypoxic states, redox systemimbalance thatleads tothe generation of free radicals, and release of proinflammatory mediators [87]. Each of these events is an essential predecessor to a tissue repair response and is important to evoke a proangiogenic state in the region of injury that creates a feasible canvas for the growth of new vessels [72▪, 87,88].

Endothelial cells are primary effector cells of the angiogenic response after ischemic injury, followed by the pericytes and smooth muscle cells. Angiogenesis involves the proliferation of endothelial cells and sprouting of the vessels that eventually increase vascular density. In animal models of stroke, endothelial proliferation has been reported as early as 12–24 h and lasts up to 21 days. Increased vascular density is observed in the peri-infarct region within 3 days after stroke with a peak activity at 7 days after the injury and coincides with endothelial proliferation up to 21 days. Postmortem brain samples from stroke patients and MRI detection methods also indicate angiogenic activity in the peri-infarct region [89,90▪].

In comparison to ischemic stroke, TBI models also demonstrate a substantial degree of angiogenesis. Upregulation of angiogenic mediators, increased capillary density and neovascularization as early as 48 h after TBI have been reported in several experimental models of TBI. A spatiotemporal investigation of different brain regions after TBI suggests that vascular remodeling peaks 4 days after TBI and is subsequently reduced at day 7 and 14 comparable to baseline in experimental models, with an exception in that the thalamus shows sustained remodeling in some models of TBI [91]. Additionally, chronic vascular remodeling has been detected up to 9 months after TBI. However, increased vascular density does not always correlate with improved neurological outcome in TBI [92]. Stroke studies show a promising interrelationship between endogenous vascular repair associated with neurological outcomes [88,93,94].

Arteriogenesis after stroke and traumatic brain injury

Acutely after stroke, reduction of cerebral blood flow occurs. Depending on the level of native collaterals and anastomotic vessels (circle of Willis, artery–artery interconnections, ophthalmic and leptomeningeal vessels), acute restoration of tissue perfusion by redistribution of blood from surrounding or distant sites can reduce the level of infarction and confer protection [70▪▪,95,96]. Both pre-existing collaterals and active or new collateralization after stroke improve clinical outcomes and enhance the benefits of thrombolytic and endovascular therapies [70▪▪,95,96].

Fluid shear stress followed by the activation of endothelial and vascular smooth muscle cells by the nitric oxide system is a primary stimulus to arteriogenesis [97,98]. Monocyte invasion, and activation of inflammatory pathways, leads to enhanced secretion of growth factors and cytokines that result in positive outward remodeling of the vasculature, forming collaterals [99▪▪,100,101]. Development of collaterals, increased cerebral blood flow, lengthening of the arteries and outward vascular remodeling have been observed acutely and up to 1 month in animal models after stroke [102–108]. Pharmacological induction of blood pressure and increasing cranial blood flow through vasodilation aimed at increasing pre-existing collateral circulation have shown positive functional outcomes and a reduction in

stroke volume [109–112]. Enhancing the formation of new collaterals with granulocyte-macrophage colony-stimulating factor has demonstrated to reduce functional deficits after stroke [113–115].

Although there are several studies addressing the importance of collateralization after stroke, there are no reports that focus on the specific arteriogenesis mechanisms after TBI. However studies report a progressive increase in vascular density from 7 to 28 days after TBI. The mean diameter of both microvessels and large vessels significantly increased 4 days after TBI, which coincides with an increased expression of endothelial nitric oxide synthase, stromal cell-derived factor-1, vascular endothelial growth factor (VEGF) and Ang-1 [73,91,116–118,119▪▪]. This positive outward remodeling of the vasculature is a characteristic of arteriogenesis, suggesting collateralization as a possible modality of neovascularization after TBI. This is then followed by an angiogenesis-mediated increase in vascular density. More studies are needed to tease out the two processes in TBI during the early and later time points.

These studies indicate that two potential aspects of collaterals can be harnessed to achieve reparative neovascularization – by enhancing tissue perfusion through native collaterals and by enhancing the formation of new collaterals.

Vasculogenesis after stroke and traumatic brain injury

Within the process of neovascularization, endothelial precursor cells play a key role and have been studied for their therapeutic efficacy to enhance vascular density. The term ‘endothelial progenitor cell’ refers to a circulating progenitor population that propagates into an endothelial lineage with vasculogenic properties, furthering into new vessels [120]. Endothelial progenitors cells (EPCs) contribute to brain vascular remodeling and neural repair after stroke by integrating into pre-existing vessels and secreting growth factors and cytokines [121]. EPCs are widely characterized by coexpression of $CD34^+$, CD133 and VEGFR-2 on the cell surface [122]. EPCs have been reported to be involved in the migration of neuronal progenitors that localize around the peri-infarct region after stroke [121,123]. Mobilization of EPCs from the bone marrow and peripheral blood has been reported in models of both ischemic stroke and TBI at the site of injury [72▪]. EPCs are detected as early as 24 h and peak at 48 h after TBI both in the peripheral circulation and around the damaged brain tissue. The amount of $CD34^+$ progenitor cells positively correlates with the degree of the angiogenesis after TBI [124]. Therapeutic administration of EPCs and conditioned media derived from EPCs [125,126] induce an enhanced neovascularization response and hence are potential tools to promote vascular repair after stroke and TBI [123,127▪▪].

CONCLUSION

Our understanding of the course of vascular events after damage and repair is broad and suggests that the initial BBB disruption after stroke/TBI is directly tied into severity of the injury. The subsequent biphasic or prolonged BBB disruption can facilitate dynamic maintenance and restoration of the neurovascular niche components. This is achieved in the long term by active reparative neovascularization after the injury. Despite rigorous research

in the vascular behavior in these injuries, there is a spectrum of unaddressed issues. From a damage perspective, the research focus has been to understand the course of BBB disruption in both the short and long term. However, we do not know how the BBB recovers. We do not know the molecular mediators that lead to BBB recovery vs. those that lead to BBB disruption. How does BBB recovery affect reparative neovascularization? From the repair aspect, we have mounting evidence of neovascularization mechanisms occurring after stroke. Reparative neovascularization after TBI is still in its infancy owing to the heterogeneous nature of the injury. Additionally, several reports show either an early absence or delayed neovascularization or even a disappearance of vasculature around the site of injury after stroke [128]. This raises important questions: do apoptotic mechanisms co-occur to clear the damaged tissue? Or does delayed loss of blood vessels prevent superfluous vascular growth and balance vascular turnover?

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