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Review Article

Understanding the Diverse Mechanisms of Stroke: Excitotoxiicty, Cell Death, and Inflammation

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Abstract :Stroke remains one of the most challenging neurological conditions worldwide, contributing heavily to mortality, disability, and long-term medical costs. Although advances in imaging, early detection, and reperfusion therapy have improved acute outcomes, there is still a striking lack of effective neuroprotective treatments. This review outlines the primary biological processes associated with ischemic injury—excitotoxicity, apoptosis, necrosis/necroptosis, altered autophagy, and post-ischemic inflammation—and describes how these mechanisms interact over time. Their interdependence affects the evolution of tissue damage and ultimately shapes recovery. A clearer understanding of how these pathways intersect may help identify new therapeutic targets. Current treatments focus almost entirely on getting blood flowing again, but they offer limited efficacy in sustaining neuronal viability or facilitating long-term functional recovery. We need a shift toward multimodal protection, immune modulation, and therapies that actually account for the specific type of clot and the patient's own biology.

Keywords : Excitotoxicity, Apoptosis, Necroptosis, Autophagy, Inflammation

INTRODUCTION

Stroke results from an interruption of cerebral blood flow, most often caused by vascular occlusion or hemorrhage. When oxygen and nutrient delivery abruptly decline, neurons rapidly lose metabolic stability and begin to die. The initial insult can also evolve into long-term problems such as cognitive impairment and mood disorders [1].

The Global Burden of Disease Study shows how much this problem is growing. In 2017 alone, there were 24.1 million new cases. Stroke isn't just a number; it accounts for 15.7 million disability-adjusted life years and roughly 700,000 deaths—figures that keep climbing. While older

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adults are hit hardest, we're seeing more cases in younger people, too. The economic impact is also substantial: Europe spends €1.3 billion on informal care, €27 billion on direct medical costs, and €12 billion on productivity loss. In the United States, indirect costs account for 66% of the $103.5 billion stroke-related economic burden. These findings highlight the need for improved disease-burden data to guide healthcare planning [2].

Advances in experimental modeling have reshaped approaches to stroke therapy, especially as many clinical trials have failed to deliver effective neuroprotective agents. Despite improvements in acute care, the long-term consequences of stroke continue to affect patients, caregivers, and healthcare systems. Strengthened translational and clinical frameworks may help accelerate progress in treatment and rehabilitation [3]. Even with better prevention, rapid diagnosis, and specialized stroke units—each associated with reduced mortality—current treatment options remain limited. Additional research is required to clarify pathogenic mechanisms and support the development of newer therapies [4].

For ischemic stroke specifically, early strategies include intravenous tissue plasminogen activator(tPA). To be effective, tPA must be administered within three hours of symptom onset to break down clots and restore cerebral blood flow [5]. Yet, even with successful recanalization, therapies that promote neurogenesis or enhance long-term recovery remain limited [6].

BODY

Ischemic stroke injury involves a non-linear, integrated cascade of multiple signaling pathways. It starts with excitotoxicity—excessive glutamate and a massive spike in intracellular Ca^{2+}. This calcium induces irreversible mitochondrial membrane depolarization. When mitochondria fail, they not only cease energy production but also trigger caspase-3 for apoptosis and engage the RIPK1/3 and MLKL axis for necroptosis. At the same time, the cell tries to save itself through autophagy, but this often backfires, worsening the damage instead of fixing it. The whole process is further inflamed by the NLRP3 inflammasome and HMGB1 release. These pathways aren't static—they evolve from the acute to the chronic phase, constantly feeding back into each other.

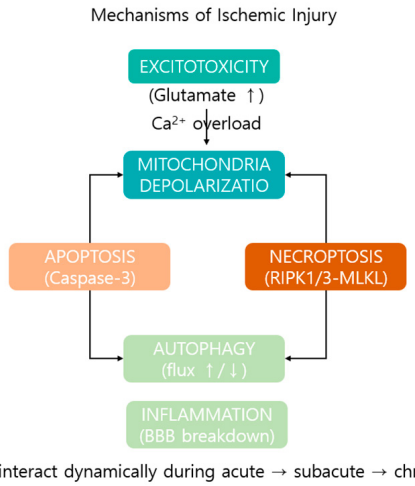

Fig. 1. Mechanisms of ischemic injury and interconnected cell death pathways.

As depicted in Fig. 1, the pathophysiology of ischemic injury is not a simple linear sequence, but rather a dense network of overlapping mechanisms. Excitotoxicity, profound mitochondrial dysfunction, and several variants of regulated cell death evolve and interact concurrently. Early calcium overload caused by excitotoxicity disrupts mitochondrial function and helps initiate downstream cell death pathways, including apoptosis and necroptosis. As mitochondrial damage progresses, it contributes to oxidative stress and enhances inflammatory signaling, while also affecting autophagic activity. Disrupted autophagic flux, in turn, can further aggravate mitochondrial dysfunction, creating a cycle that accelerates neuronal injury. Inflammatory responses, particularly those involving microglial activation and inflammasome pathways, further interact with these mechanisms and contribute to the progression of tissue damage [7].

1. Mechanism 1: excitotoxicity

Glutamate is the brain's main excitatory signal and in a stroke plays a pivotal role in early ischemic injury. During ischemia, glutamate accumulates extracellularly and becomes toxic—a process known as excitotoxicity [8]. Among glutamate receptors, NMDA receptors(NMDARs) are especially important because they allow excessive calcium influx.

NMDAR function varies depending on subunit composition. The "NMDAR subtype hypothesis" proposes that

GluN2A-containing receptors promote neuronal survival, whereas GluN2B-containing receptors contribute to cell death. Synaptic NMDARs typically activate survival pathways, while extrasynaptic receptors promote harmful signaling. However, newer data indicate that both receptor groups can participate in cell death under pathological conditions [8].

