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Review Article

Neurovascular Coupling Response Dysfunction after Ischemic Stroke: The Possible Mechanism in Cognition Impairment

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Abstract

One of the cardinal aspects of post-ischemic stroke disabilities is cognitive decline correlated with higher long-term mortality rate. There are various hypotheses about cognition impairment after ischemic stroke, but lately, neurovascular coupling (NVC) response impairment and neurovascular unit (NVU) disruption have been proposed as causes for cognitive decline. The NVC mechanism, a feature of the brain's intrinsic micro circulation, regulates local cerebral blood flow (CBF) in accordance with the underlying neuronal activity. It seems that, cerebral ischemia triggers several molecular and cellular cascades including excitotoxicity, neuroinflammation, oxidative stress and blood brain barrier (BBB) disruption which eventually leads to NVU malfunction and NVC response impairment which results in cognitive dysfunction in many stroke patients. This review tries to focus on the factors involved in NVC response that might affect cognition after ischemic stroke.

Keywords: *Neurovascular coupling response, Ischemic stroke, Cognition impairment, Mechanisms*

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Introduction

Stroke is associated with the highest odds of severe disability [1]. In 2010, there were 39.4 million disability-adjusted life years reported due to acute ischemic stroke worldwide [2]. One of the most important aspects of these disabilities is cognitive decline that frequently occurs in stroke patients [3]. 64% of patients, who have experienced stroke, have some levels of cognitive impairment [4]. In industrial countries, post-stroke cognitive decline is the second most common cause of dementia [5]. However, it is usually ignored and covered by the severe physical disability [6, 7].

According to reports, the death risk within 20 months after stroke was higher in patients who had a low cognitive score nearly 3 months after stroke [8]. Moreover, after adjustment for demographic and disease severity factors, the long-term mortality rate was 3 times higher in patients who became demented 3 months after stroke, compared to non-demented patients [9]. There are various hypotheses about cognition impairment after ischemic stroke. Lesions in certain brain regions, cerebral micro-bleeds and mixed AD-stroke pathologies are some of the main facets of cognitive impairment after stroke [6]. Moreover, specific systemic interventions including control of vasoactive, hemorheologic and metabolic mechanisms have been proposed to involve in the neuronal damage related to functional and cognitive stroke outcome [5]. Indeed, ischemic stroke causes neuronal and endothelial damages that may result in cognitive impairment [10].

Furthermore, according to recent findings, there is a strong correlation between neurovascular coupling response (NVC) and cognitive function [11]. NVC has been used as an index of synaptic activity in health and disease conditions [12] and the increase in the cerebral blood flow (CBF) following synaptic activity is necessary for physiologic brain function [13]. Dysfunction of neurovascular unit (NVU) structures in stroke causes post-stroke cognitive decline in patients [14]. The NVC mechanism adjusts local CBF in accordance with the underlying neuronal activity [15]. Clinical findings in recent years, showed that NVC response has been significantly impaired in ischemic stroke patients [15,16] and it has been depressed the CBF-induced neuronal activation. Moreover, NVC evaluation is a more sensitive method to detect the progress of cerebral ischemia than other methods that are formerly introduced [17].

From a mechanistic point of view, disruption in blood brain barrier(BBB) integrity, excitotoxicity, oxidative stress and

inflammation can play role in post-stroke NVC response [16, 18]. The aim of this study is to briefly review factors involved in NVC response which can affect cognition after ischemic stroke.

Excitotoxicity

Excitotoxicity contributes to the pathogenesis of stroke [19], which can have an impact on NCV response [20]. A major cause of excitotoxicity is activation of glutamate receptors specially the NMDA subtype which mediates calcium-dependent cell death [17].

The glutamate release during neuronal activation may interact with astrocytic glutamate receptors to increase calcium in astrocytes and result in vasodilation [21]. Moreover, astrocytes trigger intrinsic NVC responses after stroke by propagation of calcium waves and promoting homeostatic gliotransmission [22]. Astrocytes-released gliotransmitters such as D-serine, glutamate and ATP are associated with increased intracellular calcium that directly activates the neighboring neurons via NMDA receptors and subsequent excitotoxicity [23].

Also, as recent literature suggest, excitotoxic mechanisms mediated by NMDA receptors over-activation can induce significant reduction in sensory-evoked NVC responses [24].

