

The Blood-Brain Barrier and Bioenergetics in Stroke

Emily Hone¹, Sajad Sarvari², Faezeh Moakedi³, Yuxin Liu⁴, Xuefang Ren^{1,5,6*}

¹Department of Neuroscience, Rockefeller Neuroscience Institute West Virginia University, USA

²Department of Basic Pharmaceutical Sciences, West Virginia University, USA

³Department of Biochemistry, West Virginia University, USA

⁴Department of Computer Science and Electrical Engineering, West Virginia University, USA

⁵Department of Microbiology, Immunology and Cell Biology, West Virginia University, USA

⁶Experimental Stroke Core, Center for Basic and Translational Stroke Research, West Virginia University, USA

Abstract

Stroke is an overwhelming neurological disease with very limited treatment options. As blood-brain barrier (BBB) integrity is well-implicated in the prevention of brain injury, its regulation may prove beneficial for stroke patients. BBB cerebro-vascular endothelial cells primarily utilize mitochondria as their energy-producing source, and mitochondrial function has revealed importance in outcomes for tissue post-stroke. In this review, bioenergetics in relation to BBB permeability in stroke is discussed. Moreover, what causes mitochondrial dysfunction following stroke is explored.

Key words: Blood brain barrier; BBB; Mitochondria; Bioenergetics; Stroke; Ischemia

Introduction

Stroke is a debilitating disease that is presently the second leading cause of death globally [1]. Out of the many strokes that occur worldwide, ischemic stroke accounts for 85 percent [2]. Caused when blood flow is obstructed in the cerebral blood vessel, ischemic strokes lead to oxygen deprivation and ultimately neurological deficits, incapacity, and possibly death [3-5]. However, symptoms are specific to the location of the occlusion. Currently, the only FDA-approved treatment for ischemic stroke is tissue plasminogen activator (tPA). While this treatment is also used for pulmonary embolisms and myocardial infarctions, tPA has a limited time-window of 4.5 hours after onset of stroke symptoms [6]. Due to its ability to cause hemorrhagic transformation and damage to blood-brain barrier (BBB) permeability, the use of mechanical thrombectomy for large vessels is often the preferred method of treatment over tPA. This method has a 24hr window [7].

BBB permeability following a stroke

BBB permeability is well studied and implicated in a stroke. Made of multiple cell types and tight junctions, its function is to separate the central nervous system from peripheral circulation. When the BBB opens, the brain is highly susceptible to the influx of solutes, blood, immune cells, and ions that are associated with delayed brain damage. Immediately following a stroke, the BBB undergoes reversible permeability; however, after 2-3 days, the irreversible permeability settles. We have demonstrated that following a stroke, the BBB opens at both 6H and 72H [8]. As irreversible BBB permeability settles, there is an increased risk of hemorrhagic transformation in patients that received tPA [2]. An important factor for future stroke therapies may be BBB permeability control which is partly controlled through bioenergetics in the mitochondria. The mitochondria are the often called the “power-house of the cell” and function for generation of ATP in addition to cell signaling and apoptosis, control of the cell cycle, and cell growth. Generation of ATP begins in the cytoplasm with glycolysis where glucose is made into pyruvate and transported into the mitochondria. Upon multiple oxidation steps, ATP is generated where it is used for cellular processes [9,10].

The BBB and Bioenergetics

The mitochondria have important roles in our neurons and

cells in the BBB for homeostasis and maintenance. While our brain makes up only 2% of our body mass, it uses 20% of the oxygen in our bodies. Given its aerobic capacity, the mitochondria are needed for energy production through the formation of ATP and maintenance of ion gradients in the membrane. Because the cells in the brain are metabolically active, it makes the brain sensitive to blood disruption [11]. When blood flow is disturbed, the balance between glucose energy and energy from cellular processes is disrupted as well. Mitochondrial dysfunction has been recently implicated in stroke and in ischemia or reperfusion neuronal damage [12]. When an ischemic stroke occurs, bioenergetics of neurons fail [13,14]. Due to rapid energy depletion, there is cellular infarction in neurons, astrocytes, endothelial cells, and oligodendrocytes. Thus, bioenergetics are extremely important for tissue outcome in stroke Figure 1. Acute infections have demonstrated to contribute to compromised mitochondria leading to worsened stroke outcomes. Around 30-40% of stroke patients are estimated to have had some sort of infection [15]. Different studies have reported that lipopolysaccharide (LPS) particularly as a result of infection induces immune responses which leads to activation of the inflammatory pathway and exacerbated brain damage in stroke models [16]. Along with the BBB opening in stroke, body temperature is lowered, which suggests the power-house is shutting down [9]. In a study conducted by Doll et.al, LPS caused mitochondrial-dependent ischemic challenge for BBB permeability and worsened stroke outcomes. In order to determine how LPS compromised BBB integrity, 3 pharmacological inhibitors of mitochondrial respiratory complexes were used on cerebrovascular endothelial cell cultures. The three pharmacological mitochondria inhibitors included rotenone, FCCP, and oligomycin. Results revealed that rotenone caused BBB degeneration through mitochondrial dysfunction in addition to increased infarct size. Moreover, FCCP treatment 30 min before tMCAO increased infarct volume in the cortex, striatum, and total hemisphere compared to

