

Review

Mechanisms Underlying Region-Specific Vulnerability and Resistance to Ischemia-Reperfusion Injury in the Central Nervous System

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Abstract

Selective neuronal vulnerability is a hallmark of ischemic injury in the central nervous system (CNS), yet the mechanisms underlying regional differences in neuronal survival and degeneration remain incompletely understood. Cerebral ischemia from ischemic stroke or cardiac arrest triggers a complex cascade of metabolic failure, excitotoxic signaling, oxidative stress, and neuroinflammatory responses that collectively determine neuronal fate. Notably, neuronal degeneration follows highly specific anatomical patterns rather than uniformly throughout the CNS. Classical experimental studies have shown that hippocampal cornu ammonis 1 (CA1) pyramidal neurons undergo delayed neuronal death after transient global ischemia, whereas neighboring CA3 neurons remain relatively resistant. Similar heterogeneity is observed in other regions, including the olfactory bulb and spinal cord, where mitral cells and dorsal horn neurons exhibit relative resistance to ischemic injury. Accumulating evidence indicates that selective vulnerability arises from the interplay of multiple molecular and cellular mechanisms, including excitotoxic glutamatergic signaling, mitochondrial dysfunction, oxidative stress, neurovascular unit dysfunction, and neuroinflammatory responses. In addition, structural and circuit-level determinants such as hippocampal connectivity and regional neurovascular organization further influence neuronal susceptibility to ischemic stress. This review integrates evidence from experimental and clinical studies to examine the mechanisms underlying neuronal vulnerability and resistance across the CNS. Particular emphasis is placed on the interplay between neuronal metabolism, glial responses, and neurovascular regulation in shaping regional injury patterns. Understanding these mechanisms may provide important insights for the development of mechanism-based neuroprotective strategies targeting selectively vulnerable neuronal populations.

Keywords: ischemia-reperfusion injury; reactive oxygen species; neuronal vulnerability; neuroprotection; hippocampus; astrocytes; blood–brain barrier; oxidative stress

1. Introduction

Ischemic injury of the central nervous system (CNS) represents a major cause of neurological morbidity and mortality worldwide. Cerebral ischemia, most commonly resulting from ischemic stroke or cardiac arrest, leads to severe disturbances in cerebral blood flow and energy metabolism that trigger a complex cascade of molecular and cellular injury [1,2]. Despite extensive research over several decades, effective neuroprotective strategies capable of consistently improving neurological outcomes remain limited, highlighting the need for a more comprehensive understanding of the mechanisms that determine neuronal injury and survival during ischemia-reperfusion (IR) injury [3]. One of the most characteristic features of ischemic CNS injury is the phenomenon of selective neuronal vulnerability, in which neuronal degeneration occurs in distinct regional and cellular patterns rather than uniformly throughout the

brain and spinal cord. Classical experimental studies have demonstrated that brief episodes of global cerebral ischemia produce delayed neuronal death selectively in hippocampal cornu ammonis 1 (CA1) pyramidal neurons, whereas neighboring CA3 neurons remain relatively preserved [4,5]. Similar patterns of selective vulnerability have been observed in other CNS regions, including the cerebral cortex and spinal cord, where certain neuronal populations exhibit pronounced susceptibility while others display relative resistance to ischemic stress [6,7].

Although selective neuronal vulnerability has long been recognized as a hallmark of ischemic brain injury, the mechanisms responsible for this regional heterogeneity remain incompletely understood. A growing body of evidence suggests that neuronal susceptibility to ischemia reflects the interaction of multiple molecular and cellular processes, including excitotoxic signaling, mitochondrial dysfunction, oxidative stress, neurovascular impair-



ment, and neuroinflammatory responses [8,9]. These processes operate within the framework of the neurovascular unit, which integrates neuronal activity with astrocytic regulation, vascular function, and metabolic homeostasis. Importantly, differences in synaptic organization, mitochondrial resilience, antioxidant defenses, and astrocyte–vascular interactions may contribute to the distinct vulnerability profiles observed across CNS regions. Recent advances in experimental stroke research have further highlighted the importance of examining ischemic injury within an integrated systems framework. Rather than representing isolated molecular events, ischemic injury arises from dynamic interactions among neurons, glial cells, vascular components, and systemic inflammatory responses [10]. In this context, selective neuronal vulnerability reflects not only intrinsic neuronal properties but also regional differences in neurovascular organization and glial activity. The major molecular and cellular pathways that interact to determine neuronal survival or degeneration during IR injury are summarized schematically in Fig. 1. Despite substantial progress in elucidating the molecular pathways involved in ischemic injury, several important gaps remain. First, our literature survey indicates that previous studies have focused primarily on vulnerable neuronal populations, whereas relatively less attention has been given to understanding why certain neurons exhibit resistance to ischemic injury. Second, most reviews have addressed either molecular mechanisms of ischemic injury or clinical aspects of stroke separately, without fully integrating cellular vulnerability with circuit-level organization and neurovascular interactions.

The present review aims to address these gaps by providing an integrated analysis of the mechanisms underlying neuronal vulnerability and resistance to IR injury across the central nervous system. In particular, this review emphasizes the interplay among synaptic activity, mitochondrial metabolism, oxidative stress, astrocyte–vascular interactions, and neuroinflammatory responses that collectively shape regional patterns of neuronal survival and degeneration. Furthermore, this review highlights the importance of structural and network-level determinants of ischemic vulnerability, including hippocampal circuit organization, differences between CA1 and CA3 neuronal populations, and the relative resistance of specific neuronal types such as olfactory bulb mitral cells and spinal dorsal horn neurons. By integrating molecular, cellular, and circuit-level perspectives, this review seeks to provide a mechanistic framework that explains how regional heterogeneity emerges in ischemic CNS injury. Finally, the review discusses how these mechanistic insights may inform the development of more effective mechanism-based therapeutic strategies. Increasing evidence suggests that successful neuroprotective approaches will likely require multi-target interventions addressing the complex interactions among neuronal, glial, and vascular components of the neurovascular unit.

Taken together, understanding why some neurons degenerate while others survive following ischemia represents a central challenge in stroke and neuroprotection research. Elucidating the mechanisms underlying selective neuronal vulnerability and resistance may therefore provide important insights for bridging the gap between experimental neuroscience and clinical therapy for ischemic CNS injury.

2. Literature Overview and Scope

This review is based on a structured narrative synthesis of the literature addressing the mechanisms underlying selective neuronal vulnerability and resistance to IR injury in the CNS. Relevant studies were identified from major biomedical databases, including PubMed, Web of Science, and Scopus, covering publications published between 1990 and 2026. Both classical studies that established the concept of selective neuronal vulnerability and more recent investigations examining molecular and neurovascular mechanisms of ischemic injury were considered. Earlier landmark studies published prior to 1990 were included when necessary to provide historical context.

The literature survey focused on studies addressing key mechanistic aspects of ischemic injury, including excitotoxicity, mitochondrial dysfunction, oxidative stress, neurovascular unit interactions, glial responses, and structural and circuit-level determinants of neuronal vulnerability. Particular emphasis was placed on experimental studies employing established models of cerebral and spinal cord ischemia, including global and focal ischemia paradigms, as well as studies providing mechanistically relevant clinical insights.

Additional relevant publications were identified through manual screening of reference lists from key articles to ensure comprehensive coverage of both foundational and emerging findings. Rather than applying rigid inclusion or exclusion criteria, studies were selected based on their relevance to the central themes of this review and their contribution to elucidating region-specific patterns of neuronal vulnerability and resistance.

Through this integrative approach, the present review synthesizes current knowledge on the molecular, cellular, and network-level determinants of neuronal vulnerability and resistance across different regions of the CNS. A schematic overview of the literature survey is presented in Fig. 2. All figures were prepared using Adobe Illustrator 22.1 (Adobe Systems Incorporated, San Jose, CA, USA).

3. Core Pathophysiological Cascades Shared Across CNS Regions

Ischemic injury throughout the CNS is driven by a series of conserved molecular and cellular events that occur largely irrespective of anatomical location. Whether occurring in the brain or spinal cord, interruption of blood flow rapidly disrupts energy metabolism, ionic homeostasis, redox balance, and neurovascular integrity.

