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Blood-Brain Barrier Damage From An Ischemic Stroke is Caused By Neuroinflammatory Processes

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Abstract

The onset of neurological impairment in ischemic stroke is significantly influenced by BBB disruption. Tight connections between the endothelial cells that make up the BBB prevent blood borne materials and cells from entering the brain. In the aftermath of a stroke, the BBB's tight junction integrity is lost, increasing paracellular permeability, vasogenic edoema, hemorrhagic transformation, and death. Therefore, for the development of innovative treatments to treat ischemic stroke, identifying key mediators and molecular pathways involved in BBB rupture is essential.

Keywords: Neurovascular injury • Focal cerebral ischemia • Chemokines

Introduction

A growing prevalence of stroke is anticipated as a result of the ageing population, which makes it the second biggest cause of mortality worldwide. Recombinant tissue plasminogen activator, a thrombolytic medication that breaks up clots to let blood flow again, is currently the only treatment for ischemic stroke that has received FDA approval. Because of the short therapeutic window, increased intracerebral haemorrhage, and potential neurotoxicity associated with rtPA treatment, only a very tiny fraction of stroke patients are eligible for it. The American Heart Association recently approved thrombectomy as an interventional method for up to 24 hours in order to dislodge and remove the blood clot. The most significant factor limiting the therapeutic window of rtPA is the Blood-Brain Barrier (BBB) disruption caused by stroke.

According to anatomy, the BBB is made up by brain microvascular endothelial cells, which together with pericytes, astrocytes, neuronal processes, and perivascular microglia, and the basal lamina, constitute the Neurovascular Unit (NVU). The BBB phenotype is maintained in the brain endothelial cells in part by other NVU cells. As the Central Nervous System's (CNS) entry point, the Blood-Brain Barrier (BBB) regulates paracellular permeability, ion balance, nutrition transport, and brain hemodynamics. The BBB has often been shown to be disrupted by neuroinflammation after ischemic stroke.

Stress from oxidative and nitric oxide as a cause of BBB disruption

The pathophysiology of ischemic stroke is heavily influenced by the oxidative stress brought on by Reactive Oxygen Species (ROS) and other free radicals/oxidants. A significant generator of ROS in cells is the NOX family of NADPH oxidases. Numerous enzymes, including the mitochondria, xanthine oxidase, uncoupled Nitric Oxide Synthase (NOS), and cyclooxygenases, are producers of ROS in the Central Nervous System (CNS). But it appears that oxidative stress following ischemia is largely caused by the NOX family of enzymes [1].

Nitric Oxide (NO), a reactive free radical, is produced by three different types of nitric oxide synthases using L-arginine as a substrate: neuronal (nNOS or NOS1), endothelial (eNOS or NOS3), and inducible (iNOS or NOS2). After cerebral ischemia, these NOS isoforms' activity increases. One day after the start of ischemia, it has been demonstrated that nNOS is raised in neurons while eNOS is enhanced in the brain endothelium. Several cell types, including microglia and extravasated neutrophils, had higher iNOS mRNA, protein levels, and activity at later time points after transient focal cerebral ischemia in rats. iNOS was strongly elevated in invading neutrophils in a mouse model of transient MCAO.

Leukocyte infiltration into the CNS, particularly which of neutrophils, is significantly aided by adhesion molecules. To prevent the recruitment of immune cells and reduce subsequent inflammatory responses in stroke, several research groups have focused on these substances. Leukocyte migration across the endothelium is accomplished in three steps: rolling, adhesion, and trans-endothelial migration. Three classes of cell adhesion molecules—selectins (E-, P-, and L-selectin), members of the immunoglobulin superfamily (such as ICAM-1 and VCAM-1), and integrins—are primarily responsible for mediating contacts between the endothelium and circulating leukocytes [2,3].

Relationship BBB breakdown in ischemic stroke with matrix metalloproteinases

After brain ischemia and reperfusion, the MMP family of zinc-dependent endopeptidases has been recognized as one of the major mediators of BBB damage. Since type IV collagen, laminin, and fibronectin, the main components of the basal lamina surrounding cerebral vessels, are their preferred substrates, MMP-2 (gelatinase A) and MMP-9 (gelatinase B) have been the focus of cerebral ischemia studies because they both have the ability to degrade basement membranes. MMP-14, also known as Membrane Type 1 MMP (MT1-MMP), has been demonstrated to trigger pro-MMP-2, while pro-MMP-9 can be activated by stromelysin-1 (also known as MMP-3) or oxidative stress under ischemic conditions [4,5].

Conclusion

It has become clear that inflammation plays a crucial role in how BBB damage progresses and leads to brain injury and ischemic stroke. Depending on how long after cerebral ischemia occurs, neuroinflammatory pathways may be harmful or helpful. Inflammatory reactions may be beneficial at later stages of ischemic stroke by promoting recovery and promoting neurogenesis, angiogenesis, and neuroplasticity. Inflammation may initiate ischemic injury in the early stages of ischemic stroke. Numerous cellular and molecular processes, as discussed in this article, control BBB permeability following cerebral ischemia. In ischemic stroke, BBB collapse is closely related to neuronal injury, brain edoema, and hemorrhagic change. Though there is a substantial body of data from preclinical animal models of ischemic stroke showing neuroinflammation is a prospective target to lessen BBB damage, edoema, and brain injury following stroke, the clinical application of these results has been unsatisfactory. There are numerous potential causes of the translational barrier in ischemic stroke. These topics have been thoroughly covered in very recent review articles. The adequacy of the existing rodent models used to simulate the pathogenesis of stroke is a topic of intense discussion. Key stroke risk variables have not been taken into account while modelling stroke in animals. The most unchangeable risk factor for stroke is becoming older, and there is strong evidence that stroke outcomes are worse in the elderly.

Additionally, only a few preclinical studies include co-morbid disorders when evaluating prospective neuroprotective drugs. Stroke harm, including neuroinflammation, BBB breakdown, and edoema, has been shown to increase in patients with comorbidities such diabetes, hypertension, hypercholesterolemia, and obesity. Preclinical stroke research will need to adapt more clinically relevant stroke models in the future that better resemble the complicated human stroke pathology in order to support the creation of novel therapeutic approaches for this debilitating neurological disorder.

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