



Fibrinogen and/or Fibrin as a Cause of Neuroinflammation

Nurul Sulimai¹ and David Lominadze^{2*}

¹Department of Surgery, University of South Florida Morsani College of Medicine, USA

²Department of Molecular Pharmacology and Physiology, University of South Florida Morsani College of Medicine, USA

*Corresponding author: David Lominadze, Department of Surgery, USF Health-Morsani College of Medicine, USA

Received: 📅 April 6, 2021

Published: 📅 April 14, 2021

Opinion

Involvement of fibrinogen(Fg) and fibrin during various pathologies associated with neuroinflammatory diseases associated with memory reduction are well known. Elevated level of Fg, called hyperfibrinogenemia (HFg) (e.g. $\geq 4 \pm 0.1$ mg/ml of plasma during inflammation vs. $\sim 2 \pm 0.1$ mg/ml of normal plasma [1]), accompanies inflammatory diseases such as stroke [2,3], hypertension [1,4], diabetes [5] and traumatic brain injury (TBI) [6-9]. Blood level of Fg increases during inflammation in general [10]. HFg is considered not only a marker of inflammation [11] but also a cause of inflammatory responses [12-16]. Gradual extravascular deposition of Fg in the brain accelerates neurovascular damage and promotes neuroinflammation [17,18]. It has been shown that Fg is associated with an increased risk of dementia and AD [19]. Derivative of Fg, fibrin have been found postmortem in the brains of patients with TBI [18,20,8], Alzheimer's Disease (AD) [21], and multiple sclerosis (MS) [22]. Elevated blood levels of Fg (HFg) are found to be associated with increased risk of AD, cognitive decline, and dementia [19,23]. Furthermore, formations of plaques containing Fg/fibrin were found in inflammatory neurodegenerative diseases associated with memory reduction such as AD [24], MS [25], and TBI [26]. Strong association of Fg/fibrin with amyloid beta (A β) peptide was linked to severity of AD [24].

In fact, it has been shown that A β mediates formation of clots with abnormal structure and resistance to fibrinolysis [27]. This can be a possible mechanism for Fg-A β complex and subsequent plaque formation that is highly resistant to degradation. Although Fg/fibrin [28] and A β [29,30] containing plaque formations are the hallmark of AD [28,31,24], some studies indicate that content of A β has limited effect on memory [32,33]. 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, although A β is known to be associated with AD [24], a greater role of cellular prion protein (PrP^c) in memory reduction has been shown [32,33].

There are data indicating that PrP^c is involved in TBI-associated memory reduction [34]. We have recently shown that Fg can specifically associate with its receptor PrP^c on the surface of astrocyte [35,36] and others have found that Fg interacts with non-digestive PrP^{sc} [37]. Our data showed that Fg can form a complex with PrP^c in extravascular space during mild-to-moderate TBI [9]. As for the functional effects, it has been indicated that Fg that escaped from ruptured brain vessels causes astrocyte scar formation [38] and axonal damage [39]. Our data showed that Fg, which was transcytosed through endothelial cells (ECs) of non-damaged cerebral microvessels deposited in vasculo-astrocyte interfaces [40]. We found that Fg can activate astrocytes [40,41,35]. Furthermore, these effects of extravasated Fg were associated with neurodegeneration [40] and memory reduction during TBI [9,40,42].

All these data indicate an undoubtful role of Fg in inflammatory neurodegenerative diseases associated with memory impairment. However, blood-clotting proteins generate thrombin, which catalyzes the conversion of Fg (factor I) - a soluble plasma protein - into long, sticky threads of insoluble fibrin (factor Ia). Thrombin is a serine protease that is generated by proteolytic cleavage of its inactive precursor, prothrombin. Neurons and glial cells can release prothrombin and thrombin [43]. Therefore, extravasated Fg that is immobilized in extravascular space, eventually, will be converted to fibrin. In literature, the terms Fg and fibrin are often used interchangeably that creates a confusion: it becomes unclear if effects are caused by soluble Fg or its hardened, insoluble derivative - fibrin (a monomer). It has been shown that Fg does not cross blood brain barrier (BBB) in the normal brain of young mice [44]. However, our data showed that at higher (4 mg/ml) than physiological blood level, Fg not only increases EC layer permeability to albumin but itself moves through the endothelium [13]. Furthermore, we found that cerebrovascular permeability was increased in acute conditions of a HFg [12]. Similarly, cerebrovascular permeability was increased

