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Role of fibrinogen in cerebrovascular dysfunction after traumatic brain injury

Nino Muradashvili and David Lominadze

Department of Physiology and Biophysics, University of Louisville, School of Medicine, Louisville, KY, USA

Abstract

Traumatic brain injury (TBI) has been associated with various neurological disorders. However, the role of cerebrovascular dysfunction and its mechanisms associated with TBI are still not well understood. Inflammation is the main cause of vascular dysfunction. It affects properties of blood components and the vascular wall leading to changes in blood flow and in interaction of blood components and vascular endothelium exacerbating microcirculatory complications during inflammatory diseases. One of the markers of inflammation is a plasma adhesion protein, fibrinogen (Fg). At elevated levels, Fg can also cause inflammatory responses. One of the manifestations of inflammatory responses is an increase in microvascular permeability leading to accumulation of plasma proteins in the subendothelial matrix and causing vascular remodelling. This has a most devastating effect on cerebral circulation after TBI that is accompanied with an elevation of plasma level of Fg and with an increased cerebrovascular permeability in injury penumbra impairing the normal healing process. This study reviews cerebrovascular alterations after TBI, considers the consequences of increased blood–brain barrier permeability, defines the role of elevated level of Fg and discusses the potential mechanisms of its action leading to vascular dysfunction, which subsequently can cause impairment in neuronal function. Thus, possible mechanisms of vasculo-neuronal dysfunction after TBI are considered.

Keywords

Blood–brain barrier; cerebrovascular permeability; inflammation; matrix metalloproteinase-9; paracellular transport; transcellular transport

Traumatic brain injury and vascular dysfunction

Traumatic brain injury (TBI) is the leading cause of death and disability, for which no effective treatment exists other than supportive care [1]. Although the treatment of TBI in the acute phase has improved significantly, the prevention and management of long-term post-traumatic complications remain a challenge. Impairment of blood–brain barrier (BBB) has often been documented in patients with TBI [2], but the role of this type of vascular pathology and its consequences in neurological dysfunction has only recently become an object of interest.

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Correspondence: David Lominadze, PhD, University of Louisville, Department of Physiology & Biophysics, School of Medicine, Bldg. A, Room 1115, 500 South Preston Street, Louisville, KY 40202, USA. Tel: (502) 852-4902. Fax: (502) 852-6239. david.lominadze@louisville.edu.

Declaration of interest

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BBB is the regulated interface between the peripheral circulation and the central nervous system (CNS). In general, the BBB consists of the cerebrovascular endothelial cells (ECs) and vascular smooth muscle cells and, together with astrocytes, pericytes, neurons and associated extracellular matrix proteins, represent a neurovascular unit (NVU) [3]. The majority of CNS diseases are associated with disruption of the NVU. The regulation of ion balance, changes in oxygen and nutrition supply, homeostasis, transport of hormones and neurotransmitters are dependent on normal function of cerebral vessels and blood flow properties. To clarify these interactions, the term ‘vasculo-neuronal-inflammatory triad’ was used in 2011 [4]. Since any vascular or blood flow dysfunction leads to or exacerbates neuronal abnormalities, to emphasize that destructive effect in neuronal function is induced by alterations in vasculature or blood circulation, here we will use a new term, ‘vasculo-neuronal’ dysfunction.

Animal studies have shown that increased BBB permeability is involved in initiation of pathological changes such as transcriptional alterations in the vasculo-neuronal network, which eventually leads to neuronal dysfunction and degeneration. Brain imaging results have confirmed the frequent occurrence of BBB breakdown in patients with TBI and suggest that this pathology could be used as a biomarker in the clinic as well as in drug trials. Impairment of BBB after TBI has been associated with oedema formation [5–7]. Enhanced microvascular leakage was caused by disruption in vascular endothelial junction proteins (JPs) consisting of a complex of transmembrane (junctional adhesion molecule-1, occludin and claudins) and cytoplasmic (zonula occluden-1 (ZO-1), zonula occluden-2 (ZO-2), cingulin, AF-6 and 7H6) proteins, which are linked to the actin cytoskeleton [8]. TBI-mediated inflammation activates acute phase responses. Some of the acute phase proteins such as fibrinogen (Fg) itself results in inflammatory responses [9–18]. An understanding of the mechanisms involved in cerebrovascular permeability induced by trauma might lead to novel targets for possible treatment strategies in the management of patients with TBI. This article reviews experimental data, mainly of animal studies, implicating involvement of impaired cerebrovascular permeability in vascular dysfunction after TBI, which inevitably involves deficits in the vasculo-neuronal unit. This study also outlines potential targets for intervention to enhance efficacy of post-TBI care.