NMDA receptor activation stimulates nitric oxide release, crucial for the flow increase and NVC response [13]. There is some evidence that tissue plasminogen activator (t-PA),as only approved treatment for acute ischemic stroke, [2] has role in NMDA receptor-dependent homeostasis which with nitric oxide synthesis, local cerebral perfusion and its subsequent hyperemia [13]. Also, experimental studies suggest that memantine, as a non-competitive NMDA receptor antagonist, could relieve memory impairment and decrease the neural lesions caused by cerebral ischemia [25, 26]. Overall, administration of excitotoxicity inhibitors after ischemic stroke may interact with the same cellular effectors to improve neurovascular unit integrity [22] and recover impaired NVC response after ischemic stroke.

Oxidative Stress

Oxidative stress is one of the mechanisms behind stroke-induced [19] impairment in functional hyperemia [27, 28]. Evidences show that endothelial oxidative stress significantly alters cerebrovascular regulation [29]. It has been revealed that cerebral ischemia can alter oxidative stress and reactive oxygen species (ROS) such as superoxide and peroxynitrite generation [30] which impairs NVC and results in a vicious cycle of further reduction of cerebral perfusion [31, 32]. Moreover, ROS derived from NADPH oxidase can also participate in post-ischemic cerebrovascular dysregulation and its inhibition attenuates the ROS production after ischemia [33].

Oxidative stress-induced delayed neuronalinjury could cause dissociation of neuronal projections from the NVU, un-coupling and subsequent retrograde degeneration [34] which can cause cognitive impairment after stroke [31].

Blood Brain Barrier Disruption

Endothelial cells interact with the BBB factors including astrocytic end-foot processes, basal lamina and pericytes. These factors maintain circulatory homeostasis and neural function via facilitating NVC [35]. It has been suggested that, BBB disruption contributes to the pathogenesis of stroke [36]. During ischemia, NO and ROS production increases in the site of damage and endothelial cells rapidly up-regulate the expression of protease-activated receptor 1, tissue factor and matrix metalloproteinase in both ischemic core and penumbraand subsequently facilitate BBB disruption [37-39]. Furthermore, NO and ROS-induced BBB disruption facilitates neutrophil extravasation into the ischemic tissue in response to astrocytic and microglial chemokines [22]. Overall, these events lead to neurovascular un-coupling.

On the other hand, pericytes as a key component of the NVU [40] contracts following ischemia and involves in the post-ischemic stroke microvascular hemodynamic dysfunction [41]. Besides, rapid loss of endothelial cells and astrocytes' β1-integrin expression during ischemic stroke, promotes cerebrovascular permeability [42-44]. Following ischemic stroke, the release of high mobility group box 1, heat shock proteins and fibrinogen from damaged tissue triggers the activation of toll-like receptors (TLRs). The TLRs in turn, induce the expression of encoding genes for apoptosis and inflammation which leads to BBB disruption [45, 46].

BBB disruption and increased permeability after ischemic stroke destroy NVU and lead to neurovascular un-coupling [35]. However, NVU`s structural interaction provides controlled metabolic, vascular and anatomical condition that are necessary for proper communication of neuronal synapses and circuitries and subsequent cognitive functioning [47].

Inflammation

Inflammation plays a pivotal role in the ischemic stroke and other forms of ischemic brain injury pathogenesis [12, 48]. Early elevations in multiple pro-inflammatory cytokines in the cerebrospinal fluid (CSF) and plasma of ischemic stroke patients show increased levels of IL-1, IL-6, IL-8 and tumor necrosis factor α (TNF- α), [49, 50] which are responsible for cognitive impairment after stroke [20, 51]. Evidence suggest that non-steroidal anti-inflammatory drugs (NSAIDs) are effective in preventing post-stroke cognitive decline [52, 53].

Moreover, NVC response is impaired during inflammation [34]. It has been established that, in stroke, up-regulation and secretion of inflammatory mediators from activated astrocytes stimulate the adhesion molecules expression in inflammatory cells of the brain and cause neurovascular un-coupling [22, 34]. Recent findings highlight inflammatory cytokines and adhesion molecules roles in synaptic and cognitive function [54, 55]. In stroke, modulation of NVC response and NVU integrity by anti-inflammatory drugs can regulate inflammatory cytokines and adhesion molecules [22, 34, 56] which contribute to cognitive decline during the disease [14].

Conclusion

Among different neurological insults of ischemic stroke, NVC impairment remains a major problem that leads to multiple levels of cognitive and memory dysfunctions in stroke patients.