in transgenic mice exhibiting inherent HFg [45]. Using our dual-tracer probing method, we found that HFg-induced cerebrovascular protein crossing occurred mainly via transcellular pathway [46,45]. Effects of HFg on formation of caveolae and caveolar transcytosis in vitro [47], and an increased cerebrovascular permeability mainly via caveolar transcytosis have been shown [45,48,46]. All these data indicate that, most likely, blood soluble protein - Fg and not its insoluble derivative fibrin, crosses walls of small cerebral vessels during various neuroinflammatory pathologies accompanied with HFg. Crossing the walls of unruptured cerebral microvessels for fibrin that is characterized with high aggregative properties and lesser flexibility is very unlikely.

While in the extravascular space, Fg interacts with its receptors intercellular adhesion molecule 1 (ICAM-1) and PrP^c [49-51] on the surface of astrocytes [35]. It is possible that Fg can reach neurons and on their surface interact with its receptors - ICAM-1 and PrP^c. Thus, these interactions will most likely lead to formation of Fg-PrP^c complexes. As Fg is immobilized in extravascular space, it becomes an easy target for thrombin that is released from neurons and glial cells [43]. The rate of plasma Fg (0.1 mg/ml) polymerization is about $23 \pm 2 \times 10^{-5} \text{sec}^{-1}$, while release of fibrinopeptides A and B from it via enzymatic (thrombin-catalyzed cleavage) step may take from 40 to 120 min [52], maybe even faster. As a consequence of Fg's conversion to fibrin in Fg-PrP^c complex, a highly resistant to enzymatic degradation, fibrin-PrP^c complex will be formed. All further effects, including possible formation plaques, would be a result of specific properties of fibrin deposited in the brain extravascular space. Therefore, in our opinion, we need to be careful in describing effects of Fg, when in blood, crosses the vascular wall, deposits in extravascular space and forms complexes with other proteins, and fibrin (which can be formed in blood but least likely to extravasate) that is formed in extravascular space and by creating undegradable protein complexes (and possibly plaques) leads to memory reduction.

Keywords: Memory impairment; Neurodegeneration

Acknowledgement

This work was supported in part by funding from the National Institutes of Health - HL-146832.