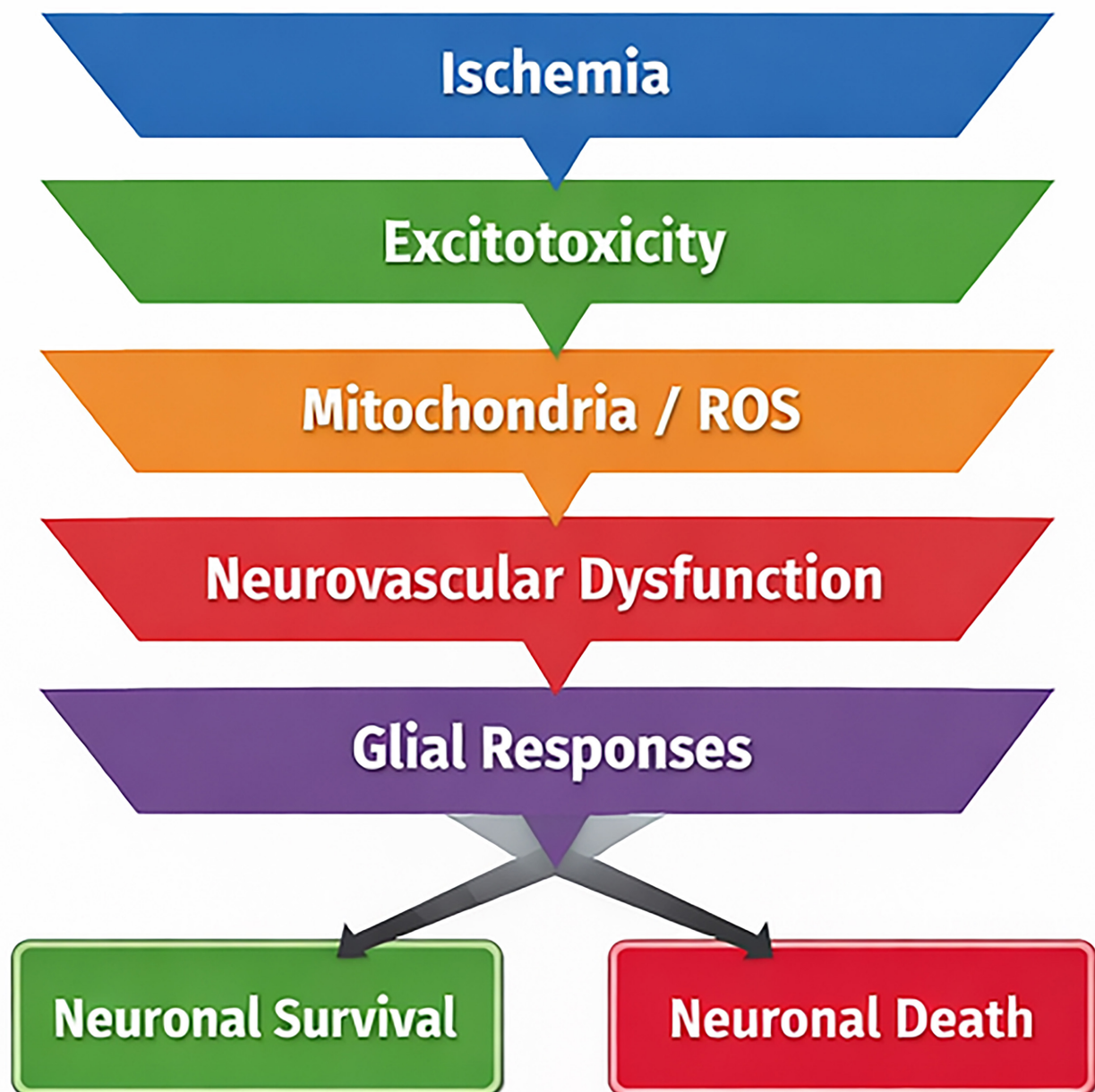


Fig. 1. Conceptual framework illustrating major mechanisms underlying selective neuronal vulnerability and resistance during ischemia-reperfusion injury. Cerebral ischemia initiates a cascade of interrelated pathological processes including excitotoxic signaling, mitochondrial dysfunction and ROS generation, neurovascular impairment, and glial responses. These mechanisms interact dynamically within the neurovascular unit and collectively influence neuronal survival or degeneration following ischemic injury. Regional differences in synaptic organization, mitochondrial resilience, antioxidant capacity, and astrocyte–vascular interactions contribute to the heterogeneous patterns of neuronal vulnerability observed across the central nervous system. ROS, reactive oxygen species.

These disturbances initiate a coordinated cascade of pathological processes—including excitotoxic signaling, mitochondrial dysfunction, oxidative stress, and inflammatory activation—that collectively characterize the ischemic response in CNS tissues [1,2,11]. This shared pathophysiological framework provides the basis upon which region-specific vulnerability or resistance subsequently emerges (Fig. 3).

Importantly, although many core features of IR injury—such as excitotoxicity, intracellular calcium overload, mitochondrial dysfunction, oxidative stress, and neuroinflammation—are consistently observed across different experimental models, the manifestation of neuronal vulnerability and resistance is influenced by the type of ischemia and experimental context. In global ischemia models, including four-vessel occlusion and two-vessel occlusion in gerbils, selective delayed neuronal death in the hip-

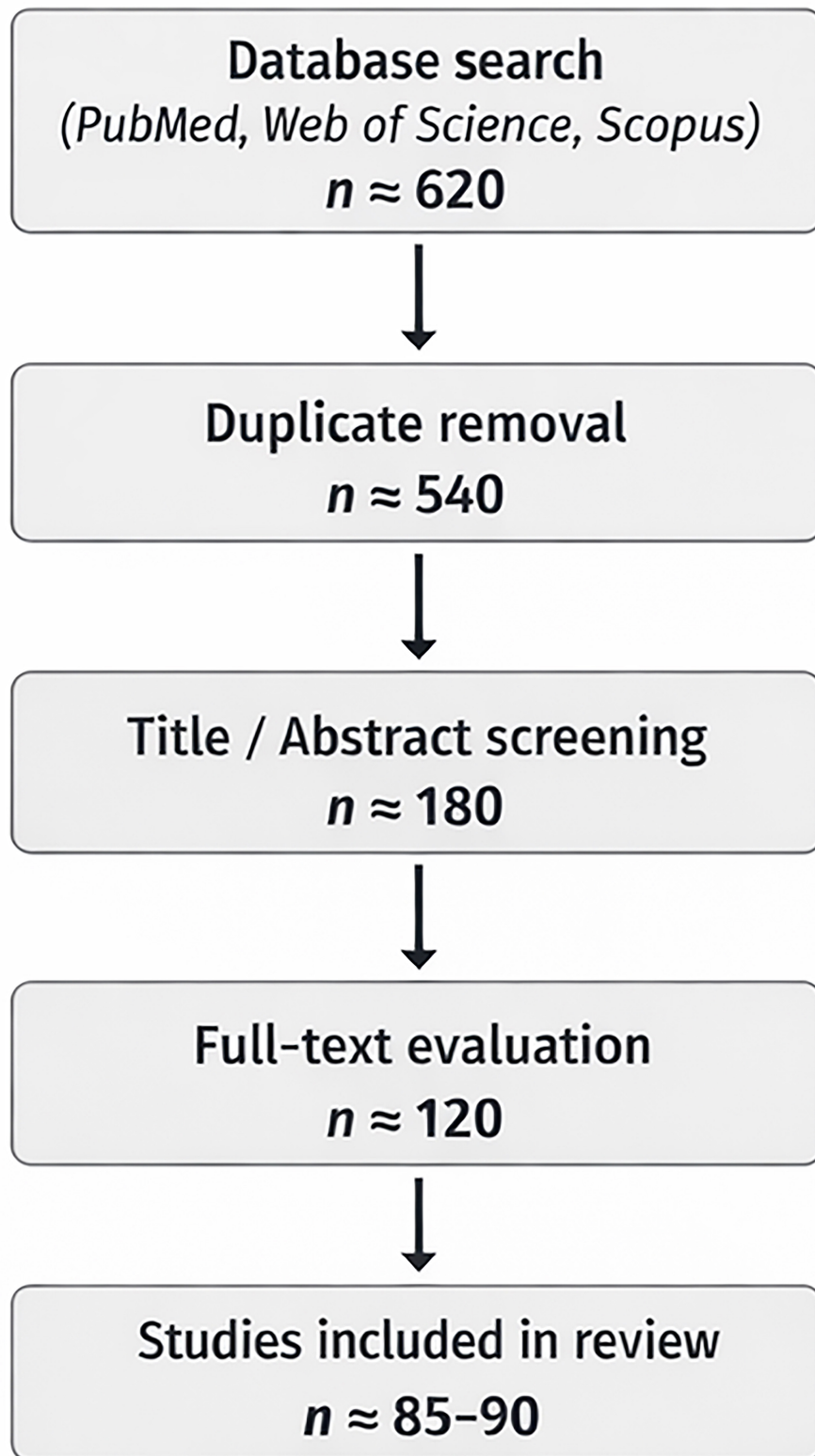


Fig. 2. Schematic overview of the literature survey and study selection process used in this review. Relevant publications were identified from major biomedical databases, including PubMed, Web of Science, and Scopus, covering studies published between 1990 and 2026. The retrieved records were screened to identify studies relevant to mechanisms of ischemia-reperfusion injury and selective neuronal vulnerability in the central nervous system. A subset of studies was selected for detailed evaluation based on their relevance to the key themes of this review. The final selection of studies provided experimental and clinical evidence regarding molecular, cellular, neurovascular, and circuit-level determinants of neuronal vulnerability and resistance to ischemic injury.

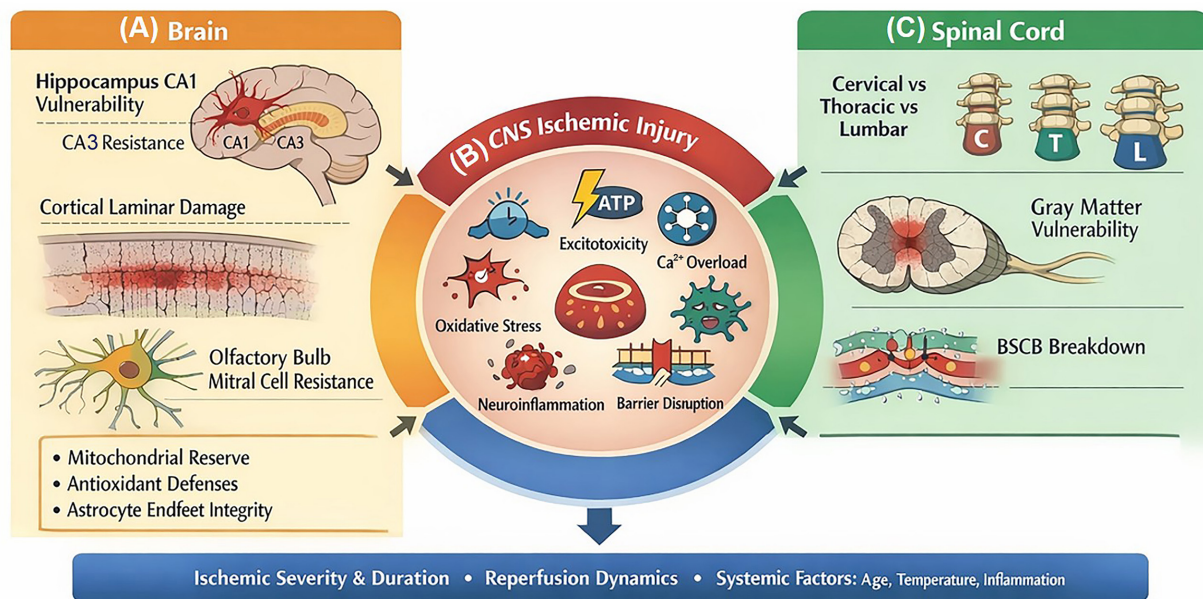


Fig. 3. Shared and region-specific pathophysiological cascades underlying ischemic injury across the central nervous system (CNS). (A) Brain-specific vulnerability patterns, including selective degeneration of hippocampal cornu ammonis 1 (CA1) neurons, cortical laminar injury, and relative resistance of olfactory bulb mitral cells. These differences reflect region-specific patterns of neuronal vulnerability associated with intrinsic cellular and microenvironmental properties. (B) Core shared mechanisms of CNS ischemic injury, including energy failure, excitotoxicity, intracellular calcium overload, oxidative stress, neuroinflammation, and blood–brain barrier disruption. These interconnected processes form a central hub linking region-specific responses to ischemic insults. (C) Spinal cord-specific vulnerability patterns, highlighting regional differences along the cervical, thoracic, and lumbar segments, as well as preferential vulnerability of gray matter and disruption of the blood–spinal cord barrier (BSCB). ATP, adenosine triphosphate.