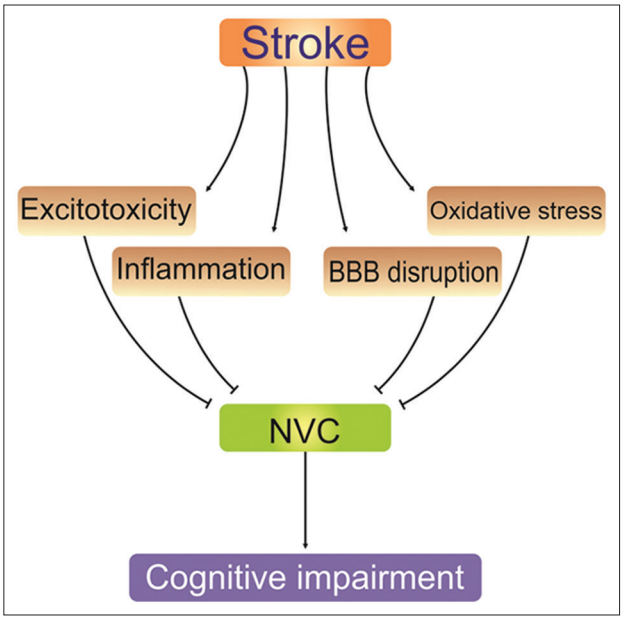

Figure 1. The possible mechanisms of stroke-induced un-coupling in neurovascular response and subsequent cognitive impairment.
BBB: Blood brain barrier; NVC: Neurovascular coupling.

As mentioned, cerebral ischemia triggers several molecular and cellular cascades including excitotoxicity, neuroinflammation, oxidative stress and BBB disruption that eventually lead to mal-adoption of NVU Figure 1. Given these, it seems that studying mutual communication between neuronal compartments and vascular functions may provide an opportunity to understand cerebral ischemia-induced neuronal damages better. Also, due to reliability and validity of NVC in detecting neuronal and vascular impairments of the ischemic brain, it can be considered as a useful target to investigate the novel therapeutics and strategies for reduction of post-stroke cognitive impairments and other functional disabilities.

References

1. Adamson J, Beswick A, Ebrahim S: Is stroke the most common cause of disability? *J Stroke Cerebrovasc Dis* 2004, 13(4):171-177.
2. Farhoudi M, Mehrvar K, Sadigh-Eteghad S, Majdi A, Mahmoudi J: A review on molecular mechanism of reocclusion following thrombolytic therapy in ischemic stroke patients. *J Exp Clin Neurosci* 2014, 1(1):10-15.
3. Henon H, Durieu I, Lebert F, Pasquier F, Leys D: Influence of prestroke dementia on early and delayed mortality in stroke patients. *J Neurol* 2003, 250(1):10-16.
4. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE et al: National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke* 2006, 37(9):2220-2241.
5. Danovska M, Peychinska D: Post-stroke cognitive impairment – phenomenology and prognostic factors. *Journal of IMAB* 2012, 18(3):290-297.
6. Sun JH, Tan L, Yu JT: Post-stroke cognitive impairment: epidemiology, mechanisms and management. *Ann Transl Med* 2014, 2(8).
7. Haring HP: Cognitive impairment after stroke. *Curr Opin Neurol* 2002, 15(1):79-84.
8. Woo J, Kay R, Yuen YK, Nicholls MG: Factors influencing long-term survival and disability among three-month stroke survivors. *Neuroepidemiology* 1992, 11(3):143-150.
9. Tatemichi TK, Paik M, Bagiella E, Desmond DW, Pirro M, Hanzawa LK: Dementia after stroke is a predictor of long-term survival. *Stroke* 1994, 25(10):1915-1919.
10. Shaafi S, Mahmoudi J, Pashapour A, Farhoudi M, Sadigh-Eteghad S, Akbari H: Ketogenic Diet Provides Neuroprotective Effects against Ischemic Stroke Neuronal Damages. *Adv Pharm Bull* 2014, 4:479-481.