References

- Letcher RL, Chien S, Pickering TG, Sealey JE, Laragh JH (1981) Direct relationship between blood pressure and blood viscosity in normal and hypertensive subjects. Role of fibrinogen and concentration. *The American Journal of Medicine* 70 (6): 1195-1202.
- D Erasmo E, Acca M, Celi FS, Medici F, Palmerini T, Pisani D (1993) Plasma fibrinogen and platelet count in stroke. *Journal of Medicine* 24 (2-3):185-191.
- del Zoppo GJ, Levy DE, Wasiewski WW, Pancioli AM, Demchuk AM, et al. (2009) Hyperfibrinogenemia and functional outcome from acute ischemic stroke. *Stroke* 40(5): 1687-1691.
- Lominadze D, Joshua IG, Schuschke DA (1998) Increased erythrocyte aggregation in spontaneously hypertensive rats. *Am J Hypertens* 11(7): 784-789.
- Lee AJ, Lowe GDO, Woodward M, Tunstall-Pedoe H (2007) Fibrinogen in relation to personal history of prevalent hypertension, diabetes, stroke, intermittent claudication, coronary heart disease, and family history: The Scottish Heart Health Study. *British Heart Journal* 69(4): 338-342.
- Chhabra G, Rangarajan K, Subramanian A, Agrawal D, Sharma S, Mukhopadhyay A (2010) Hypofibrinogenemia in isolated traumatic brain injury in Indian patients. *Neurology India* 58(5): 756-757.
- Pahatouridis D, Alexiou G, Zigouris A, Mihos E, Drosos D, et al. (2010) Coagulopathy in moderate head injury. The role of early administration of low molecular weight heparin. *Brain Injury* 24(10): 1189-1192.
- Sun Y, Wang J, Wu X, Xi C, Gai Y, Liu H, et al. (2011) Validating the incidence of coagulopathy and disseminated intravascular coagulation in patients with traumatic brain injury-analysis of 242 cases. *British Journal of Neurosurgery* 25(3): 363-368.
- Muradashvili N, Benton RL, Saatman KE, Tyagi SC, Lominadze D (2015) Ablation of matrix metalloproteinase-9 gene decreases cerebrovascular permeability and fibrinogen deposition post traumatic brain injury in mice. *Metab Brain Dis* 30(2): 411-426.
- Schneider B, Mutel V, Mathéa Pietri M, Ermonval M, Mouillet-Richard S, Kellermann O (2003) NADPH oxidase and extracellular regulated kinases 1/2 are targets of prion protein signaling in neuronal and nonneuronal cells. *Proc Natl Acad Sci USA* 100(23): 13326-13331.
- Danesh J, Lewington S, Thompson SG, Lowe GD, Collins R, et al. (2005) Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA* 294(14): 1799-1809.
- Muradashvili N, Qipshidze N, Munjal C, Givvmani S, Benton RL, et al. (2012) Fibrinogen-induced increased pial venular permeability in mice. *J Cereb Blood Flow Metab* 32(1): 150-163.
- Tyagi N, Roberts AM, Dean WL, Tyagi SC, Lominadze D (2008) Fibrinogen induces endothelial cell permeability. *Molecular & Cellular Biochemistry* 307(1-2): 13-22.
- Patibandla PK, Tyagi N, Dean WL, Tyagi SC, Lominadze D (2009) Fibrinogen induces alterations of endothelial cell tight junction proteins. *Journal of Cellular Physiology* 221(1): 195-203.
- Lominadze D, Dean WL, Tyagi SC, Roberts AM (2010) Mechanisms of fibrinogen-induced microvascular dysfunction during cardiovascular disease. *Acta Physiol Scand* 198(1): 1-13.
- Davalos D, Akassoglou K (2012) Fibrinogen as a key regulator of inflammation in disease. *Seminars In Immunopathology* 34(1): 43-62.
- Paul J, Strickland S, Melchor JP (2007) Fibrin deposition accelerates neurovascular damage and neuroinflammation in mouse models of Alzheimer's disease. *The Journal of Experimental Medicine* 204(8): 1999-2008.
- Hay JR, Johnson VE, Young AM, Smith DH, Stewart W (2015) Blood-brain barrier disruption is an early event that may persist for many years after traumatic brain injury in humans. *Journal of Neuropathology and Experimental Neurology* 74(12): 1147-1157.
- Van Oijen M, Witteman JC, Hofman A, Koudstaal PJ, Breteler MMB (2005) Fibrinogen is associated with an increased risk of Alzheimer disease and vascular dementia. *Stroke* 36(12): 2637-2641.
- Jenkins DR, Craner MJ, Esiri MM, DeLuca GC (2018) The contribution of fibrinogen to inflammation and neuronal density in human traumatic brain injury. *Journal of Neurotrauma* 35(19): 2259-2271.
- Fiala M, Liu QN, Sayre J, Pop V, Brahmandam V, et al. (2002) Cyclooxygenase-2-positive macrophages infiltrate the Alzheimer's disease brain and damage the blood-brain barrier. *European Journal of Clinical Investigation* 32(5): 360-371.
- Yates RL, Esiri MM, Palace J, Jacobs B, Perera R, DeLuca GC (2017)