pocampal CA1 region is a well-established hallmark [12]. In contrast, focal ischemia models such as middle cerebral artery occlusion (MCAO) produce regionally heterogeneous infarction patterns involving cortical and subcortical structures [13]. Furthermore, differences in species, vascular anatomy, ischemic duration, and reperfusion dynamics contribute to variability in the spatial distribution and severity of injury. These observations indicate that selective neuronal vulnerability reflects both conserved molecular mechanisms and model-dependent variations, highlighting the importance of interpreting experimental findings within the context of specific ischemia paradigms.

Notably, the extent and pattern of neuronal vulnerability are highly time-dependent, with ischemic duration and reperfusion dynamics critically influencing both the spatial distribution of injury and the relative contribution of underlying pathological mechanisms [14]. In focal ischemia models such as MCAO, shorter occlusion periods typically result in partially reversible injury with selective neuronal damage, whereas prolonged or permanent occlusion leads to more extensive infarction involving both cortical and subcortical regions. Moreover, the temporal progression of ischemic injury is characterized by an evolving sequence of pathological events, in which early excitotoxicity and calcium overload are followed by mitochondrial dysfunction, oxidative stress, and neuroinflammatory responses.

These temporal dynamics further modulate region-specific vulnerability and contribute to the heterogeneity of ischemic outcomes. Importantly, these mechanisms do not contribute equally to neuronal injury but instead form a hierarchical cascade. Excitotoxic glutamatergic signaling and the resulting intracellular Ca^{2+} overload represent primary initiating events, whereas mitochondrial dysfunction and oxidative stress act as major downstream amplifiers of cellular injury. Neuroinflammatory responses and barrier disruption further contribute as secondary processes that exacerbate and propagate tissue damage. This hierarchical organization provides a mechanistic framework for understanding how shared pathological processes give rise to region-specific patterns of neuronal vulnerability.

3.1 Energy Failure and Excitotoxicity

The earliest event following CNS ischemia is the rapid depletion of adenosine triphosphate (ATP) due to impaired oxidative phosphorylation. Energy failure compromises Na^+/K^+ -ATPase activity, leading to membrane depolarization and uncontrolled release of glutamate into the extracellular space [2]. Excessive activation of ionotropic glutamate receptors, particularly N-methyl-D-aspartate receptor (NMDA) receptors and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, results in sustained depolarization and a massive influx of Ca^{2+} and

Na⁺ into neurons. This process, commonly referred to as glutamate-mediated excitotoxicity, represents a fundamental mechanism of neuronal injury in ischemic conditions and has been demonstrated in both cerebral and spinal cord ischemia models [15,16]. Recent studies further demonstrate that ischemia-induced glutamate accumulation is amplified by impaired astrocytic glutamate uptake and dysfunction of excitatory amino acid transporters (EAATs), which normally maintain extracellular glutamate homeostasis [17,18]. Although excitotoxic signaling is broadly shared across CNS regions, its downstream consequences vary considerably among neuronal populations, depending on neuronal subtype, synaptic organization, and intrinsic buffering capacity [19,20]. Accordingly, the presence of excitotoxic signaling alone does not necessarily determine neuronal fate, as neurons in certain CNS regions can remain viable despite substantial glutamate exposure. These observations underscore the importance of downstream modulatory mechanisms that influence the severity and progression of ischemic injury [2,21].

3.2 Calcium Overload and Mitochondrial Dysfunction

Sustained Ca²⁺ influx during ischemia and early reperfusion acts as a critical link between excitotoxic signaling and irreversible cellular injury. Elevated intracellular Ca²⁺ disrupts mitochondrial membrane potential, impairs ATP synthesis, and promotes the opening of the mitochondrial permeability transition pore, ultimately triggering apoptotic or necrotic cell death pathways [20,22]. Mitochondrial Ca²⁺ overload also enhances the generation of reactive oxygen species (ROS), further amplifying cellular damage [23,24]. More recent investigations have highlighted the role of mitochondrial dynamics—including excessive mitochondrial fission and impaired mitophagy—in exacerbating neuronal vulnerability during IR injury [25,26]. Mitochondrial dysfunction represents a critical convergence point for multiple ischemic insults and is consistently observed across CNS regions [2,11]. Experimental evidence also indicates that neuronal populations differ substantially in mitochondrial reserve capacity and metabolic flexibility, factors that strongly influence susceptibility to ischemia-induced bioenergetic collapse [27,28]. Such differences in mitochondrial resilience are suggested to contribute to region-specific thresholds for irreversible neuronal injury during ischemia, based primarily on evidence from experimental models.

3.3 Oxidative and Nitrosative Stress

Reperfusion of ischemic CNS tissue is accompanied by a burst of oxidative and nitrosative stress resulting from mitochondrial dysfunction, activation of nicotinamide adenine dinucleotide phosphate oxidases, and uncoupling of nitric oxide synthase [23,24]. Excess ROS and reactive nitrogen species damage lipids, proteins, and nucleic acids, exacerbating neuronal and glial injury [29,30]. Ad-

ditional sources of ROS during reperfusion include xanthine oxidase activation, leakage from the mitochondrial electron transport chain, and inflammatory cell infiltration, all of which amplify oxidative damage within the ischemic penumbra [31,32]. Oxidative stress is a common pathological feature in both brain and spinal cord ischemia and is closely linked to mitochondrial failure and inflammatory signaling [2,11]. Despite the universality of oxidative stress, regional differences in endogenous antioxidant systems—such as superoxide dismutase, glutathione peroxidase, and catalase—critically influence the extent of oxidative damage [33,34]. Variability in antioxidant enzyme expression and redox buffering capacity across neuronal populations is thought to contribute to selective neuronal vulnerability in ischemic brain injury, although much of this evidence is derived primarily from experimental studies [33,35,36].

3.4 Neuroinflammation and Glial Activation

Ischemia rapidly activates resident glial cells, particularly microglia and astrocytes, thereby initiating a robust neuroinflammatory response. Microglial activation leads to the production of proinflammatory cytokines, chemokines, and additional ROS, while reactive astrocytes undergo morphological and functional changes that can be either protective or detrimental [37,38]. Recent studies have further identified diverse reactive astrocyte states, suggesting that astrocytic responses to ischemia are functionally heterogeneous and context-dependent [39,40]. In both brain and spinal cord ischemia, neuroinflammation contributes to secondary injury progression and delayed neuronal death [37,41,42]. Although inflammatory signaling pathways are largely conserved across CNS regions, the magnitude, temporal dynamics, and phenotypic characteristics of glial responses can differ substantially between anatomical regions [43,44]. Region-specific differences in microglial priming, astrocytic support functions, and neuron–glia interactions therefore are thought to play an important role in determining whether inflammatory responses exacerbate injury or support tissue repair [44,45].

3.5 Barrier Disruption and Secondary Injury

Disruption of the blood–brain barrier (BBB) in cerebral ischemia and the blood–spinal cord barrier (BSCB) in spinal cord ischemia represents another shared hallmark of CNS ischemic injury [46,47]. Barrier breakdown permits plasma protein extravasation, leukocyte infiltration, and edema formation, thereby intensifying inflammatory and oxidative damage [48,49]. Recent imaging and molecular studies have demonstrated that BBB disruption after IR follows a phased (often biphasic) time course, with an early, potentially reversible increase in permeability followed by a delayed phase associated with sustained barrier injury and inflammatory amplification [50,51,52]. While the BBB and BSCB share fundamental structural features,

regional differences in vascular density, tight junction composition, and astrocytic endfeet organization can influence the spatial and temporal patterns of barrier failure [53]. Importantly, barrier dysfunction is not merely a consequence of ischemic injury but also is thought to contribute actively to secondary injury mechanisms, including leukocyte infiltration, cytokine amplification, and oxidative stress propagation [47,54]. The extent and reversibility of barrier disruption are likely to significantly influence long-term neurological outcomes across CNS regions.

3.6 Shared Cascades as a Framework for Regional Divergence

Collectively, energy failure, excitotoxicity, Ca^{2+} overload, oxidative stress, neuroinflammation, and barrier disruption form a conserved pathological core that is common to CNS ischemia (Fig. 3). However, these cascades do not operate in isolation. Instead, their integration with region-specific cellular properties, metabolic reserves, and microenvironmental contexts is thought to determine whether neurons undergo delayed degeneration, rapid necrosis, or sustained survival. Consequently, understanding these shared mechanisms provides an essential framework for interpreting the regional variability of ischemic vulnerability as discussed in the following sections.