Effect of inflammation on vasculature

Inflammation is a complex of different biological responses of vascular tissue to harmful stimuli. Acute inflammation is characterized by marked vascular changes such as increased permeability, vasodilation and worsening in haemorheology, induced by the actions of various inflammatory mediators [19]. A wide variety of human diseases are associated with inflammation that include stroke [20], myocardial infarction [21], hypertension [22, 23], diabetes [24, 25], atherosclerosis [26] and traumatic brain injury [2, 27, 28]. Inflammation is a key contributor to many vascular diseases and plays a major role in autoimmune diseases [29], allergic reactions [30] and cancer [31].

Inflammatory processes may induce endothelial dysfunction and vascular remodelling [22, 32]. The normal endothelium forms a stable anti-inflammatory interface between circulating blood components and cells within all tissues of the body. The barrier built by the endothelium and its associated structures, e.g. glycocalyx and basement membrane, are sufficient to maintain the plasma volume and venous return and prevent tissue oedema [33]. However, an alteration of EC properties and, thus, a dysfunction of endothelial lining, in most of the cases, are induced by inflammation. One of the manifestations of inflammation is an increase in permeability of blood vessels, which results in leakage of plasma substances and proteins out of the blood stream and their deposition in the subendothelial matrix (SEM) and interstitium [34]. Accumulation of plasma proteins in the interstitium in

result of an increased vascular permeability exacerbates complications of blood circulation during vascular diseases and causes oedema [34, 35], which occurs during mainly early stages of acute inflammation [36].

Traumatic brain injury and coagulopathy

TBI-induced disbalance among the coagulation factors can lead either to hypercoagulation with microthrombogenesis and ischaemia or to hypocoagulation with possible development of haemorrhagic lesions [37]. Pathogenesis of traumatic coagulopathy and its possible treatment options are discussed in the recent publications [38, 39]. Traumatic coagulopathy that occurs as a result of tissue trauma and/or systemic hypoperfusion is characterized with global anticoagulation and hyper-fibrinolysis [40]. While most of the patients (>60%) may develop haemocoagulative disorders after severe TBI [41], coagulopathy is rare (<1%) after mild TBI [42]. As severe trauma is associated with bleeding and, therefore, with loss of active factors (such as Fg, thrombin, von Willebrand factor (vWF) and platelets) affecting coagulation and thrombogenesis, development of hypocoagulation state is likely. However, after a mild TBI mainly the vascular wall damage occurs that is associated with lesser massive bleeding. This can lead to inflammation-mediated increase in blood content of Fg [43] and promote hypercoagulation and thrombogenesis.

Traumatic brain injury and role of fibrinogen

TBI is followed with development of inflammation [2, 27, 28] and as such it is accompanied with elevation of blood content of Fg [44–46]. Fg is a high molecular weight (~340 kD) plasma adhesion glyco protein considered a high risk factor for many cardiovascular and cerebrovascular diseases [43, 47]. Inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-1 (IL-1), which are elevated after TBI [28, 48], are involved in synthesis of Fg [49, 50]. While Fg at the normal concentration (~2 mg/ml) has no discernible effects, at elevated level (Fg level of 4 mg/ml, i.e. hyperfibrinogenaemia, HFg) Fg is considered not only a marker of inflammation [51] and a high risk factor for cardiovascular diseases [43, 47], but also a cause of inflammatory responses [9, 12, 13, 35, 52]. It has been shown that Fg dose-dependently regulates production of endothelin-1 (ET-1) [11] enhancing arteriolar constriction [10]. These findings shed a new light on a role of Fg in inflammation-induced microvascular dysfunction.

