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CEREBRAL STROKE: UNRAVELING THE COMPLEX WEB OF ISCHEMIC INJURY AND NEUROVASCULAR REPAIR

Ruchi Dashora[1*], Ravina Patidar[2], Somvardhan Singh Jaitawat[2], Dr. Siddhraj Singh Sisodia[3], Aditya Pant[4]

[1,2]PG Scholar, Department of Pharmacology, Bhupal Nobles' College of Pharmacy, Udaipur, Rajasthan, India, 313001.
[3]Professor and HOD, Department of Pharmacology, Bhupal Nobles' College of Pharmacy, Udaipur, Rajasthan, India, 313001.
[4]Assistant Professor, Department of Pharmacology, Bhupal Nobles' College of Pharmacy, Udaipur, Rajasthan, India, 313001.

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***Corresponding Author: Ruchi Dashora**
PG Scholar, Department of Pharmacology, Bhupal Nobles' College of Pharmacy, Udaipur, Rajasthan, India, 313001.
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ABSTRACT

Cerebral ischemic strokes account for 85% of all strokes and are a major global cause of death and disability. Even if reperfusion treatments like thrombolysis and thrombectomy are routine care, the results are still suboptimal because of irreversible neural damage. This review of stroke pathogenesis emphasizes the role and mechanisms of inflammation, oxidative stress, and excitotoxicity in the ischemic penumbra. We evaluate diagnostic neuroimaging (CT, MRI, PET) to guide treatment and determine whether tissue is recoverable. Emerging therapies like gene editing, stem cells, mitochondrial-targeted drugs, and nanomedicine have promise for neuroprotection, despite the fact that there are still translational barriers between the bench and the bedside. Customized treatments may be possible with the use of AI and omics-based personalized medicine approaches. The primary areas of focus for the future include the creation of biomarkers, early detection technologies, and public health campaigns targeting modifiable risk factors. To overcome these challenges and improve stroke outcomes worldwide, interdisciplinary collaboration is required.

KEYWORDS: Ischemic stroke, Neuroimaging, Reperfusion therapy, Ischemic penumbra, Stem cell therapy, Oxidative Stress, Precision medicine.

INTRODUCTION

Acerebral stroke is a condition characterized by an obstructed blood supply, leading to oxygen deficiency in the brain tissues. Cerebral stroke is a major cause of death and the leading cause of long-term disability in developed countries **(Feigin et.al.,2014)**. Approximately 10.3 million new stroke cases, 6.5 million stroke-related deaths, 113 million stroke-related disability-adjusted life-years (DALYs), and 25.7 million stroke survivors were reported globally in 2013 **(Feigin et.al.,2014)**. 75.2% of all stroke-related deaths and 81.0% of the corresponding DALYs lost occurred in developing countries, which accounted for the majority of the stroke burden. Stroke is a particularly serious problem in Asia, where more than 60% of the world's population resides and many of its countries are "developing" economies. Stroke risk factors can be broadly divided into two categories: modifiable and non-modifiable. Age, gender, ethnicity, and genetic predisposition are non-modifiable risks; after the age of 55, the incidence doubles every ten years, and men are more at risk than women **(Katan and Luft, 2018)**. Up to 90% of stroke cases are caused by modifiable risk factors, which include obesity, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, physical inactivity, high alcohol intake, and hypertension **(O'Donnell et. al.,2010)**. The biggest factor is hypertension, which increases the risk of stroke by two to four times, whereas atrial fibrillation increases the risk of ischemic stroke by five times because of embolic events **(Lewington et.al.,2002)**. Stroke risk is also increased by lifestyle variables such as poor diet and psychological stress **(Mukharjee and Patil,2011)**. Reducing the worldwide burden of stroke requires public health strategies that focus on these modifiable factors.

