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SHORT COMMUNICATION

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Ischemic Stroke Induces Neuronal Necrosis in Affected Brain Regions

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About the Study

Ischemic stroke is a devastating event that occurs when blood flow to a part of the brain is obstructed, leading to tissue damage and neuronal death. It is the most common type of stroke, accounting for about 87% of all stroke cases. This blockage can result from a thrombus (a blood clot that forms in one of the brain's arteries) or an embolus (a blood clot that forms elsewhere in the body and travels to the brain). The consequent reduction in blood flow deprives brain tissues of oxygen and essential nutrients, initiating a cascade of cellular and molecular events that culminate in neuronal necrosis, or the death of brain cells within the affected area.

Pathophysiology of ischemic stroke

When an ischemic stroke occurs, the immediate reduction in cerebral blood flow triggers a complex pathophysiological response. Neurons, glial cells, and endothelial cells within the ischemic core (the area directly affected by the blockage) suffer severe damage due to hypoxia (lack of oxygen) and glucose deprivation. Within minutes, the lack of oxygen disrupts cellular metabolism, leading to a depletion of Adenosine Triphosphate (ATP), the energy currency of the cell [1].

This energy crisis causes the failure of ion pumps, particularly the sodium-potassium pump, resulting in ionic imbalances. Sodium and calcium ions flood into neurons, while potassium ions leak out, leading to cellular depolarization [2]. The influx of calcium is particularly detrimental as it activates various enzymes that can damage cellular structures, including proteases, phospholipases, and endonucleases. This enzymatic activity degrades proteins, lipids, and nucleic acids, further contributing to cell injury [3].

Mechanisms of neuronal necrosis

Neuronal necrosis in ischemic stroke is primarily driven by excitotoxicity, oxidative stress, and inflammation. Excitotoxicity refers to the excessive activation of glutamate receptors, particularly the N-methyl-D-aspartate (NMDA) receptors, due to the massive release of glutamate, a neurotransmitter, from damaged neurons [4]. This overstimulation leads to increased calcium influx, exacerbating cellular damage and triggering necrosis.

Oxidative stress arises from the overproduction of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) during ischemia and reperfusion (the restoration of blood flow). These reactive molecules cause oxidative damage to proteins, lipids, and DNA, further impairing cellular function and integrity. Neurons are particularly vulnerable to oxidative stress due to their high metabolic rate and relatively low antioxidant defences [5].

Inflammation also plays a important role in neuronal necrosis. Ischemic injury activates resident microglia (the brain's immune cells) and attracts peripheral immune cells, such as neutrophils and macrophages, to the site of injury. These immune cells release pro-inflammatory cytokines, chemokines, and other mediators that exacerbate tissue damage and promote necrosis. The blood-brain barrier, which normally protects the brain from harmful substances, becomes compromised, allowing more immune cells and potentially neurotoxic substances to infiltrate the brain tissue [6].

Clinical implications and treatment strategies

The consequences of neuronal necrosis in ischemic stroke are profound, often leading to significant neurological deficits depending on the location and extent of the brain damage. Common symptoms include hemiparesis (weakness on one side of the

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body), aphasia (language difficulties), and cognitive impairments. In severe cases, ischemic stroke can result in permanent disability or death.

Prompt treatment is crucial to minimize neuronal death and improve outcomes. The primary goal of acute stroke management is to restore blood flow to the affected area as quickly as possible [7]. Thrombolytic therapy with Tissue Plasminogen Activator (tPA) is the only FDA-approved treatment for acute ischemic stroke, which can dissolve the clot and restore blood flow if administered within a narrow therapeutic window (typically within 4.5 hours of symptom onset).

Endovascular therapy, which involves mechanical thrombectomy to physically remove the clot, has also emerged as a powerful treatment for certain patients with large vessel occlusions. This intervention extends the therapeutic window and offers hope for patients who cannot receive tPA or for whom tPA alone is insufficient [8].

Beyond acute management, secondary prevention strategies are essential to reduce the risk of recurrent stroke. These strategies include antiplatelet or anticoagulant therapy, management of risk factors such as hypertension, diabetes, and hyperlipidemia, and lifestyle modifications like smoking cessation, regular physical activity, and a healthy diet.

Future directions in research and therapy

While significant strides have been made in the treatment of ischemic stroke, ongoing research continues to explore novel therapeutic approaches aimed at reducing neuronal necrosis and improving recovery. Neuroprotective agents, which aim to protect neurons from the cascade of damage following ischemia, are a major focus. These agents target various mechanisms of injury, including excitotoxicity, oxidative stress, and inflammation [9].

Stem cell therapy is another promising avenue, with the potential to promote tissue repair and neurogenesis (the growth of new neurons) in the ischemic brain. Preclinical studies have shown that stem cells can differentiate into various cell types, secrete neurotrophic factors, and modulate the immune response, offering multifaceted benefits for stroke recovery [10].

Moreover, advancements in neuroimaging and biomarker research are enhancing our ability to diagnose and monitor ischemic stroke more accurately and swiftly. Improved imaging techniques can help identify viable tissue that might be salvageable with reperfusion therapies, guiding more targeted and effective interventions.

Ischemic stroke results in neuronal necrosis within the impacted brain regions, leading to significant morbidity and mortality. Understanding the mechanisms underlying neuronal death and developing effective treatment strategies are critical to improving outcomes for stroke patients. While current therapies focus on rapid reperfusion to minimize damage, ongoing research into neuroprotection, stem cell therapy, and advanced diagnostics holds promise for the future. As our knowledge and technological capabilities continue to advance, so too does the potential to mitigate the devastating impact of ischemic stroke and enhance the quality of life for survivors.

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