Increased blood content of Fg, i.e. HFg, accompanies inflammatory diseases such as stroke [53, 54], hypertension [55, 56] and occurs after TBI [44–46]. There is supporting evidence of a decrease in cerebral blood flow following cortical contusion injury (CCI) [57, 58], which appears to be a result of vasoconstriction leading to an increase in blood flow resistance [59]. In addition, impaired dilatory responses of pial vessels were found after the fluid percussion injury in rats [60]. These results point to a possible role of Fg-mediated enhanced production of ET-1 [10, 11] after CCI. However, it was found that, besides the ET-1 production, Fg binding to ECs alters EC structure (formation of filamentous actin, F-actin) [12] and enhances caveolar transcytosis [61]. These events, that occur independent of Fg-induced ET-1 production [11, 13], lead to an increased cerebrovascular permeability and have a significant effect on vascular remodelling in brain vasculature [9, 14, 35, 62].

Recent findings indicate that, apart from its key role in controlling blood loss following the vascular injury, undegraded Fg dose-dependently increases EC layer permeability and itself extravasates at sites of inflammation or increased vascular permeability [12] where it is immobilized in SEM [63] and then converted to fibrin [64]. It was found that HFg (a total blood content of Fg 4 mg/ml) causes increased pial venular permeability through activation of matrix metallo-proteinase-9 (MMP-9) [9] affecting cell JPs [9, 14] and caveolae

formation [9]. These findings emphasize a new role of Fg during inflammation development and indicate its strong involvement in cerebrovascular permeability.

Microvascular permeability, role of fibrinogen

ECs have two main functions. They maintain tissue homeostasis and contribute to the functions of the vessel wall through establishing communications between blood and adjacent tissue. The vascular endothelium is a barrier and a permeable filter at the same time [65]. Blood plasma components, such as proteins, may pass through the endothelial barrier via two major transcellular and paracellular transport pathways [34, 66, 67].

Movement of plasma components via the paracellular pathway occurs between ECs and involves alterations in JPs and their interbinding forces [34]. The transcellular transport of proteins, transcytosis is implemented by their movement across the EC and involves caveolae, fenestrae and transendothelial channels [66]. The combination and the functional balance of these two, transcellular and paracellular, pathways govern the net transport of blood plasma substances in microcirculation.

An increase in plasma content of Fg increases blood viscosity [56] and therefore increases shear stress [68–70]. This contributes to an activation of ECs [69, 71] and upregulates expression of various plasma adhesion molecules and integrins [72, 73]. Among them are well-known Fg receptors such as $\alpha_5\beta_1$ and $\alpha_v\beta_3$ integrins [74, 75] and intercellular adhesion molecule-1 (ICAM-1) [74, 76, 77]. It was recently found that at an increased blood level Fg enhances expression and activation of ICAM-1 in mouse cortical vessels [9]. Although expression of ICAM-1 was viscosity- and thus shear stress-dependent, its function was Fg-specific [9]. It has been shown that enhanced binding of Fg to ICAM-1 [10, 78] activates extracellular signal-regulated kinases 1 and 2 (ERK-1/2) [11, 79], which increase production of ET-1 [11], that in turn, is involved in vascular tone modulation [10]. In addition, Fg binding to vascular endothelium activates MMP-9 [9] and alters paracellular and transcellular transport pathways by decreasing expression of JPs [9, 16] and increasing expression of Caveolin-1 (Cav-1) and plasmalemma vesicle associated protein-1 (PV-1) [9]. The latter two events point to a possibility that at higher level Fg can be involved in formation of caveolae [61].