I. CLASSIFICATION OF STROKE

The two primary types of cerebral stroke, hemorrhagic and ischemic, each have unique subtypes and origins. Ischemic strokes, which are caused by artery blockage and result in infarction and hypoperfusion in the brain, are considered to account for about 85% of strokes. It is further separated into thrombotic stroke by local thrombosis, mainly due to atherosclerosis in big or small vessels, and embolic stroke by thromboemboli that originate elsewhere, usually the heart or carotid arteries. Cryptogenic strokes, which have no known cause despite much research, and lacunar strokes, which are small, severe infarcts caused by occlusion of penetrating arteries, are other categories **(Sacco et al., 2013; Adams et al., 1993)**. In around 15% of cases, bleeding into the brain parenchyma (intracerebral hemorrhage, or ICH) or subarachnoid space (subarachnoid hemorrhage, or SAH) results in hemorrhagic stroke. SAH is typically caused by ruptured aneurysms or arteriovenous malformations, whereas ICH is often linked to vascular anomalies, cerebral amyloid angiopathy, or hypertension **(van Asch et al., 2010; Sudlow & Warlow, 1997)**. Other rare types include venous strokes caused by cerebral venous sinus thrombosis and transient ischemic attacks (TIAs), which are short episodes of neurological impairment without infarction **(Easton et al., 2009)**. These classifications serve as a reference for diagnostic and therapeutic procedures, emphasizing the significance of rapid imaging (CT/MRI) to differentiate between various stroke types and initiate appropriate treatment.

II. PATHOPHYSIOLOGY OF ISCHEMIC STROKE

A complex chain of events that leads to energy failure and neuronal injury is initiated by the disruption of cerebral blood flow in the pathophysiology of cerebral ischemic stroke. As blood flow drops below 18–20 mL/100 g/min, neurons transition from aerobic to anaerobic metabolism, causing adenosine triphosphate (ATP) to be rapidly depleted and lactic acid to accumulate **(Moskowitz et al., 2010)**. This energy failure disrupts the Na+/K+-ATPase pumps, causing membrane depolarization and an overabundance of excitatory neurotransmitters, including glutamate **(Dirnagl et al., 1999)**. The resultant over activation of NMDA and AMPA receptors triggers cytotoxic pathways, including the

activation of lipases, proteases, and the generation of free radicals, resulting in a massive influx of calcium **(Lo et al., 2003)**. While collateral circulation may allow the surrounding penumbra, an area with marginally sustained perfusion, to survive for hours, irreversible necrosis occurs in the ischemic core within minutes (blood flow <10 mL/100g/min) **(Heiss, 2012)**. According to **Eltzschig and Eckle (2011) and Chamorro et al. (2012)**, reperfusion injury may exacerbate damage by oxidative stress from reactive oxygen species (ROS), inflammation mediated by cytokines (TNF-α, IL-1β), and disruption of the blood-brain barrier by matrix metalloproteinases (MMPs). Peri-infarct depolarizations, endothelial activation, and microvascular thrombosis all contribute to the damage's prolongation **(Shih et al., 2013)**. Modern therapies such as endovascular thrombectomy and thrombolysis aim to protect the penumbra by reestablishing blood flow within the therapeutic window **(Powers et al., 2019)**.

2.1 ISCHEMIC PENUMBRA

The "ischemic penumbra," a key idea in acute ischemic stroke, is the hypo perfused brain tissue that surrounds the irreversibly damaged core infarct. This area experiences reduced cerebral blood flow, typically 10–20 mL/100g/min; this is insufficient to sustain normal neuronal activity but sufficient to briefly preserve cellular viability **(Astrup et al., 1981)**. While maintaining ion homeostasis, the penumbra is characterized by electrical failure (loss of neuronal activity), in contrast to the infarct core, where energy failure results in fast cell death. As long as blood flow is restored within a limited therapy window, the presence of the penumbra emphasizes the potential for tissue preservation.

The transition of penumbra into infarction is caused by a number of pathologic events, such as excitotoxicity, oxidative stress, inflammation, and apoptosis. Delays in reperfusion cause irreversible harm because the penumbra eventually merges with the infarct core **(Heiss, 2011)**. In order to improve the chance of penumbral salvage, stroke systems of care place a high priority on prompt imaging, diagnosis, and treatment; early intervention is still crucial. Future research may look more closely at neuroprotective strategies that extend penumbral life in an attempt to enhance outcomes for individuals who are unable to receive reperfusion therapy immediately.

