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The Blood-Brain Barrier and Bioenergetics in Stroke

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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

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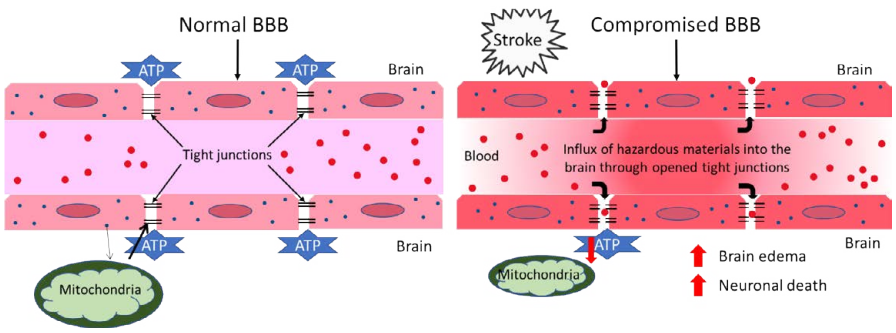

Figure 1: Bioenergetics failure leads to adverse stroke outcomes. When a stroke occurs, mitochondria are rapidly compromised leading to decreased production of ATP, increased reactive oxygen species (ROS) and decreased BBB permeability. Due to the compromised BBB integrity, solutes, ions, immune cells, 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-a 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 mitochondrial 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.

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