Role of pial microvessels after TBI

It is well known that pial vessels are the resistance vessels that control global blood supply to the brain, while the intraparenchymal vessels are involved in the regulation of local cerebral blood flow [80]. As the primary injury caused by a head trauma affects mainly pial vessels and since content of Fg increases after local vascular injury [54] and TBI [44–46], it becomes imperative to investigate the role of increased blood content of Fg in pial microvessels in penumbra of the injury induced by trauma.

Although it is known that blood content of Fg increases after a moderate TBI [44–46], its role in cerebrovascular permeability, their remodelling and in the post-injury healing process has never been studied.

Paracellular transport and role of fibrinogen

ECs are connected to each other by JPs. There are three types of JPs: tight junction proteins (TJPs), gap junction proteins (GJPs) and adherence junction proteins (AJPs) [34]. The allocation of endothelial junctions varies by function of organ-specific requirements [34]. It is well accepted that brain microvessels are less permeable to plasma components than microvessels in, for example, skeletal muscle. The EC layer in brain vessels is a first line of

BBB. It is considered that endothelial junctions in the brain vessels have tighter arranged JPs [81].

The properties of the endothelium vary based of vessel type. Arteries have a well-organized system of TJPs, while in venules, junctions are poorly organized. JPs in the endothelium are responsible for vascular homeostasis and permeability that requires precise regulation of opening and closing of cell–cell contacts [82]. JPs also transfer intracellular signals [83]. Only one-fifth of the cell junctions in the endothelium are TJPs [84]. They are responsible for maintaining the integrity of the endothelial barrier [85].

Occludin, claudins and tight junction associated proteins such as ZO-1 and ZO-2 are the main TJPs [34] and are expressed in ECs. Occludin is located at the apical side of ECs [34, 86] and bound to the main cytoskeleton protein actin via proteins of the ZO family [34]. Alterations in JPs affect vascular permeability through the paracellular pathway [19].

It was shown that high content of Fg causes an increase in EC layer permeability through F-actin formation [12]. Formation of F-actin may cause an increase in rigidity and retraction of cells, leading to widening of gaps between the ECs by pulling edges of a cell toward the cell centre [35, 87, 88]. Increased content of Fg causes down-regulation of expression and translocation to cytosol of TJPs, such as occludin, ZO-1 and ZO-2 [13].

Vascular endothelial cadherin (VE-cadherin) or endothelial specific adhesion molecule Cadherin-5 is located at the basolateral side of ECs [34, 89] and it is present in all types of vessels [83]. VE-cadherin mediates Ca^{2+} -dependent interactions through the extracellular domain [90]. Presence of VE-cadherin at cell contacts essentially indicates the extent of permeability of blood vessels [14, 89].

It was found that Fg, by increasing formation of F-actin, enhanced cultured EC layer permeability and opened gaps between the cells in a dose-dependent manner [12]. In another *in vitro* study, it was shown that an increase in content of Fg in culture medium decreased mouse brain EC layer junctional integrity and its attachment to SEM by causing down-regulation of VE-cadherin and altering its orderly distribution along the cells' membranes [14]. Although its expression was lesser, VE-cadherin was still present in ECs [12]. Therefore, it is possible that VE-cadherin was partially translocated to cytosol from the surface of the cell membrane [14]. These effects of Fg were confirmed *in vivo*, where an increase in blood content of Fg (by intra-arterial infusion) caused a decrease in VE-cadherin expression in mouse pial vessels that was associated with enhanced cerebrovascular permeability [9].

GJPs are responsible for cell-to-cell communications. These proteins are presented by connexins [83]. Connexins are organized in connexons, which can play the role of channels for the intercellular passage for small molecular weight molecules [83]. There is a lack of information on the effect of Fg on GJPs.

Transcellular transport and role of fibrinogen

Caveolae, fenestrae, transendothelial channels, vesiculo-vacuolar organelles and endothelial pockets are the main components of transcellular transportation [91, 92]. Vesiculo-vacuolar organelles are morphologically defined as chains of various size vesicles connected to each other that form an intricate transendothelial channel spanning the cytoplasm of the ECs from one side of the cell to the other [92]. Transendothelial channels are ~60–70 nm diameter channels that run across the EC [91]. They seem to be formed by the fusion of one caveolae or by chains of two-to-four caveolae [91, 92].