III. NEUROIMAGING MODALITIES IN THE DIAGNOSIS OF CEREBRAL ISCHEMIC STROKE

Cerebral ischemic stroke requires neuroimaging for diagnosis, treatment planning, and management, and data from multiple modalities complement each other. The first imaging modality employed in acute stroke cases is still computed tomography (CT) due to its accessibility and short acquisition time. According to **Wintermark et al. (2013)**, non-contrast CT (NCCT) can quickly rule out bleeding and detect early ischemia signs during the first three to six hours, such as loss of gray-white matter distinction or the hyperdense artery sign. CT angiography (CTA), which provides excellent vision of the intracranial and extracranial vasculature, can be used to identify large artery occlusions that may benefit from endovascular therapy **(Goyal et al., 2016)**. The distinction between the infarct core and the salvageable penumbra can be made using CT perfusion (CTP) imaging, which maps cerebral blood flow (CBF), blood volume (CBV), and mean transit time (MTT) **(Campbell et al., 2012)**.Magnetic resonance imaging (MRI) has a higher sensitivity for acute ischemia, particularly when paired with diffusion-weighted imaging (DWI), which can detect cytotoxic edema just minutes after a stroke **(Lövblad et al., 2004)**. While the apparent diffusion coefficient (ADC) map displays restricted diffusion, perfusion-weighted imaging (PWI) displays the hemodynamic state of brain tissue. Particularly over extended periods, the DWI-PWI mismatch concept has changed patient selection for reperfusion therapy **(Albers et al., 2018)**. Microbleeds that may influence treatment decisions can be detected by susceptibility-weighted imaging (SWI), and the cerebral vasculature can be evaluated non- invasively using magnetic resonance

angiography (MR angiography). Although PET is not commonly used in the treatment of acute stroke, it provides unique metabolic information through tracers such 18F-fluorodeoxyglucose (FDG) and 15O-water. PET can evaluate oxygen metabolism and cerebral blood flow, revealing areas of poor perfusion and perhaps recoverable tissue **(Heiss et al., 2001)**. The pathophysiology of stroke can be better understood because to new hybrid imaging technologies like PET-MRI, which allow for the simultaneous assessment of metabolism, perfusion, and tissue viability **(Sobesky et al., 2005)**. PET's limited availability and longer acquisition time, however, limit its application to research settings.

IV. CURRENT THERAPEUTIC STRATEGIES

The current techniques to treating cerebral ischemic stroke focus on neuroprotection and rapid reperfusion to minimize brain damage. Although recombinant tissue plasminogen activator (rtPA)-assisted intravenous thrombolysis remains the cornerstone of acute treatment, its use is limited by the risk of bleeding and its brief half-life **(Powers et al., 2019)**. It begins to function within 4.5 hours of the beginning of symptoms. Large arterial occlusions can now be treated with mechanical thrombectomy, which significantly improves outcomes when performed within 6 to 24 hours. This is especially true when combined with state-of-the-art imaging to identify tissue that can be saved **(Nogueira et al., 2018)**. In order to reduce brain damage, current treatments for cerebral ischemic stroke include neuroprotection and quick reperfusion. The mainstay of acute treatment is recombinant tissue plasminogen activator (rtPA)-assisted intravenous thrombolysis; however, its use is restricted by its short half-life and bleeding risk **(Powers et al., 2019)**. Four and a half hours after the onset of symptoms, it starts to work. Nowadays, mechanical thrombectomy, which can be finished in 6 to 24 hours, is an effective treatment for large artery occlusions. When paired with cutting-edge imaging to pinpoint tissue that can be preserved, this is particularly true **(Nogueira et al., 2018)**.