4. Region-Specific Vulnerability in the Brain

Selective neuronal vulnerability is one of the most reproducible yet conceptually challenging features of cerebral ischemia. Although ischemic cascades such as energy failure, excitotoxicity, oxidative stress, and inflammation are broadly shared across brain regions, neuronal survival varies markedly even within closely connected structures [2,4,21]. To illustrate this phenomenon, three representative brain regions were selected for comparison: the hippocampus, the cerebral cortex, and the olfactory bulb. These regions occupy distinct positions along the spectrum of ischemic susceptibility and therefore provide complementary models for examining mechanisms of neuronal vulnerability and resistance. The hippocampus provides the canonical model of selective neuronal vulnerability, particularly the well-characterized delayed neuronal death of CA1 pyramidal neurons [4,5]. The cerebral cortex exemplifies laminar and region-dependent injury patterns shaped by neurovascular architecture and metabolic demand [8,55]. In contrast, the olfactory bulb—specifically its mitral cells—has been shown to exhibit remarkable resistance to transient global ischemia and therefore serves as a model of intrinsic neuronal resilience [56,57]. Examining these regions together provides a framework for understanding how intrinsic neuronal properties, local circuitry, and microenvironmental factors interact to determine ischemic outcomes across different brain structures (Fig. 4). These region-specific differences can be more clearly understood within an integrated mechanistic framework. In

highly vulnerable regions such as the hippocampal CA1, strong excitatory synaptic input and limited calcium buffering capacity are thought to promote excessive Ca^{2+} influx, which may trigger mitochondrial dysfunction and subsequent oxidative stress amplification. In contrast, resistant neuronal populations such as mitral cells in the olfactory bulb are suggested to exhibit enhanced mitochondrial resilience, greater antioxidant capacity, and more effective astrocyte–vascular support, which may limit the propagation of downstream injury cascades, although much of the supporting evidence is derived from experimental models. Cortical neurons display intermediate vulnerability, reflecting a balance between intrinsic neuronal susceptibility and extrinsic factors such as vascular architecture and metabolic demand. Thus, selective neuronal vulnerability emerges not from isolated mechanisms but from the differential integration of shared injury pathways with region-specific cellular and microenvironmental properties.

4.1 Hippocampus: Canonical Selective Vulnerability of CA1 Pyramidal Neurons

The hippocampus represents the most extensively studied model of selective neuronal vulnerability following transient global ischemia. Within this structure, pyramidal neurons in the CA1 subfield undergo profound delayed neuronal death, whereas adjacent CA3 pyramidal neurons exhibit substantial resistance under comparable ischemic conditions [4,21]. This striking contrast was first described in gerbil models of forebrain ischemia and has since been confirmed across species and experimental paradigms [4,5,21]. Importantly, CA1 and CA3 neurons are exposed to similar reductions in cerebral blood flow during global ischemia, indicating that differential vulnerability cannot be attributed solely to perfusion deficits. Instead, CA1 neurons are characterized by exaggerated excitatory synaptic activity, impaired calcium buffering, and pronounced mitochondrial dysfunction during ischemia and early reperfusion [15,20]. For example, in rat models of focal cerebral ischemia and excitotoxic injury, disruption of NMDA receptor–postsynaptic density protein 95 (PSD95) signaling interactions markedly reduces ischemic neuronal death, highlighting the central role of glutamate-mediated excitotoxicity in neuronal vulnerability [15]. Likewise, biochemical and physiological study of isolated neuronal mitochondria and cultured neurons demonstrate that mitochondrial Ca^{2+} overload and impaired oxidative phosphorylation critically compromise neuronal survival during metabolic stress [20]. These processes promote sustained oxidative stress and activation of cell death pathways, which ultimately manifest as delayed neuronal degeneration rather than immediate necrosis [2,21]. Recent studies further indicate that mitochondrial bioenergetic failure, impaired antioxidant defenses, and altered synaptic metabolism are likely to collectively contribute to CA1 vulnerability during IR injury [31,33,35].

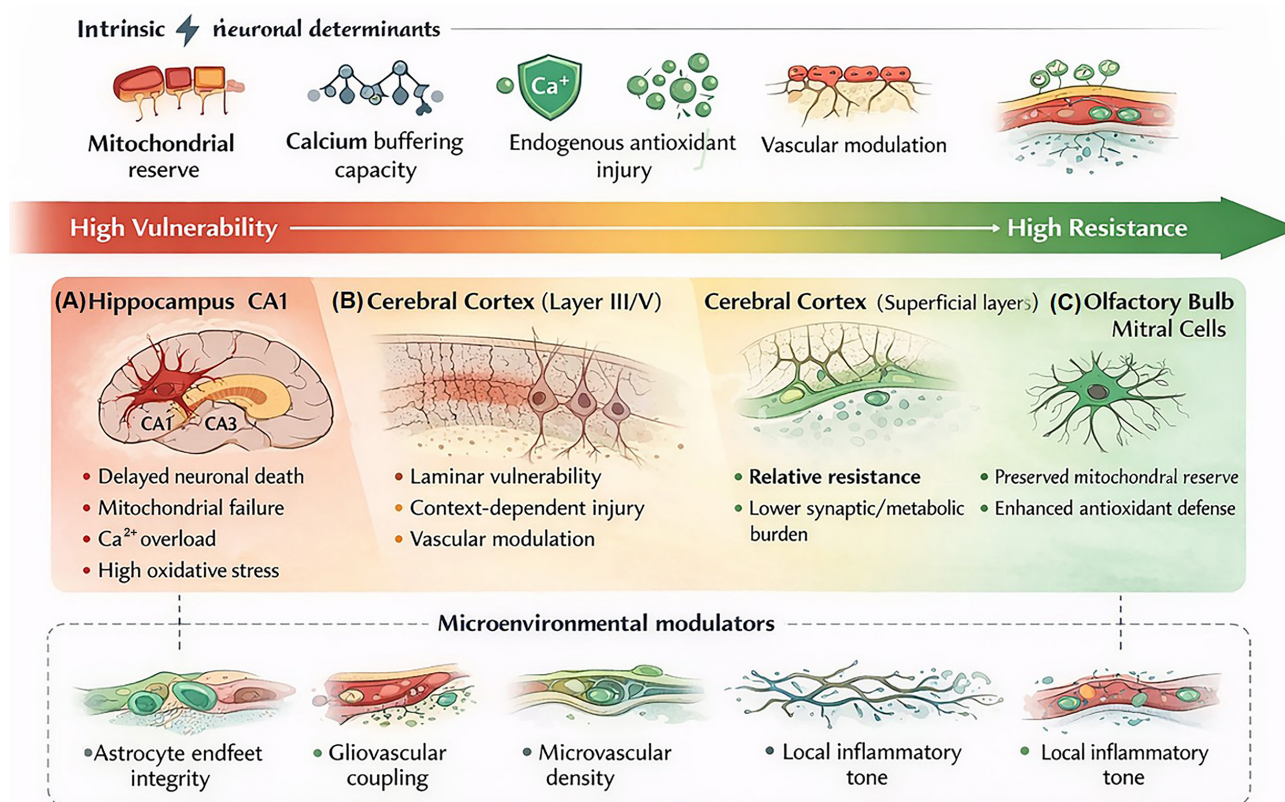


Fig. 4. Region-specific vulnerability–resistance spectrum in the ischemic brain. (A) Highly vulnerable neuronal populations, exemplified by hippocampal CA1 pyramidal neurons undergoing delayed neuronal death driven by mitochondrial dysfunction, calcium overload, and oxidative stress. (B) Intermediate, context-dependent vulnerability of cortical neurons, characterized by laminar susceptibility influenced by metabolic demand and microvascular architecture. (C) Intrinsic resistance of olfactory bulb mitral cells, thought to be supported by enhanced antioxidant capacity, metabolic flexibility, and preserved astrocytic support. These patterns illustrate that ischemic outcomes are determined by regionally encoded cellular and microenvironmental properties rather than uniform injury mechanisms.

In contrast, CA3 pyramidal neurons are suggested to exhibit greater tolerance to calcium overload and oxidative stress, supported by more robust mitochondrial reserve capacity and intrinsic antioxidant defenses [27,33]. Experimental studies using electrophysiological recordings and metabolic analyses in hippocampal slice preparations have shown that CA3 neurons maintain more stable mitochondrial membrane potential and ATP production during periods of intense synaptic activity, indicating a higher bioenergetic reserve compared with CA1 neurons [27]. In addition, biochemical and molecular analyses in rodent models of cerebral ischemia demonstrate that antioxidant defense systems—including superoxide dismutase and glutathione-related pathways—are more effectively maintained in resistant neuronal populations, thereby limiting oxidative damage [33]. Astrocytic support and preservation of gliovascular coupling are thought to contribute to CA3 resistance, although direct causal evidence remains limited [8,46]. Ultrastructural and imaging studies of the neurovascular unit have shown that astrocyte endfeet maintain close interactions with cerebral microvessels and regulate ion and

water homeostasis through channels such as aquaporin-4 (AQP4), thereby stabilizing the local microenvironment during metabolic stress [8,46].

Together, these observations illustrate how intrinsic neuronal metabolism and neuron–glia interactions jointly shape hippocampal vulnerability to ischemia.

4.2 Cerebral Cortex: Laminar and Region-Dependent Vulnerability

While the hippocampus highlights vulnerability at the level of discrete neuronal populations, ischemic injury in the cerebral cortex is characterized by laminar rather than uniform regional patterns. Cortical neurons exhibit layer-specific susceptibility, with pyramidal neurons in layers III and V being particularly vulnerable to ischemic insults [55,58]. These layers contain long-range projection neurons with high synaptic density and metabolic demand, rendering them especially sensitive to disruptions in energy supply and ionic homeostasis [27,59]. Physiological and metabolic studies combining electrophysiological recordings with energy consumption measurements in cortical

and hippocampal neurons have demonstrated that excitatory projection neurons exhibit exceptionally high ATP demand during synaptic transmission, reflecting the energetic cost of action potential generation and glutamatergic signaling [59]. In addition, analyses of mitochondrial function and neuronal activity in brain slice preparations indicate that neurons with sustained high firing rates require substantial mitochondrial ATP production to maintain ionic gradients and synaptic activity [27]. Recent experimental and imaging studies further have demonstrated that cortical vulnerability is strongly influenced by local microvascular architecture and neurovascular coupling mechanisms [1,8].