Endothelial pockets are very rare structures that resemble a pocket or a large vacuole that contain fenestrae [92]. Information on endothelial pockets is very scarce. They have been identified in a very low number only in fenestrated endothelium [93].

The fenestrae are characteristic structural elements of all fenestrated endothelia. They are round openings or windows cutting through the ECs, have a remarkably constant diameter of ~62–68 nm and occur only in the attenuated parts of the cell [91, 92]. They permit water and small molecules across the endothelial barrier [94].

Caveolae are distinct flask-shaped invaginated structures present at the surface of many cell types including ECs [91]. Its outer diameter is ~70 nm and at the neck opening is ~20 nm [95]. Therefore, they can take up larger molecular weight proteins such as albumin [34]. Caveolar walls are enriched in cholesterol, glycosphingolipids and sphingomyelin [96]. One of the main components of the caveolae wall is a protein Cav-1 [97].

Cav-1 is a 22 kD integral membrane protein and is expressed in endothelial, epithelial and other cells. It is the major protein of endothelial caveolae and is necessary for caveolae assembly [97]. It is considered as the biochemical marker and structural protein of caveolae in most types of cells [96]. Cav-1 regulates the content of cholesterol in caveolae [98]. It binds to cholesterol and is involved in shuttling of cholesterol from the endoplasmic reticulum to the plasma membrane [98].

PV-1 is an integral membrane-associated protein of caveolae found in fenestral and stomatal diaphragms in fenestrated endothelia and transendothelial channels [91, 99–102] and is considered as a functional biomarker for altered vascular permeability following CNS trauma [103] and disruption of BBB [103, 104]. In CNS and, thus, in the brain, PV-1 formation is limited [104]. However, its association with caveolae, fenestrae, or both is still unclear.

It has been shown that increased levels of Fg led to formation of caveolae or fenestrae, which was evidenced by the enhanced expression of PV-1 [9, 91] and Cav-1 in mouse brain ECs [61]. These results were accompanied with an Fg-induced increase in cerebrovascular permeability [9]. These data indicate a strong involvement of Fg binding to EC in caveolae formation and, thus, in transcytosis.

Traumatic brain injury and the role of matrix metalloproteinase-9

Matrix metalloproteinases (MMPs) are zinc-dependent endoproteases expressed in various cell types including ECs [105]. They are involved in both physiological and pathological processes, especially in SEM degradation and vascular remodelling that disrupt the BBB [106]. Activation of MMP-9, the most abundant MMP, plays an important role in decreasing of brain vascular endothelial layer integrity and causing macromolecular leakage [107]. Activated MMP-9 degrades EC JPs [108] and thus causes disruption of EC layer integrity.

It has been shown that blood content of MMP-9 increases after TBI in mice [109, 110]. It was suggested that MMP-9 activity occurs through activation of ERK-1/2 signalling [109]. These data coincide with the finding that increased Fg binding to endothelial ICAM-1 increases the cultured EC layer [12] and cerebrovascular [9] permeability through ERK-1/2 signalling [11, 12] and increases activation of MMP-9 [9], suggesting a direct involvement of Fg in MMP-9 activation. This effect of Fg has been confirmed in the study, where activity of MMP-9, detected by in-tissue zymography, has been increased in pial vessels in response to intra-arterial infusion of Fg in mouse circulation [9].

MMP-9 gene knockout (MMP9^{-/-}) mice have better morphological and motor outcomes after TBI than their control counterparts [111] and BBB disruption was also attenuated in MMP9^{-/-} mice after transient focal ischaemia [112]. This study indicates that Fg-induced activation of MMP-9 is involved in down-regulation of VE-cadherin expression [9]. Others have shown that MMP-9 compartmentalizes within caveolae structure [113], indicating its possible role in caveolae formation.