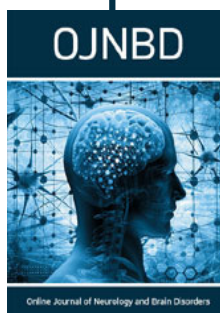
- Fibrin(ogen) and neurodegeneration in the progressive multiple sclerosis cortex. *Annals of Neurology* 82(2): 259-270.
23. Xu G, Zhang H, Zhang S, Fan X, Liu X (2008) Plasma fibrinogen is associated with cognitive decline and risk for dementia in patients with mild cognitive impairment. *International Journal of Clinical Practice* 62 (7): 1070-1075.
 24. Ahn HJ, Zamolodchikov D, Cortes-Canteli M, Norris EH, Glickman JF, et al. (2010) Alzheimer's disease peptide β -amyloid interacts with fibrinogen and induces its oligomerization. *Proc Natl Acad Sci USA* 107(50): 21812-21817.
 25. Vos CMP, Geurts JGG, Montagne L, van Haastert ES, Bö L, et al. (2005) Blood-brain barrier alterations in both focal and diffuse abnormalities on postmortem MRI in multiple sclerosis. *Neurobiology of Disease* 20 (3): 953-960.
 26. Johnson VE, Stewart W, Smith DH (2010) Traumatic brain injury and amyloid- β pathology: a link to Alzheimer's disease? *Nat Rev Neurosci* 11(5): 361-370.
 27. Zamolodchikov D, Strickland S (2012) A β delays fibrin clot lysis by altering fibrin structure and attenuating plasminogen binding to fibrin. *Blood* 119(14): 3342-3351.
 28. Cortes-Canteli M, Strickland S (2009) Fibrinogen, a possible key player in Alzheimer's disease. *Journal of Thrombosis and Haemostasis* 7: 146-150.
 29. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science* 297(5580): 353-356.
 30. Cleary JP, Walsh DM, Hofmeister JJ, Shankar GM, Kuskowski MA, et al. (2005) Natural oligomers of the amyloid- β protein specifically disrupt cognitive function. *Nat Neurosci* 8(1): 79-84.
 31. Cortes-Canteli M, Paul J, Norris EH, Bronstein R, Ahn HJ, et al. (2010) Fibrinogen and β -Amyloid association alters thrombosis and fibrinolysis: A possible contributing factor to Alzheimer's Disease. *Neuron* 66(5): 695-709.
 32. Gimbel DA, Nygaard HB, Coffey EE, Gunther EC, Laurén J, et al. (2010) Memory impairment in transgenic Alzheimer mice requires cellular prion protein. *The Journal of Neuroscience* 30(18): 6367-6374.
 33. Chung E, Ji Y, Sun Y, Kascsak R, Kascsak R, et al. (2010) Anti-PrPC monoclonal antibody infusion as a novel treatment for cognitive deficits in an Alzheimer's disease model mouse. *BMC Neurosci* 11:130.
 34. Rubenstein R, Chang B, Grinkina N, Drummond E, Davies P, et al. (2017) Tau phosphorylation induced by severe closed head traumatic brain injury is linked to the cellular prion protein. *Acta Neuropathologica Communications* 5(1): 30.
 35. Sulimai N, Brown J, Lominadze D (2021) Fibrinogen Interaction with Astrocyte ICAM-1 and PrPC Results in the Generation of ROS and Neuronal Death. *International Journal of Molecular Sciences* 22(5): 2391.
 36. Charkviani M, Muradashvili N, Sulimai NH, Lominadze D (2020) Fibrinogen - Cellular Prion Protein Complex Formation on Astrocytes. *Journal of Neurophysiology* 124(2): 536-543.
 37. Fischer MB, Roeckl C, Parizek P, Schwarz HP, Aguzzi A (2000) Binding of disease-associated prion protein to plasminogen. *Nature* 408(6811): 479-483.
 38. Schachtrup C, Ryu JK, Helmrick MJ, Vagena E, Galanakis DK, et al. (2010) Fibrinogen triggers astrocyte scar formation by promoting the availability of active TGF- β after vascular damage. *The Journal of Neuroscience* 30(17): 5843-5854.