4.1 EMERGING THERAPIES FOR CEREBRAL ISCHEMIC STROKE: NOVEL APPROACHES BEYOND REPERFUSION

Treatment for cerebral ischemic stroke is developing quickly as a result of a number of cutting-edge therapeutic medicines that prioritize precision medicine, neuroprotection, and neuroregeneration. Stem cell therapy has shown considerable promise in preclinical and early clinical studies because different cell types, such as neural stem cells (NSCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs), can enhance immunomodulation, neurogenesis, and angiogenesis. These cells work via tissue repair, paracrine signaling, and mitochondrial transfer. Research is being done to optimize the timing and mode of delivery (intravenous, intra-arterial, or intracerebral) in order to enhance therapeutic efficacy **(Savitz et.al., 2019)**. Drugs that target the mitochondria are another innovative approach to addressing the critical role that mitochondrial dysfunction plays in ischemia injury. Compounds that restore bioenergetics, reduce oxidative stress, and inhibit apoptosis, such as SS-31, a mitochondrial-targeted peptide, and urolithin A, a mitophagy enhancer, offer neuroprotection beyond the acute phase **(Sims et.al.,2020)**. Nanomedicine has created new opportunities for drug delivery by employing prepared nanoparticles to enhance the bioavailability of neuroprotective medications, encourage blood-brain barrier (BBB) penetration, and facilitate targeted therapy. For instance, lipid-based and polymeric nanoparticles loaded with compounds such as citicoline or anti-inflammatory drugs have shown improved efficacy in preclinical stroke models **(Teleanu et.al.,2022)**. Furthermore, as highly targeted interventions, gene and RNA - based therapies are being investigated. CRISPR-Cas9 gene editing and RNA interference (RNAi) approaches target detrimental pathways such the generation of pro-inflammatory cytokines. The potential of microRNA (miRNA) regulators to influence post-stroke recovery processes, including as synaptic plasticity and axonal regeneration, is also being studied **(Khoshnam et.al., 2017)**. These treatments, which address

both acute injury and long-term functional recovery, constitute a revolutionary move toward individualized stroke treatment, even if they are still primarily in the experimental stage.

V. CHALLENGES AND FUTURE PERSPECTIVES

With ongoing translational gaps in stroke research impeding the creation of efficient treatments, cerebral ischaemic stroke continues to be a major worldwide health concern. Numerous neuroprotective drugs have failed in clinical trials despite encouraging preclinical results because of variations in animal models and human pathophysiology, underscoring the need for better bench-to-bedside approaches **(Fisher and Savitz,2022)**. Advanced neuroimaging, proteomics, and genomes are examples of personalized medical tools that offer hope for tailored therapies by accounting for individual differences in stroke risk, development, and response to treatment **(Bonkhoff and Grefkes,2022)**. But they need to overcome obstacles like prohibitive costs, ethical quandaries, and the challenge of integrating multi-omic data if they are to realize their full potential. Early diagnostic and prevention strategies, such as wearable technologies, biomarker identification, and AI-driven risk prediction models, are becoming crucial tools for reducing the burden of stroke **(Bhasin et.al.,2011)**. Prospects for the future include enhanced public health programs focusing on modifiable risk factors and the creation of innovative neurorestorative therapies, such as brain-computer interfaces and stem cell-based regeneration **(Campbell and Khatri,2020)**. To close these gaps and revolutionize stroke care in the ensuing decades, cooperation between researchers, physicians, and legislators will be crucial.

VI. CONCLUSION

Worldwide, cerebral ischemic stroke continues to be a major cause of death and disability, and converting preclinical discoveries into successful clinical treatments is extremely difficult. Due to irreparable neuronal injury, many patients continue to experience long-term deficits even after advancements in reperfusion techniques like thrombolysis and thrombectomy. Novel therapeutic techniques, including as gene editing, mitochondrial-targeted medications, stem cell transplantation, and nanomedicine, present encouraging prospects for neuroprotection and recovery. Nevertheless, closing translational gaps, enhancing early detection, and boosting tailored therapy continue to be significant obstacles. To increase treatment windows and better functional outcomes, future advancements will rely on interdisciplinary cooperation, improved neuroimaging methods, and AI-driven precision medicine. The next ten years may see revolutionary developments in stroke care by tackling these issues, which would lessen the disease's worldwide burden and enhance patient recovery.

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