11. Sorond FA, Hurwitz S, Salat DH, Greve DN, Fisher ND: Neurovascular coupling, cerebral white matter integrity, and response to cocoa in older people. *Neurology* 2013, 81(10):904-909.
12. Jin R, Yang G, Li G: Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. *J Leukoc Biol* 2010, 87(5):779-789.
13. Park L, Gallo EF, Anrather J, Wang G, Norris EH, Paul J et al: Key role of tissue plasminogen activator in neurovascular coupling. *Proc Natl Acad Sci U S A* 2008, 105(3):1073-1078.
14. Federico A, Guekht A, Brainin M: Current Perspectives in Post-stroke Cognitive Impairment. *Eur Neurol Rev* 2013, 8(2):136-140.
15. Lin WH, Hao Q, Rosengarten B, Leung WH, Wong KS: Impaired neurovascular coupling in ischaemic stroke patients with large or small vessel disease. *Eur J Neurol* 2011, 18(5):731-736.
16. Jackman K, Iadecola C: Neurovascular regulation in the ischemic brain. *Antioxid Redox Signal* 2015, 22(2):149-160.
17. Gupta K, Hardingham GE, Chandran S: NMDA receptor-dependent glutamate excitotoxicity in human embryonic stem cell-derived neurons. *Neurosci Lett* 2013, 543:95-100.
18. Zhang L, Zhang ZG, Chopp M: The neurovascular unit and combination treatment strategies for stroke. *Trends Pharmacol Sci* 2012, 33(8):415-422.
19. Hachinski V: The 2005 Thomas Willis Lecture: stroke and vascular cognitive impairment: a transdisciplinary, translational and transactional approach. *Stroke* 2007, 38(4):1396.
20. Kliper E, Bashat DB, Bornstein NM, Shenhar-Tsarfaty S, Hallevi H, Auriel E et al: Cognitive decline after stroke: relation to inflammatory biomarkers and hippocampal volume. *Stroke* 2013, 44(5):1433-1435.
21. Takano T, Tian GF, Peng W, Lou N, Libionka W, Han X et al: Astrocyte-mediated control of cerebral blood flow. *Nat Neurosci* 2006, 9(2):260-267.
22. Posada-Duque RA, Barreto GE, Cardona-Gomez GP: Protection after stroke: cellular effectors of neurovascular unit integrity. *Front Cell Neurosci* 2014, 8:231.
23. Massey PV, Johnson BE, Moult PR, Auberson YP, Brown MW, Molnar E et al: Differential roles of NR2A and NR2B-containing NMDA receptors in cortical long-term potentiation and long-term depression. *J Neurosci* 2004, 24(36):7821-7828.
24. Harris S, Bruyns-Haylett M, Kennerley A, Boorman L, Overton PG, Ma H et al: The effects of focal epileptic activity on regional sensory-evoked neurovascular coupling and postictal modulation of bilateral sensory processing. *J Cereb Blood Flow Metab* 2013, 33(10):1595-1604.
25. Kilic U, Yilmaz B, Reiter RJ, Yuksel A, Kilic E: Effects of