 39. Davalos D, Kyu Ryu J, Merlini M, Baeten KM, Le Moan N, et al. (2012) Fibrinogen-induced perivascular microglial clustering is required for the development of axonal damage in neuroinflammation. *Nat Commun* 3: 1227.
 40. Muradashvili N, Tyagi SC, Lominadze D (2017) Localization of fibrinogen in the vasculo-astrocyte interface after cortical contusion injury in mice. *Brain Sciences* 7 (7):77.
 41. Clark VD, Layson A, Charkviani M, Muradashvili N, Lominadze D (2018) Hyperfibrinogenemia-mediated astrocyte activation. *Brain Research* 1699: 158-165.
 42. Muradashvili N, Charkviani M, Sulimai N, Tyagi N, Lominadze D, et al. (2020) Effects of fibrinogen synthesis inhibition on vascular cognitive impairment during traumatic brain injury in mice. *Brain Research*: 147208.
 43. Arai T, Miklossy J, Klegeris A, Guo JP, McGeer PL (2006) Thrombin and prothrombin are expressed by neurons and glial cells and accumulate in neurofibrillary tangles in Alzheimer disease brain. *J Neuropathol Exp Neurol* 65(1): 19-25.
 44. Yang AC, Stevens MY, Chen MB, Lee DP, Stähli D, et al. (2020) Physiological blood-brain transport is impaired with age by a shift in transcytosis. *Nature* 583(7816): 425-430.
 45. Muradashvili N, Tyagi R, Tyagi N, Tyagi SC, Lominadze D (2016) Cerebrovascular disorders caused by hyperfibrinogenemia. *The Journal of Physiology* 594(20): 5941-5957.
 46. Muradashvili N, Tyagi R, Lominadze D (2012) A dual-tracer method for differentiating transendothelial transport from paracellular leakage in vivo and in vitro. *Frontiers in Physiology* 3: 166-172.
 47. Muradashvili N, Benton R, Tyagi R, Tyagi S, Lominadze D (2014) Elevated level of fibrinogen increases caveolae formation; Role of matrix metalloproteinase-9. *Cell Biochem Biophys* 69(2): 283-294.
 48. Muradashvili N, Khundmiri SJ, Tyagi R, Gartung A, Lominadze D, et al. (2014) Sphingolipids affect fibrinogen-induced caveolar transcytosis and cerebrovascular permeability. *Am J Physiol Cell Physiol* 307(2): 169-179.
 49. Héry C, Sébire G, Peudenier S, Tardieu M (1995) Adhesion to human neurons and astrocytes of monocytes: the role of interaction of CR3 and ICAM-1 and modulation by cytokines. *J Neuroimmunol* 5(1-2): 101-109.
 50. Jing L, Wang JG, Zhang JZ, Cao CX, Chang Y, et al. (2014) Upregulation of ICAM-1 in diabetic rats after transient forebrain ischemia and reperfusion injury. *J Inflamm (Lond)* 11(1): 35.
 51. Graner E, Mercadante AF, Zanata SM, Forlenza OV, Cabral A (2000) Cellular prion protein binds laminin and mediates neuritogenesis. *Brain Res Mol Brain Res* 76(1): 85-92.
 52. Gorkun OV, Veklich YI, Weisel JW, Lord ST (1997) The conversion of fibrinogen to fibrin: recombinant fibrinogen typifies plasma fibrinogen. *Blood* 89(12): 4407-4414.



This work is licensed under Creative Commons Attribution 4.0 License

To Submit Your Article Click Here: [Submit Article](#)

DOI: [10.32474/OJNBD.2021.05.000217](https://doi.org/10.32474/OJNBD.2021.05.000217)



Online Journal of Neurology and Brain Disorders

Assets of Publishing with us

- Global archiving of articles
- Immediate, unrestricted online access
- Rigorous Peer Review Process
- Authors Retain Copyrights
- Unique DOI for all articles