Beyond laminar organization, cortical vulnerability is further modulated by regional context. Experimental studies demonstrate that somatosensory and motor cortices can exhibit differential susceptibility, depending on ischemic duration, reperfusion dynamics, and systemic modifiers such as temperature [2,55]. Recent neurovascular imaging and experimental studies further indicate that regional cortical injury patterns are closely linked to heterogeneity in collateral circulation, capillary perfusion dynamics, and local metabolic demand across cortical territories [1,8,60]. Notably, such regional differences are often conditional rather than absolute, emphasizing that cortical vulnerability reflects a context-dependent interaction between neuronal phenotype and local vascular architecture. These findings highlight the importance of vascular architecture and neurovascular coupling in shaping cortical ischemic injury patterns.

Compared with the hippocampus, where intrinsic neuronal vulnerability dominates, cortical injury is more strongly influenced by microvascular topology and collateral circulation. Variations in penetrating arteriole density, capillary spacing, and astrocyte endfeet coverage are thought to shape the spatial distribution of ischemic damage [8,53]. High-resolution vascular imaging and anatomical mapping studies have shown that penetrating arterioles supply discrete cortical columns, and occlusion or reduced perfusion in these vessels can lead to columnar patterns of cortical ischemic injury, underscoring the importance of microvascular geometry in determining regional vulnerability [61,62]. Thus, cortical ischemia represents an intermediate model in which neuronal susceptibility is thought to emerge from the interaction between cellular metabolic demand and vascular supply constraints.

4.3 Olfactory Bulb: A Model of Intrinsic Ischemic Resistance

In marked contrast to the hippocampus and cerebral cortex, the olfactory bulb has been shown to exhibit a striking resistance to transient global ischemia. Mitral cells, the principal projection neurons of the olfactory bulb, survive ischemic durations that reliably induce delayed neuronal death in hippocampal CA1 neurons [4,21,56]. Experimental studies using gerbil models of transient forebrain

ischemia induced by bilateral common carotid artery occlusion have demonstrated that mitral cells remain morphologically and functionally preserved despite ischemic durations that produce extensive CA1 neuronal degeneration, as assessed by histological staining and immunohistochemical markers of neuronal survival [56]. This resistance has been consistently observed in gerbil models of forebrain ischemia, even under conditions of severe metabolic stress [56,57]. The survival of mitral cells is particularly noteworthy because these neurons are glutamatergic and highly active, features typically associated with ischemic vulnerability. Their resistance therefore underscores that survival is not simply a consequence of reduced excitatory signaling [15,58]. Experimental work using in vitro neuronal cultures and rodent ischemia models has shown that excessive glutamatergic signaling typically exacerbates Ca^{2+} influx and excitotoxic injury through NMDA receptor activation; therefore, the survival of glutamatergic mitral cells suggests the presence of intrinsic protective mechanisms rather than reduced excitatory drive [15]. Instead, mitral cells are thought to possess enhanced endogenous antioxidant capacity, more effective mitochondrial stress handling, and sustained astrocytic support during ischemia and reperfusion [57].

Experimental work has further suggested that intrinsic antioxidant systems and mitochondrial resilience are likely to contribute significantly to neuronal resistance to ischemic stress across brain regions [33,36]. Studies using rodent models of focal and global cerebral ischemia, together with biochemical analyses of postischemic brain tissue, have demonstrated increased oxidative damage markers and alterations in endogenous antioxidant enzymes such as superoxide dismutase and glutathione peroxidase [33]. Complementary clinical investigations in patients with ischemic stroke, employing blood-based measurements of oxidative stress biomarkers and antioxidant enzyme activity, further support the association between redox imbalance and neuronal injury severity [36].

Taken together, the olfactory bulb provides a useful experimental model for investigating mechanisms of intrinsic neuronal resistance to ischemic stress.

4.4 Integrative Perspective: Vulnerability and Resistance as Regionally Encoded Outcomes

Collectively, these three brain regions delineate a continuum of ischemic responses (Fig. 4). The hippocampus exemplifies neuron-intrinsic vulnerability, the cerebral cortex illustrates context-dependent laminar susceptibility shaped by vascular architecture, and the olfactory bulb has been shown to represent intrinsic resistance supported by metabolic and antioxidant resilience. This regional heterogeneity indicates that neuronal fate following ischemia is not determined solely by the severity of the insult but is also influenced by region-specific cellular and microvascular properties. Regional differences in neuronal susceptibility and resis-

Table 1. Regional vulnerability and resistance of neuronal populations to ischemia across the CNS.

CNS region	Neuronal population	Vulnerability pattern	Representative experimental evidence	References
Hippocampus	CA1 pyramidal neurons	Highly vulnerable	Delayed neuronal death after transient global ischemia demonstrated in experimental models	[4,5,21]
Hippocampus	CA3 pyramidal neurons	Relatively resistant	Structural preservation following identical ischemic insults in global ischemia models	[4,5,21]
Cerebral cortex	Cortical pyramidal neurons	Moderately vulnerable	Selective cortical neuronal degeneration in focal and global ischemia models; laminar vulnerability influenced by metabolic demand and vascular architecture	[1,2,6,55,59,60,61,62]
Olfactory bulb	Mitral cells	Highly resistant	Preservation of mitral cell populations after global cerebral ischemia despite hippocampal degeneration	[56,57]
Spinal cord	Ventral horn motor neurons	Highly vulnerable	Early degeneration observed in experimental spinal cord ischemia models, particularly after aortic occlusion	[63,64,65,66,67]
Spinal cord	Dorsal horn neurons	Relatively resistant	Relative structural preservation following ischemic injury in spinal cord ischemia models	[64,65,68,69,70]

Abbreviations: CNS, central nervous system.

tance across the brain are summarized in Table 1 (Ref. [1,2,4,5,6,21,55,56,57,59,60,61,62,63,64,65,66,67,68,69,70]). Understanding how these diverse responses arise from common ischemic cascades provides a conceptual foundation for the subsequent comparison with spinal cord ischemia and for the development of region-tailored neuroprotective strategies. Together, these regional comparisons highlight that selective vulnerability in cerebral ischemia is thought to emerge from the interaction between neuronal metabolic demand, mitochondrial resilience, and local neurovascular architecture.

5. Region-Specific Vulnerability in the Spinal Cord

Spinal cord ischemia represents one of the most devastating complications of aortic disease and thoracoabdominal aortic surgery, often resulting in severe and irreversible neurological deficits such as paraplegia. Although selective neuronal vulnerability has been extensively investigated in the brain, ischemic injury in the spinal cord also demonstrates pronounced regional and cellular heterogeneity. Clinical and experimental studies indicate that disruption of segmental arterial supply—particularly during aortic pathology or surgical repair—can critically compromise spinal cord perfusion and thereby precipitate ischemic injury [63,71]. Recent epidemiological analyses indicate that spinal cord infarction represents approximately 0.3–1% of all strokes, yet it produces substantial long-term disability in affected patients [72]. Despite its relatively low incidence, the clinical impact of spinal cord ischemia is considerable because neurological recovery is often limited once extensive neuronal injury has occurred.

As in the brain, ischemic injury in the spinal cord reflects the interaction between metabolic demand, vascular architecture, and intrinsic neuronal properties. However, the spatial distribution of vulnerability differs substantially because of the distinctive vascular organization and longitudinal perfusion system of the spinal cord. Modern anatomical and imaging studies have highlighted the importance of the anterior spinal artery and its collateral network in maintaining spinal cord perfusion, and disruption of this vascular system frequently has been shown to produce ischemic injury within ventral spinal cord territories [63,71]. Experimental models of spinal cord ischemia—including transient occlusion of the thoracic or abdominal aorta in rabbits and rodents—have been widely used to investigate mechanisms of spinal ischemic injury and neuronal vulnerability [64,65,73]. These models consistently demonstrate that neuronal injury is most pronounced in the ventral horn of the lumbar spinal cord, where motor neurons exhibit high metabolic demand and limited tolerance to ischemia. These experimental observations are consistent with clinical patterns of spinal cord infarction, in which injury to the anterior spinal artery territory often results in preferential impairment of motor pathways. Therefore, similar to selective vulnerability observed in specific brain regions, spinal cord ischemia is thought to exhibit region-dependent patterns of neuronal injury. Understanding these patterns provides an important framework for interpreting mechanisms of spinal cord ischemia and for developing targeted neuroprotective strategies.

5.1 Ventral Horn Motor Neurons: Selective Vulnerability

Among spinal cord neurons, α -motor neurons in the ventral horn are particularly vulnerable to IR injury. Histopathological analyses of experimental spinal cord ischemia consistently demonstrate early degeneration of these neurons following transient interruption of spinal cord blood flow [64,65,66]. In these classic studies, transient spinal cord ischemia was induced in animal models—primarily rabbits and rodents—by temporary occlusion of the thoracic or abdominal aorta, followed by histological examination of lumbar spinal cord tissue using light microscopy and neuronal staining techniques to assess postischemic neuronal survival. More recent experimental studies using rodent and rabbit models of thoracic aortic occlusion combined with histological and behavioral analyses have confirmed that ventral horn motor neurons represent the primary neuronal population affected during spinal cord ischemia, with neuronal loss correlating strongly with the severity of postischemic motor deficits [63,67]. In experimental models of transient spinal cord ischemia produced by temporary aortic occlusion, selective loss of ventral horn motor neurons occurs within hours to days after reperfusion, leading to persistent motor deficits [63,67]. In these studies, spinal cord ischemia was typically induced in rodent or rabbit models through temporary thoracic or abdominal aortic cross-clamping, followed by neurological assessment of hindlimb motor function and histological examination of lumbar spinal cord tissue. These pathological changes include chromatolysis, mitochondrial swelling, and eventual neuronal degeneration, indicating severe metabolic disruption during ischemia [66]. Ultrastructural analyses using electron microscopy in rabbit and rat models of aortic cross-clamping have further demonstrated mitochondrial swelling, disruption of endoplasmic reticulum structure, and progressive cytoplasmic vacuolization in degenerating motor neurons of the lumbar spinal cord following IR [65,66]. Recent molecular investigations further have demonstrated that ischemia-induced excitotoxic signaling, mitochondrial dysfunction, and oxidative stress contribute to progressive motor neuron degeneration after reperfusion in experimental spinal cord ischemia models [67]. These findings derive primarily from rodent spinal cord injury or ischemia models in which molecular mechanisms were examined using immunohistochemistry, Western blotting, quantitative polymerase chain reaction (PCR), and assays of oxidative stress markers.