*Corresponding author: Xuefang Ren, M.D., Ph.D, Department of Neuroscience, West Virginia University, 64 Medical Center Drive, Morgantown, WV26506 USA, Tel: (304)581-1892, Email: xuren@hsc.wvu.edu

Received July 02, 2020; Accepted July 16, 2020; Published July 23, 2020

Citation: Hone E, Sarvari S, Moakedi F, Liu Y, Ren X (2020) The Blood-Brain Barrier and Bioenergetics in Stroke. J Neuroinfect Dis 11: 298.

Copyright: © 2020 Hone E, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

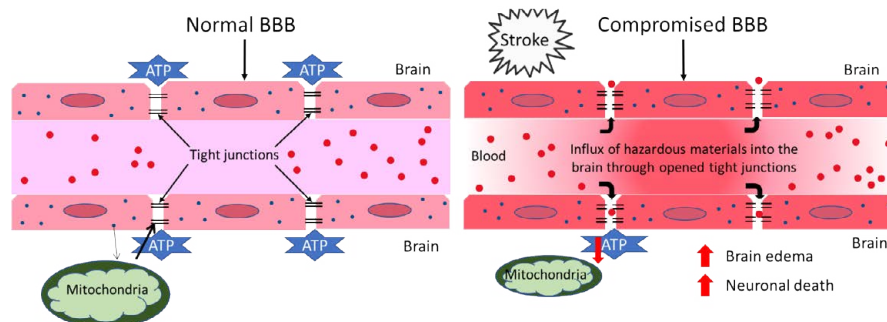


Figure 1: Bioenergetics failure leads to adverse stroke outcomes. When a stroke occurs, mitochondria are rapidly compromised leading to decreased production of ATP, increased reactive oxygen species (ROS) and decreased BBB permeability. Due to the compromised BBB integrity, solutes, ions, immune cells, and other hazardous materials are able to free flow into the brain causing adverse stroke outcomes such as brain edema and neuronal death.

counterparts [17]. Challenge of TNF- α has also demonstrated to compromise mitochondrial potential through release of cytochrome C into the cytosol [18]. reactive oxygen species (ROS) are well implicated in mitochondrial dysfunction in stroke models [19]. As ischemia/reperfusion injury (IR) occurs, glucose and oxygen deprivation in the mitochondria cause the production of harmful ROS and the release of cytochrome C. ROS production overwhelms the cerebral antioxidant defense methods, triggering the apoptotic pathway, and such ROS production is harmful to BBB permeability [20].

Conclusion and Perspectives

As the mitochondria are well-implicated in stroke pathophysiology, mitophagy proves to be important. Despite that mitochondria have important functions in energy production and homeostasis, they cause damage through the production of ROS and the initiation of apoptosis. Mitochondrial autophagy is an important regulator in mitochondrial control, as mitophagy removes dysfunctional mitochondria in a selective process. Modifications of mitochondria could be involved by microRNAs, which is another potential therapeutic target for stroke. Such as a recent study on miR-34a, particularly, is implicated in many diseases and signaling processes like neural physiological processes and the p53 network. In a study conducted by Hu *et al.*, primary cerebrovascular endothelial cells showed increased levels of miR-34a after 1H tMCAO and at the time of BBB opening. Further, miR-34a targeted cytochrome C, and BBB permeability was significantly reduced in miR-34a knockout mice [21]. These findings suggest miR-34a may be a promising stroke therapeutic. Given mitochondrial dysfunction implications in stroke, this selective removal method could be an important therapeutic in stroke; however, little is known on how mitophagy and microRNAs relates to stroke BBB disruption. Moreover, studies should be conducted on the BBB and bioenergetic protective role in stroke.

Acknowledgement

The authors thank Dr. James Simpkins for his support of the study and editing the manuscript. The work was supported by AHA (16SDG31170008 to XR), NSF (NSF1916894 to YL and XR), WVCTSI (NIH/NIGMS U54GM104942 to XR), WVU Bridge Funding Grant (to XR) and NIH (P20 GM109098 to JWS).