memantine and melatonin on signal transduction pathways vascular leakage and brain injury after focal cerebral ischemia in mice. *Neuroscience* 2013, 237:268-276.

26. Babu CS, Ramanathan M: Post-ischemic administration of nimodipine following focal cerebral ischemic-reperfusion injury in rats alleviated excitotoxicity, neurobehavioural alterations and partially the bioenergetics. *Int J Dev Neurosci* 2011, 29(1):93-105.
27. Iadecola C: Cerebral circulatory dysregulation in ischemia. *Cerebrovascular diseases* 1998, 1:319-332.
28. Rodrigo R, Fernandez-Gajardo R, Gutierrez R, Manuel Matamala J, Carrasco R, Miranda-Merchak A et al: Oxidative stress and pathophysiology of ischemic stroke: novel therapeutic opportunities. *CNS Neurol Disord Drug Targets* 2013, 12(5):698-714.
29. Faraci FM: Oxidative Stress The Curse That Underlies Cerebral Vascular Dysfunction? *Stroke* 2005, 36(2):186-188.
30. Traystman RJ, Kirsch JR, Koehler RC: Oxygen radical mechanisms of brain injury following ischemia and reperfusion. *J Appl Physiol* 1991, 71(4):1185-1195.
31. Liu H, Zhang J: Cerebral hypoperfusion and cognitive impairment: the pathogenic role of vascular oxidative stress. *Int J Neurosci* 2012, 122(9):494-499.
32. Chrissobolis S, Faraci FM: The role of oxidative stress and NADPH oxidase in cerebrovascular disease. *Trends Mol Med* 2008, 14(11):495-502.
33. Girouard H, Iadecola C: Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. *J Appl Physiol* 2006, 100(1):328-335.
34. Stanimirovic DB, Friedman A: Pathophysiology of the neurovascular unit: disease cause or consequence? *J Cereb Blood Flow Metab* 2012, 32(7):1207-1221.
35. Zhang L, Zhang ZG, Chopp M: The neurovascular unit and combination treatment strategies for stroke. *Trends in pharmacological sciences* 2012, 33(8):415-422.
36. Di Legge S, Hachinski V: Vascular cognitive impairment (VCI). *Progress towards knowledge and treatment Dement Neuropsychol* 2010, 4:l.
37. Liu XS, Zhang ZG, Zhang L, Morris DC, Kapke A, Lu M et al: Atorvastatin downregulates tissue plasminogen activator-aggravated genes mediating coagulation and vascular permeability in single cerebral endothelial cells captured by laser microdissection. *J Cereb Blood Flow Metab* 2006, 26(6):787-796.
38. Zhang ZG, Chopp M, Goussev A, Lu D, Morris D, Tsang W et al: Cerebral microvascular obstruction by fibrin is associated with upregulation of PAI-1 acutely after onset of focal embolic ischemia in rats. *J Neurosci* 1999, 19(24):10898-10907.
39. Rosell A, Lo EH: Multiphasic roles for matrix metalloproteinases after stroke. *Curr Opin Pharmacol* 2008, 8(1):82-89.
40. Dore-Duffy P, Cleary K: Morphology and properties of pericytes. *Methods Mol Biol* 2011, 686:49-68.
41. Yemisci M, Gursoy-Ozdemir Y, Vural A, Can A, Topalkara K, Dalkara T: Pericyte contraction induced by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. *Nat med* 2009, 15(9):1031-1037.
42. del Zoppo GJ, Milner R: Integrin–matrix interactions in the cerebral microvasculature. *Arterioscler Thromb Vasc Biol* 2006, 26(9):1966-1975.
43. Tagaya M, Haring H-P, Stuiver I, Wagner S, Abumiya T, Lucero J et al: Rapid loss of microvascular integrin expression during focal brain ischemia reflects neuron injury. *J Cereb Blood Flow Metab* 2001, 21(7):835-846.
44. Wagner S, Tagaya M, Koziol JA, Quaranta V, del Zoppo GJ: Rapid disruption of an astrocyte interaction with the extracellular matrix mediated by integrin α6β4 during focal cerebral ischemia/ reperfusion. *Stroke* 1997, 28(4):858-865.
45. Nagyőszi P, Wilhelm I, Farkas AE, Fazakas C, Dung NTK, Haskó J et al: Expression and regulation of toll-like receptors in cerebral endothelial cells. *Neurochemistry international* 2010, 57(5):556-564.
46. Caso JR, Pradillo JM, Hurtado O, Lorenzo P, Moro MA, Lizasoain I: Toll-like receptor 4 is involved in brain damage and inflammation after experimental stroke. *Circulation* 2007, 115(12):1599-1608.
47. Rosenberg GA: Neurological diseases in relation to the blood-brain barrier. *J Cereb Blood Flow Metab* 2012, 32(7):1139-1151.
48. Whitehead SN, Massoni E, Cheng G, Hachinski VC, Cimino M, Balduini W et al: Triflusal reduces cerebral ischemia induced inflammation in a combined mouse model of Alzheimer's disease and stroke. *Brain Res* 2010, 1366:246-256.
49. Tarkowski E, Rosengren L, Blomstrand C, Wikkelso C, Jensen C, Ekholm S et al: Early intrathecal production of interleukin-6 predicts the size of brain lesion in stroke. *Stroke* 1995, 26(8):1393-1398.
50. Vila N, Castillo J, Davalos A, Chamorro A: Proinflammatory cytokines and early neurological worsening in ischemic stroke. *Stroke* 2000, 31(10):2325-2329.
51. Rothenburg LS, Herrmann N, Swardfager W, Black SE, Tennen G, Kiss A et al: The relationship between inflammatory markers and post stroke cognitive impairment. *J Geriatr Psychiatry Neurol* 2010, 23(3):199-205.
52. Diener HC, Sacco RL, Yusuf S, Cotton D, Ounpuu S, Lawton WA et al: Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol* 2008, 7(10):875-884.
53. Gorelick PB: Role of inflammation in cognitive impairment: results of observational epidemiological studies and clinical trials. *Ann N Y Acad Sci* 2010, 1207:155-162.
54. Novak V: Cognition and Hemodynamics. *Curr Cardiovasc Risk Rep* 2012, 6(5):380-396.
55. Rafnsson SB, Deary IJ, Smith FB, Whiteman MC, Rumley A, Lowe GD et al: Cognitive decline and markers of inflammation and hemostasis: the Edinburgh Artery Study. *J Am Geriatr Soc* 2007, 55(5):700-707.
56. Mihaylova S, Killian A, Mayer K, Pullamsetti SS, Schermuly R, Rosengarten B: Effects of anti-inflammatory vagus nerve stimulation on the cerebral microcirculation in endotoxinemic rats. *J Neuroinflammation* 2012, 9:183.