Mechanistically, the vulnerability of ventral horn neurons is thought to be associated with high excitatory synaptic input, extensive dendritic arborization, and elevated metabolic demand. Electrophysiological and metabolic studies indicate that spinal motor neurons require substantial ATP production to maintain membrane excitability and neuromuscular transmission, rendering them particularly sensitive to ischemia-induced energy failure [20,55]. These conclusions are supported by electrophysiological recordings

and metabolic analyses performed in neuronal cultures, spinal cord slices, and experimental animal models, demonstrating the high energetic demand associated with sustained neuronal firing and synaptic transmission. Recent molecular studies of spinal cord ischemia also have shown that motor neurons exhibit pronounced susceptibility to excitotoxic signaling, oxidative stress, and mitochondrial dysfunction, mechanisms that resemble those observed in vulnerable neuronal populations of the brain [67]. These mechanistic insights are derived primarily from experimental rodent models, combined with molecular and histological analyses of post-injury spinal cord tissue.

5.2 Dorsal Horn Neurons: Relative Resistance

In contrast to the pronounced vulnerability of ventral horn motor neurons, neurons in the dorsal horn of the spinal cord exhibit comparatively greater resistance to ischemic injury. Histological analyses in experimental models of spinal cord ischemia demonstrate that sensory interneurons often remain structurally preserved under conditions that produce substantial motor neuron loss [64,65]. In these experimental studies, spinal cord ischemia was induced in rabbit models by transient abdominal aortic occlusion, followed by neurological assessment and histopathological examination of spinal cord tissue using light microscopy to evaluate neuronal survival. Several factors are thought to contribute to this relative resistance. Dorsal horn neurons generally display lower metabolic demand and receive different patterns of synaptic input compared with motor neurons [27,59]. These findings are supported by electrophysiological recordings, metabolic analyses, and computational energy-budget studies of neuronal signaling performed in neuronal cultures, brain or spinal cord slice preparations, and experimental animal models. Moreover, differences in local microvascular organization are likely to influence oxygen and nutrient delivery during ischemia [63]. Anatomical and vascular imaging studies of spinal cord perfusion have demonstrated that variations in microvascular density and collateral circulation can influence the spatial distribution of ischemic injury within spinal cord tissue. Recent clinical imaging and systematic reviews of spontaneous spinal cord infarction further support the concept of regional vulnerability within the spinal cord, demonstrating that ventral gray matter and corticospinal tracts are more frequently affected than dorsal sensory pathways [68,69,70]. These conclusions are derived primarily from clinical studies in human patients, using magnetic resonance imaging (MRI), diffusion-weighted imaging, and systematic analysis of clinical and neuroradiological findings in spontaneous spinal cord infarction. These observations suggest that both vascular anatomy and neuronal metabolic characteristics are likely to contribute to the heterogeneous distribution of ischemic injury within the spinal cord.

5.3 Neurovascular Architecture and Vulnerability

The vascular organization of the spinal cord differs substantially from that of the brain and plays a critical role in determining ischemic injury patterns. The spinal cord is primarily supplied by the anterior spinal artery, which provides blood flow to the ventral two-thirds of the cord, including motor neuron-rich regions of the ventral horn [63]. These observations are supported by anatomical and surgical studies of human spinal cord vasculature, as well as experimental vascular mapping studies that examined segmental arterial contributions to spinal cord perfusion. Because the anterior spinal artery receives segmental input from radicular arteries—including the artery of Adamkiewicz—interruption of these vessels can lead to profound reductions in perfusion of the ventral spinal cord [63,71]. These observations are based primarily on clinical anatomical studies and radiological analyses of patients undergoing thoracoabdominal aortic surgery, in which angiographic and intraoperative vascular imaging have demonstrated the critical contribution of radicular arteries to anterior spinal cord perfusion. Clinical studies indicate that occlusion or hypoperfusion of this arterial network frequently produces anterior spinal artery syndrome, characterized by motor paralysis and loss of pain and temperature sensation due to ischemia of corticospinal and spinothalamic pathways [71]. Recent advances in MRI and spinal vascular imaging have improved the detection and characterization of spinal cord ischemia and revealed that the distribution of injury closely corresponds to the vascular territories of the spinal arterial network [70]. These findings are derived primarily from clinical imaging studies in human patients, including diffusion-weighted imaging and vascular imaging techniques that allow detailed visualization of spinal cord infarction patterns and vascular territories.

5.4 Integrative Perspective: Parallels and Distinctions Between Brain and Spinal Cord

Taken together, spinal cord ischemia demonstrates a pattern of selective neuronal vulnerability that parallels, but is not identical to, that observed in the brain. In both structures, neuronal survival is influenced by intrinsic metabolic properties, excitotoxic signaling, mitochondrial resilience, and oxidative stress. However, the spatial determinants of injury differ. In the brain, vulnerability often reflects cell-intrinsic susceptibility within complex cortical and hippocampal circuits, whereas in the spinal cord, vascular supply patterns are thought to exert a stronger influence on regional injury distribution. Recent clinical and experimental research has increasingly emphasized that disruption of spinal cord perfusion networks—particularly the anterior spinal artery and its collateral branches—is a major determinant of ischemic injury patterns [69,70]. Regional differences in neuronal susceptibility and resistance across the spinal cord are summarized in Table 1. Understanding these similarities and differences provides important in-

sights into the mechanisms underlying central nervous system ischemia and highlights the need for region-specific neuroprotective strategies.

6. Mechanisms Underlying Vulnerability and Resistance

Selective neuronal vulnerability in CNS ischemia arises from the interaction of multiple cellular and molecular mechanisms that determine neuronal fate following IR injury. Rather than reflecting a single pathological pathway, neuronal survival or degeneration results from the integrated effects of synaptic activity, mitochondrial function, oxidative stress, and vascular architecture within the neurovascular unit [8,60]. These mechanisms can be broadly organized into a functional hierarchy in which synaptic activity and excitotoxic signaling act as primary drivers of injury, mitochondrial dysfunction and oxidative stress serve as key amplification processes, and neuroinflammation and vascular dysfunction contribute to secondary injury progression. The relative contribution and interaction of these mechanisms vary across neuronal populations, thereby shaping region-specific vulnerability and resistance. These determinants operate across multiple cellular compartments and interact dynamically to shape regional patterns of neuronal vulnerability and resistance throughout the brain and spinal cord [1,2,3,6]. As illustrated in Fig. 5, these mechanisms are thought to be organized into a hierarchical and integrative framework in which primary drivers, downstream amplifiers, and secondary processes collectively determine neuronal vulnerability and resistance across the CNS. While certain neuronal populations, such as hippocampal CA1 pyramidal neurons, cortical neurons, and spinal motor neurons exhibit pronounced vulnerability to ischemia, other neurons—including CA3 pyramidal neurons, olfactory bulb mitral cells, and dorsal horn neurons—display greater resistance to ischemic stress. It should be noted that the level of evidence supporting these mechanisms varies, with some processes being directly demonstrated in experimental models, whereas others are inferred or remain hypothetical. These mechanistic insights have important implications for the development of neuroprotective strategies (see Section 7.2).

6.1 Synaptic Activity and Excitotoxic Signaling

Synaptic activity is a critical determinant of neuronal susceptibility to ischemic injury. Under physiological conditions, glutamatergic neurotransmission is tightly regulated by presynaptic release mechanisms and astrocytic uptake via EAATs [74,75]. During ischemia, however, depletion of ATP disrupts glutamate uptake and leads to excessive extracellular glutamate accumulation, resulting in overstimulation of NMDA and AMPA receptors [58]. Activation of these receptors triggers a large influx of Ca^{2+} into neurons, initiating excitotoxic cascades that activate proteases, phospholipases, and endonucleases, ultimately lead-