Role of fibrinogen in loss of memory after TBI

Impaired memory, particularly short-term memory, is one of the universal problems of people with the head injury [114]. A significant contribution of Fg in development of Alzheimer's disease (AD) has been shown [115–117]. A strong association of Fg with Amyloid beta (A β) peptide was linked to severity of AD [115]. Although Fg [116] and A β [118, 119] plaque formation is the hallmark of AD [115–117], mechanisms of this plaque formation and its deposition in cerebral vasculature and SEM are not clear. It has been shown that A β mediates formation of clots with abnormal structure and resistance to fibrinolysis [120]. However, some studies indicate that content of A β has limited effect on memory [121, 122]. These results suggest that formation of Fg-A β complex can have a greater effect on loss of memory than deposition of Fg or A β alone. Thus, as deposition of Fg with or without conversion to fibrin increases vascular permeability at the site of deposition [64, 123] and at higher levels, Fg increases EC layer permeability and itself crosses the EC layer [12] and cerebral vascular walls [9] affecting both paracellular transport [9, 12–14] and caveolar transcytosis [9, 62], the role of Fg in formation of the Fg-A β complex can be a major indicator for loss of short-term memory after TBI.

Regulation of blood content of fibrinogen

Fg is synthesized and assembled inside hepatocytes and fibroblasts [49, 50, 124]. While cytokines such as IL-1, IL-6 and oncostatin promote its synthesis [49, 50], IL-3, IL-4 and IL-10, which have a protective effect against vascular injury causing atherosclerosis, down-regulate the biosynthesis of Fg [50, 125]. It was reported that neutralization of IL-1 improved histological and cognitive outcome after TBI in mice [126]. Studies on defibrinogenating effects of batroxobin [127] and peroxisome proliferator-activated receptor- α [128] produced some positive outcomes and are still ongoing. Ancrod, a thrombin-like α -fibrinogenase enzyme purified from the venom of *Agkistrodon rhodostoma*, has been used for defibrination in animal studies [129–131] and in humans [54, 132–134]. While some studies report promising effects of Ancrod in treatment of acute ischaemic stroke [54, 134], others indicate that Ancrod did not improve its outcome [133]. The problem associated with Ancrod treatment is an enhanced bleeding [133, 134]. Ancrod, besides the Fg, down-regulates other high molecular weight blood proteins such as factor VIII, vWF [135] and maybe others that are involved in coagulation and thrombogenesis. Therefore, the resultant excessive bleeding is not surprising. These results indicate that defibrinating treatment therapy should be used with extreme caution.

Conclusion

Thus, increased content of Fg causes an increase in blood viscosity and the resultant increase in shear stress, which activates ECs. Activation of ECs results in up-regulation of ICAM-1 expression [9]. At a higher level, Fg binding to over-expressed ICAM-1 is increased, leading to activation of ERK-1/2. ERK-1/2 signalling triggers production of ET-1, formation of F-actin, translocation of JPs and formation of functional caveolae. These effects enhance gap opening between the ECs and increase caveolae motility leading to enhanced microvascular permeability. In addition, increased binding of Fg to ECs leads to an enhanced activity of

MMP-9 [9, 14], which has been implicated in digestion of JPs [108] and association with caveolae [113]. Activation of MMP-9 has been involved in an increase in cerebrovascular permeability [9, 107] that can lead to enhanced deposition of Fg and subsequent formation of the Fg-A β complex. Formation of degradation-resistant Fg-A β plaques can most likely enhance loss of memory after injury. Therefore, cerebrovascular permeability can be a first and the most important step in vasculo-neuronal dysfunction leading to alterations in cognitive function. To define a prevailing role of paracellular or transcellular transport pathway during HFg, a newly developed dual-tracer probing method was used [62]. It was found that an increase in content of Fg enhances cerebrovascular and EC layer permeability via mainly the transcellular pathway [62]. However, the prevailing role of one or the other transport pathway during TBI still has to be defined.

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