NMDARs influence pathways such as PI3K-Akt, ERK, and CREB-dependent transcription [9]. During acute ischemia, receptor activity changes rapidly—initial overactivation is followed by a prolonged suppression phase [10]. Later reductions may help minimize secondary injury and support neurogenesis. These observations suggest that therapeutic strategies must adjust NMDAR signaling with careful timing, reducing harmful activation without entirely blocking beneficial pathways [11].

2. Mechanism 2: apoptosis

Neurons use mitochondria to buffer intracellular calcium but ischemia causes calcium overload, mitochondrial depolarization, and dysfunction. Damaged mitochondria release cytochrome c through the mitochondrial permeability transition pore, triggering a caspase cascade that culminates in DNA fragmentation. Because apoptosis requires energy, it is more prominent in the penumbra, where limited metabolism is still present [12].

Bcl-2 family proteins fine-tune mitochondrial apoptosis by regulating cytochrome c release. Once pro-apoptotic proteins become activated, downstream caspases—particularly caspase-3—execute the cell-death program by cleaving structural and regulatory proteins [13]. Targeting multiple points along this pathway may offer better neuroprotection than inhibiting a single component [14].

3. Mechanism 3: necrosis and necroptosis

Necrosis was once viewed solely as uncontrolled cell death, but regulated forms such as necroptosis are now recognized. Necroptosis relies on RIPK1, RIPK3, and the effector MLKL and typically occurs when caspase-8 is impaired [15,16].

In ischemic tissue, cells may exhibit mixed features of apoptosis and necrosis. For example, lysosomal rupture is consistent with necrosis, while caspase-3 activation and cytochrome c release suggest apoptosis [17]. Because these pathways overlap, therapies targeting only one may not be sufficient. Coordinated modulation of RIPK signaling alongside apoptotic mechanisms may provide broader protection [18].

Table 1. Comparison of necrosis and necroptosis in ischemic injury

Feature	Necrosis	Necroptosis
Regulation	Uncontrolled	Regulated (RIPK1/RIPK3/MLKL)
Tigger	Severe energy loss	Caspase-8 inhibition
Morphology	Swelling, rupture	Swelling, regulated rupture
Relevance in stroke	Core region dominant	Renumbra & mixed injury

Necrosis is characterized by rapid ATP depletion, loss of plasma membrane integrity, and passive organelle swelling in the ischemic core. In contrast, necroptosis is a programmed process occurring primarily in the penumbra, mediated by specific genetic signaling under conditions of partial energy preservation (Table 1).

4. Mechanism 4: autophagy

Autophagy removes damaged cellular components via lysosomal degradation. During ischemia, autophagy can be either protective or harmful depending on its extent and timing. Excessive activation may worsen injury, while moderate activation may support cell survival [19].

Studies in ischemic and hemorrhagic models show variable autophagic responses. Autophagy is generally protective when flux remains intact but harmful when dysregulated. Additionally, ischemia-induced excitotoxicity can disrupt autophagic flow [17,20].

For this reason, therapies should aim to restore normal autophagic flux rather than uniformly inhibiting or enhancing the process [19,21].

5. Mechanism 5: inflammation

Inflammation is another major contributor to ischemic injury. Following stroke, glial activation, immune-cell infiltration, and release of damage-associated signals shape the inflammatory environment [22].

BBB disruption allows leukocytes and T cells to enter the brain, where they clear debris but may also exacerbate inju-

ry, especially when reperfusion is delayed. These processes contribute to "no-reflow," in which microvascular perfusion remains impaired even after large vessels are reopened. Pericyte recruitment helps restore BBB integrity and moderate immune infiltration [23]. Therapeutic approaches that account for timing and cell specificity may better balance beneficial and harmful inflammatory responses [24].

Stroke pathology is a moving target. It starts with a total breakdown of ionic balance—a massive calcium surge that effectively shuts down the mitochondria. This immediate crisis then gives way to a more organized struggle in the penumbra, where apoptosis and necroptosis dictate who lives and dies. Autophagy plays dual roles in cell fate, depending on the metabolic stress. The focus shifts to chronic inflammation, which drives the final wave of tissue loss and remodeling. Because this landscape is constantly changing, "one-size-fits-all" neuroprotection just doesn't work; clinical success depends entirely on hitting the right mechanism at the right time [25,26].

CONCLUSION

This review outlined how excitotoxicity, apoptosis, necrosis/necroptosis, altered autophagy, and inflammation interact to shape ischemic injury and recovery. The complexity of this cascade highlights why current treatments focused mainly on reperfusion remain insufficient.

Despite extensive clinical testing, many neuroprotective agents—especially those targeting single mechanisms—have failed. The unsuccessful trials of the anti-inflammatory drug Natalizumab and the anti-excitotoxic drug NA-1 illustrate the limitations of one-dimensional therapies [27]. Natalizumab's failure suggests that reducing peripheral immune-cell infiltration without modulating microglial activity is inadequate. NA-1's results imply that preventing neuronal excitotoxicity alone, without addressing non-neuronal contributors, is similarly insufficient.

Improving reperfusion success rates in Acute Ischemic Stroke (AIS) is also crucial. Recent studies show that thrombus composition significantly influences outcomes. RBC-rich thrombi are associated with shorter procedure times, better recanalization, and greater tPA sensitivity, whereas fibrin-rich thrombi tend to resist both mechanical and pharmacological treatment.

The future progress in stroke care will depend on combining multimodal neuroprotection, immunomodulation, improved imaging, and treatment strategies tailored to clot characteristics and patient-specific factors [28]. Deeper insight into the underlying mechanisms may help pave the way for next-generation therapies that reduce tissue damage and support recovery.

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