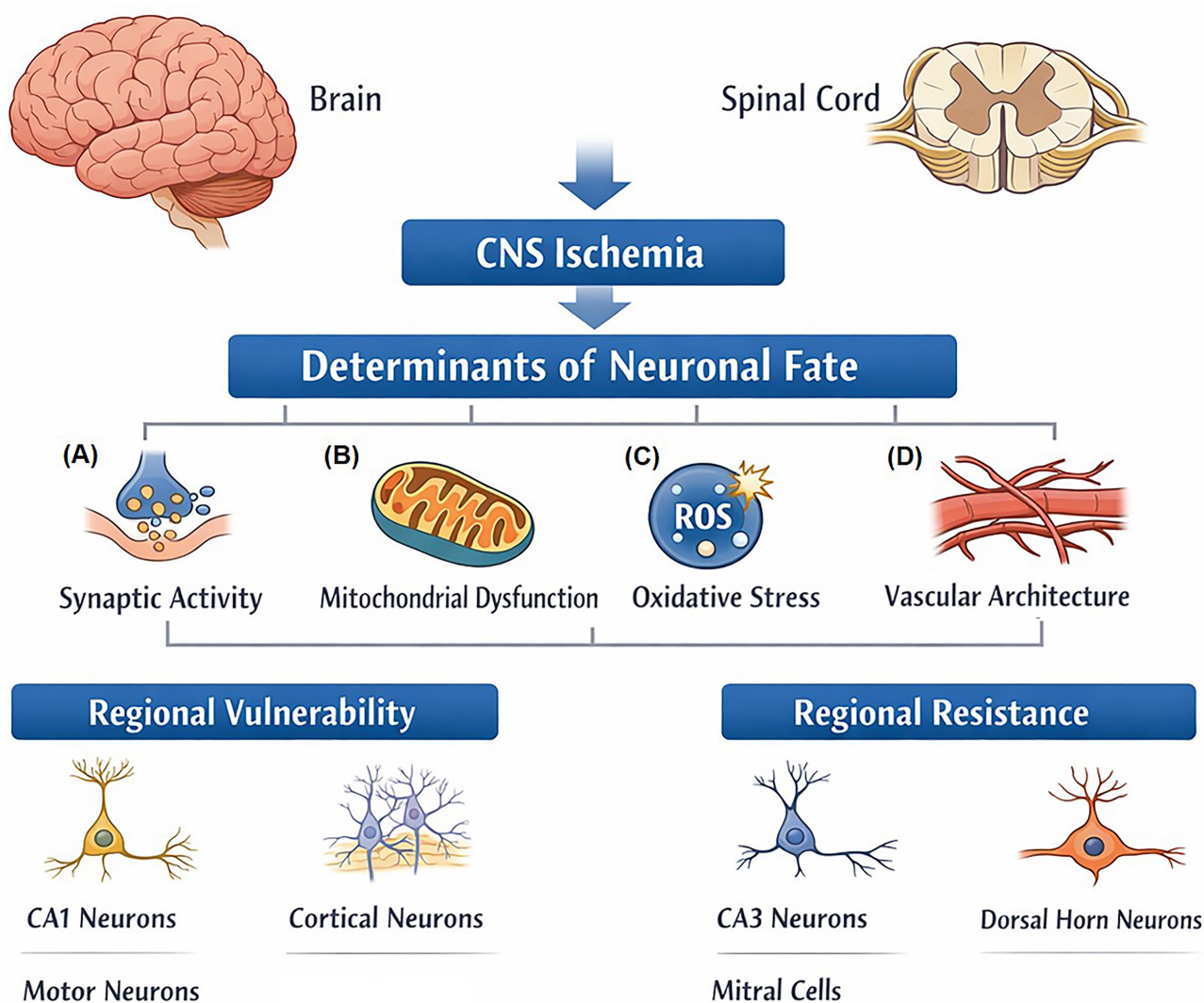


Fig. 5. Determinants of neuronal vulnerability and resistance in central nervous system (CNS) ischemia. Ischemia affecting the brain and spinal cord initiates a cascade of pathological processes that collectively determine neuronal fate. Key determinants include (A) synaptic activity and excitotoxic signaling, (B) mitochondrial dysfunction and metabolic failure, (C) oxidative stress resulting from excessive ROS production, and (D) vascular architecture and neurovascular unit integrity. These interacting mechanisms provide a mechanistic framework underlying region-specific neuronal vulnerability and resistance across the CNS. These processes result in selective vulnerability of certain neuronal populations—such as hippocampal CA1 neurons, cortical neurons, and spinal motor neurons—while other neurons, including hippocampal CA3 neurons, olfactory bulb mitral cells, and dorsal horn neurons, exhibit greater resistance to ischemic stress. ROS, reactive oxygen species.

ing to neuronal death [76,77]. Electrophysiological studies in rodent hippocampal preparations subjected to anoxic or ischemic conditions have demonstrated profound ionic disturbances, glutamate release, and neuronal depolarization during ischemic stress, providing experimental evidence for excitotoxic neuronal injury [78,79]. Regional differences in synaptic organization and cell-type-specific injury responses are thought to significantly influence vulnerability to excitotoxic damage [12]. For example, hippocampal CA1 neurons receive strong excitatory input from CA3 neurons through the Schaffer collateral pathway, which may amplify excitatory signaling during ischemia [80,81]. Thus,

excessive glutamatergic signaling and Ca^{2+} influx during ischemia are likely to disproportionately affect neurons with dense excitatory synaptic connectivity, thereby contributing to the well-known selective vulnerability of hippocampal CA1 pyramidal neurons.

6.2 Mitochondrial Dysfunction and Metabolic Failure

Mitochondria are central regulators of neuronal survival during ischemia. Because neurons rely heavily on oxidative phosphorylation for ATP production, interruptions in oxygen and glucose supply rapidly compromise energy metabolism. ATP depletion leads to failure of ion

pumps such as Na^+/K^+ -ATPase, resulting in membrane depolarization and intracellular ionic imbalance [2,8]. Excessive intracellular Ca^{2+} accumulation during ischemia and early reperfusion further disrupts mitochondrial function by impairing oxidative phosphorylation and inducing mitochondrial permeability transition. These processes promote the release of pro-apoptotic factors such as cytochrome c and trigger activation of programmed cell death pathways [82,83]. Transmission electron microscopy in rodent models of transient global cerebral ischemia reveals mitochondrial swelling, cristae disruption, and matrix vacuolization in vulnerable hippocampal neurons during the early reperfusion period [7]. Regional differences in mitochondrial resilience are thought to contribute significantly to selective neuronal vulnerability. Classic studies using experimental models of transient forebrain ischemia demonstrated that brief ischemic episodes induce delayed neuronal death selectively in hippocampal CA1 pyramidal neurons, whereas neighboring CA3 neurons remain relatively preserved [4,5]. Experimental studies of transient forebrain ischemia have consistently demonstrated delayed degeneration of CA1 pyramidal neurons several days after reperfusion, a hallmark of delayed neuronal death [4,5,84]. Recent studies combining mitochondrial respiration assays and biochemical analyses in rodent ischemia models have shown that impaired mitochondrial respiratory capacity and increased mitochondrial ROS production are closely associated with neuronal vulnerability following IR injury [85]. Mitochondrial dysfunction is closely linked to ROS generation during reperfusion, which is thought to further amplify neuronal injury and contributes to the selective vulnerability of hippocampal CA1 neurons.

6.3 Oxidative Stress and Antioxidant Defenses

Oxidative stress is a major contributor to neuronal injury following reperfusion [24,86]. Restoration of oxygen supply after ischemia promotes rapid production of ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals. These molecules damage cellular lipids, proteins, and nucleic acids, thereby exacerbating neuronal degeneration [24,85,87]. Multiple experimental approaches have demonstrated increased ROS production following cerebral ischemia. For example, biochemical assays measuring lipid peroxidation products such as malondialdehyde, combined with immunohistochemical detection of oxidative stress markers including 4-hydroxynonenal and 8-hydroxy-2'-deoxyguanosine in rodent models of transient global ischemia, reveal pronounced oxidative damage in vulnerable hippocampal CA1 neurons during the delayed phase of neuronal degeneration [24,86]. The brain is particularly susceptible to oxidative damage because of its high metabolic rate, abundant polyunsaturated fatty acids, and relatively limited antioxidant capacity. In addition, mitochondria represent a major source of ROS during reperfusion, as impaired electron transport chain function promotes

electron leakage and superoxide generation [85,87]. However, regional differences in antioxidant defense systems are thought to influence neuronal survival. Experimental studies using enzymatic assays and immunoblot analyses in rodent ischemia models demonstrate heterogeneous distribution of antioxidant enzymes across hippocampal subregions [86]. Comparative analyses measuring the activity of superoxide dismutase, catalase, and glutathione peroxidase in hippocampal tissue samples from ischemic rodents indicate lower antioxidant capacity in CA1 neurons relative to more resistant regions such as CA3 and the dentate gyrus, suggesting that reduced ROS detoxification may contribute to selective neuronal vulnerability [86,87]. Additional studies indicate that activation of endogenous antioxidant pathways, particularly the nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent transcriptional program, may limit oxidative injury following IR. Experimental activation of Nrf2 signaling in rodent stroke models increases expression of antioxidant enzymes and attenuates neuronal damage, highlighting the importance of endogenous redox defense mechanisms in determining neuronal survival [85,88]. Taken together, excessive ROS production combined with relatively limited antioxidant defenses is likely to predispose vulnerable neuronal populations—such as hippocampal CA1 pyramidal neurons—to oxidative injury following IR.

6.4 Vascular Architecture and Astrocyte–Vascular Interactions

The structural organization of the neurovascular unit represents another critical determinant of neuronal vulnerability. The neurovascular unit consists of neurons, astrocytes, endothelial cells, pericytes, and extracellular matrix components that collectively regulate cerebral blood flow, metabolic exchange, and BBB integrity [8,9]. Astrocytes play a particularly important role within this system. Astrocytic endfeet form extensive contacts with cerebral microvessels and regulate ion homeostasis, water balance, and metabolic coupling between neurons and blood vessels through mechanisms collectively referred to as neurovascular coupling [8,89,90]. Channels such as AQP4 and inwardly rectifying potassium channel Kir4.1 located in astrocytic endfeet contribute to potassium buffering and water transport [91]. Experimental studies using immunofluorescence labeling of AQP4 combined with confocal microscopy in rodent ischemia models demonstrate loss of polarized AQP4 distribution in astrocytic endfeet surrounding cerebral microvessels following IR injury [91,92]. Ultrastructural analyses using transmission electron microscopy in rodent models of global cerebral ischemia further reveal swelling and structural disorganization of astrocytic endfeet adjacent to cerebral capillaries, often accompanied by perivascular edema and BBB disruption in vulnerable brain regions [9,91]. Recent evidence further suggests that disruption of astrocyte–vascular interactions and loss of AQP4

polarization are likely to impair potassium and water homeostasis, thereby contributing to neuronal dysfunction during IR. Thus, disruption of astrocyte–vascular interactions within the neurovascular unit represents an important mechanism linking vascular dysfunction to neuronal vulnerability during IR injury, and may contribute to regional differences in neuronal susceptibility.