References

- Feigin VL, Norrving B, Mensah GA (2017) Global Burden of Stroke. J Circulation res 120: 3 439-48.
- Simpkins AN, Dias C, Leigh R (2016) National Institutes of Health Natural History of Stroke I. Identification of Reversible Disruption of the Human Blood-Brain Barrier Following Acute Ischemia. Stroke 47: 2405-8.
- Cheng Y, Xi G, Jin H, Keep RF, Feng J, et al (2014) Thrombin-Induced Cerebral Hemorrhage: Role of Protease-Activated Receptor-1. J Translat stroke res, 5: 472-5.
- Khanna A, Kahle KT, Walcott BP, Gerzanich V, Simard JM (2014) Disruption of Ion Homeostasis in The Neurogliovascular Unit Underlies The Pathogenesis of Ischemic Cerebral Edema. Translational stroke res, 5: 3-16.
- Berger C, Fiorelli M, Steiner T, Schäbitz W-Rd, Bozzao L, et al (2001) Hemorrhagic Transformation of Ischemic Brain Tissue: Asymptomatic or Symptomatic? Stroke, 32: 1330-5.
- Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, et al (2014) Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. The Lancet, 384: 1929-35.
- Elgendy IY, Mahmoud AN, Mansoor H, Mojadidi MK, Bavry AA (2016) Evolution of Acute Ischemic Stroke Therapy From Lysis to Thrombectomy: Similar or Different To Acute Myocardial Infarction? Int J Cardio 222: 441-7.
- Hone AE, Hu H, Sprowls AS, Farooqi I, Grasmick K, et al (2018) Biphasic Blood-Brain Barrier Openings After Stroke. Neurol Dis and Stroke Int 1: 1-4.
- Hu H, Doll DN, Sun J, Lewis SE, Wimsatt JH, et al (2016) Mitochondrial Impairment in Cerebrovascular Endothelial Cells is Involved in the Correlation between Body Temperature and Stroke Severity. Aging Dis 7: 14-27.
- Doll DN, Hu H, Sun J, Lewis SE, Simpkins JW (2015) Mitochondrial Crisis in Cerebrovascular Endothelial Cells Opens the Blood Brain Barrier. Stroke 46: 1681-89.
- Nicholls DG, Brand MD, Gerencser AA (2015) Mitochondrial Bioenergetics and Neuronal Survival Modelled in Primary Neuronal Culture and Isolated Nerve Terminals. J Bioenerg Biomembr, 47: 63-74.
- Russo E, Nguyen H, Lippert T, Tuazon J, Borlongan CV, et al (2018) Mitochondrial Targeting as a Novel Therapy For Stroke. Brain Circ 4: 84-94.
- Bukeirat M, Sarkar SN, Hu H, Quintana DD, Simpkins JW, et al (2016) MiR-34a Regulates Blood-Brain Barrier Permeability and Mitochondrial Function by Targeting Cytochrome c. J Cereb Blood Flow Metab, 36: 387-92.
- Pundik S, Xu K, Sundararajan S (2012) Reperfusion Brain Injury: Focus on Cellular Bioenergetics. J Neuro, 79: S44-51.
- Ren X, Simpkins JW (2015) Deciphering the Blood-Brain Barrier Damage in Stroke: Mitochondrial Mechanism. J Neuroinfect Dis 6: S2
- Doll DN, Hu H, Sun J, Lewis SE, Simpkins JW (2015) Mitochondrial Crisis in Cerebrovascular Endothelial Cells Opens the Blood-brain Barrier. Stroke 46: 1681-89.
- Grasmick KA, Hu H, Hone EA, Farooqi I, Rellick SL, et al (2018) Uncoupling of the Electron Transport Chain Compromises Mitochondrial Oxidative Phosphorylation and Exacerbates Stroke Outcomes. J Neuroinfect Dis 9: 4.
- Doll DN, Rellick SL, Barr TL, Ren X, Simpkins JW (2015) Rapid Mitochondrial Dysfunction Mediates TNF- α -induced Neurotoxicity. J Neurochem 132: 443-51.
- Peerschke EI, Yin W, Ghebrehwet B (2010) Complement Activation on Platelets: Implications for Vascular Inflammation and Thrombosis. J Molec Immuno 47: 2170-5.
- Alluri H, Stagg HW, Wilson RL, Clayton RP, Sawant DA (2010) Reactive Oxygen Species-caspase-3 Relationship in Mediating Blood-Brain Barrier Endothelial Cell Hyperpermeability Following Oxygen-Glucose Deprivation and Reoxygenation. Microcirculat 21: 187-95.
- Hu H, Hone EA, Provencher EAP, Sprowls SA, Farooqi I, et al (2020) MiR-34a Interacts with Cytochrome c and Shapes Stroke Outcomes. Sci Rep 10: 3233.