6.5 Neuroinflammation and Glial Responses

Neuroinflammation represents a major secondary component of IR injury and plays a critical role in determining neuronal survival or degeneration following cerebral ischemia. After ischemic injury, resident microglia are rapidly activated and release a variety of inflammatory mediators, including cytokines, chemokines, ROS, and nitric oxide, which are likely to amplify neuronal damage and contribute to secondary injury [37,93]. Evidence for microglial activation following ischemia has been demonstrated in both human and experimental studies. Experimental studies of cerebral ischemia have demonstrated pronounced microglial activation and morphological transformation in regions undergoing neuronal degeneration [93]. Similarly, postmortem analyses of human ischemic brain tissue demonstrate accumulation of activated microglia within infarcted and peri-infarct regions, supporting the clinical relevance of experimental findings [37]. Astrocytes also undergo significant functional changes following ischemia. Experimental studies using glial fibrillary acidic protein (GFAP) immunohistochemistry in rodent ischemia models demonstrate reactive astrogliosis characterized by astrocyte hypertrophy and increased GFAP expression in affected brain regions [94]. While astrocyte activation can contribute to inflammatory signaling, astrocytes also play protective roles by regulating extracellular ion homeostasis, limiting glutamate accumulation, and supporting metabolic recovery of neurons. Recent single-cell transcriptomic studies have demonstrated region- and cell-type-specific glial responses following ischemia, highlighting the heterogeneity of neuroinflammatory responses across different cellular and anatomical contexts [95]. Studies in experimental stroke models have revealed diverse microglial activation states with both detrimental and protective functions, highlighting the complexity of glial responses following ischemia [93]. Thus, the balance between pro-inflammatory and protective glial responses is likely to represent an important determinant of neuronal fate during IR injury and may contribute to regional differences in neuronal vulnerability across the central nervous system.

6.6 Structural and Network-Level Determinants

Beyond molecular and cellular mechanisms, the structural organization of neuronal circuits also plays an important role in determining regional vulnerability to ischemic injury. Differences in synaptic connectivity, excitatory–inhibitory balance, and intrinsic electrophysiological prop-

erties influence neuronal responses to metabolic stress and are thought to contribute to the heterogeneous patterns of neuronal degeneration observed following IR injury [6,80]. The hippocampus provides one of the most well-characterized examples of circuit-dependent vulnerability. Within the classical trisynaptic circuit, excitatory input from dentate gyrus granule cells is transmitted to CA3 pyramidal neurons via mossy fibers and subsequently relayed to CA1 pyramidal neurons through the Schaffer collateral pathway [80]. Neuroanatomical tracing studies and electrophysiological recordings in rodent hippocampal slice preparations demonstrate that CA1 neurons receive dense excitatory input from CA3 neurons, which may amplify glutamatergic signaling during ischemia. This circuit organization may partly explain the striking difference in vulnerability between hippocampal subregions. Experimental studies of transient forebrain ischemia consistently demonstrate delayed neuronal death in CA1 pyramidal neurons while neighboring CA3 neurons remain largely preserved [4,5]. These findings suggest that differences in synaptic architecture and excitatory drive contribute to regional susceptibility to excitotoxic injury. In contrast to the vulnerability of CA1 neurons, several neuronal populations in other brain regions exhibit remarkable resistance to ischemic injury. One notable example is the mitral cell population of the olfactory bulb. Experimental studies using rodent models of transient global cerebral ischemia combined with histological and immunohistochemical analyses demonstrate that olfactory bulb mitral cells remain largely preserved even when vulnerable hippocampal neurons undergo delayed degeneration, suggesting the presence of intrinsic protective mechanisms within this neuronal population. Similarly, neurons within the dorsal horn of the spinal cord display relatively high resistance to ischemic injury compared with motor neurons located in the ventral horn. Histopathological analyses in experimental spinal cord ischemia models have shown that ventral horn motor neurons undergo early degeneration whereas dorsal horn neurons often remain structurally preserved, indicating that differences in neuronal phenotype and network organization may influence susceptibility to ischemic stress. These observations indicate that structural and network-level determinants play an important role in shaping neuronal responses to ischemia. Differences in synaptic connectivity, neuronal phenotype, and circuit architecture are likely to interact with molecular mechanisms such as excitotoxicity, mitochondrial dysfunction, oxidative stress, and neurovascular alterations to determine whether neurons undergo degeneration or survive following IR injury. Thus, integration of cellular and circuit-level mechanisms helps explain the striking regional differences in vulnerability and resistance observed across the central nervous system, including the susceptibility of hippocampal CA1 neurons and the relative resilience of CA3 neurons, olfactory bulb mitral cells, and dorsal horn neurons.

Table 2. Major mechanisms underlying selective neuronal vulnerability and resistance during IR injury.

Mechanism	Cellular processes	Representative experimental evidence	Contribution to neuronal vulnerability	References
Excitotoxic signaling	Excess glutamate accumulation leading to NMDA and AMPA receptor activation and Ca ²⁺ influx	Electrophysiological recordings and calcium imaging in hippocampal slice oxygen–glucose deprivation models; ischemia-related glutamate transporter dysfunction	Promotes intracellular Ca ²⁺ overload, activation of proteases and endonucleases, and disproportionate injury in neurons with dense excitatory synaptic connectivity, particularly hippocampal CA1 pyramidal neurons	[15,16,17,18,19,58,74,75,76,77,78,79]
Mitochondrial dysfunction	ATP depletion, impaired oxidative phosphorylation, and mitochondrial permeability transition	Electron microscopy, mitochondrial physiology studies, and mitochondrial respiration assays in rodent ischemia models	Leads to bioenergetic failure, membrane depolarization, and activation of apoptotic and necrotic pathways; regional differences in mitochondrial resilience strongly influence neuronal survival	[20,22,25,26,27,28,82,83,84,85]
Oxidative stress	Reperfusion-induced generation of ROS and oxidative damage to lipids, proteins, and nucleic acids	Lipid peroxidation assays, oxidative stress marker analyses, and antioxidant pathway studies in experimental ischemia	Amplifies postischemic neuronal injury by damaging cellular macromolecules; neurons with lower endogenous antioxidant capacity, such as CA1 neurons, are especially susceptible	[23,24,29,30,31,32,33,34,35,36,85,86,87,88]
Neurovascular dysfunction	BBB disruption, astrocyte endfoot damage, impaired neurovascular coupling, and edema formation	Imaging and ultrastructural studies demonstrating barrier disruption, AQP4 redistribution, and vascular alterations	Reduces metabolic and ionic support to neurons, promotes edema and inflammatory infiltration, and worsens injury in regions with vulnerable gliovascular organization	[8,9,46,47,48,49,50,51,52,53,54,89,90,91,92,96]
Neuroinflammation	Activation of microglia and astrocytes with cytokine and chemokine release	Immunohistochemical detection of glial activation markers and transcriptomic analyses in experimental stroke models	Contributes to secondary injury through inflammatory amplification, oxidative stress, and cytokine-mediated toxicity, although context-dependent glial responses may also support repair	[37,38,39,41,42,43,44,45,93,94]
Network architecture	Differences in synaptic connectivity, excitatory drive, and circuit organization	Neuroanatomical tracing and electrophysiological studies of hippocampal circuits and regional neuronal organization	Determines region-specific excitatory burden and metabolic demand; circuit properties help explain why CA1 neurons are highly vulnerable whereas CA3, mitral, and dorsal horn neurons are relatively resistant	[6,21,27,55,56,57,59,66,68,80,81]

Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AQP4, aquaporin-4; ATP, adenosine triphosphate; BBB, blood–brain barrier; IR, ischemia-reperfusion; NMDA, N-methyl-D-aspartate receptor; ROS, reactive oxygen species.

Taken together, selective neuronal vulnerability emerges from the interaction of molecular, cellular, and circuit-level mechanisms. Variations in synaptic organization, mitochondrial resilience, antioxidant capacity, neurovascular coupling, and glial responses collectively determine whether neurons undergo degeneration or survive following IR injury. The principal molecular, cellular, and network-level mechanisms contributing to selective neuronal vulnerability and resistance during IR injury are summarized in Table 2 (Ref. [6,8,9,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,66,68,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,96]).

7. Therapeutic Implications, Limitations, and Future Perspectives

Understanding the mechanisms underlying selective neuronal vulnerability provides important insights into the development of therapeutic strategies for ischemic brain injury. Because neuronal degeneration following IR injury results from complex interactions among excitotoxicity, mitochondrial dysfunction, oxidative stress, neurovascular impairment, and neuroinflammation, effective therapeutic approaches are likely to require multi-target strategies rather than interventions directed at a single molecular pathway [2,3]. Experimental and clinical research has increasingly emphasized that ischemic brain injury should not be viewed solely as a neuron-centered disorder but rather as a complex neurovascular and systemic process involving interactions among neurons, astrocytes, endothelial cells, and immune responses. Accordingly, therapeutic strategies targeting the neurovascular unit and systemic inflammatory responses have emerged as promising approaches for improving translational success in stroke therapy [1,8,10].

7.1 Mechanism-Based Therapeutic Strategies

Mechanistic insights into ischemic brain injury have led to the investigation of several classes of neuroprotective strategies. One of the earliest approaches has been inhibition of excitotoxic signaling. Excessive glutamate release and activation of NMDA receptors contribute significantly to calcium overload and neuronal death during ischemia. Pharmacological NMDA receptor antagonists have demonstrated neuroprotective effects in experimental stroke models, although clinical translation has been limited due to adverse effects and narrow therapeutic windows [58,77]. Recent analyses suggest that excitotoxic signaling interacts closely with mitochondrial dysfunction and oxidative stress, indicating that therapies targeting glutamate toxicity alone may be insufficient without simultaneous modulation of downstream injury pathways [10].

Mitochondrial protection represents another promising therapeutic strategy. Because mitochondrial dysfunction plays a central role in ischemic neuronal injury, ap-

proaches aimed at stabilizing mitochondrial bioenergetics or preventing mitochondrial permeability transition have been shown to exert protective effects in experimental models [82,84]. Preservation of mitochondrial integrity is therefore likely to represent an important strategy for maintaining neuronal survival in selectively vulnerable brain regions.

Oxidative stress also represents a major therapeutic target. Antioxidant strategies aimed at scavenging ROS or enhancing endogenous antioxidant systems have been widely investigated in experimental stroke models. In particular, activation of the Nrf2 signaling pathway increases the expression of antioxidant enzymes and has been shown to reduce neuronal injury in experimental cerebral ischemia [86,87].

In addition to neuronal mechanisms, preservation of neurovascular unit integrity has emerged as an important therapeutic objective. Disruption of astrocyte–vascular interactions and BBB dysfunction contribute to secondary neuronal injury after ischemia. Therapeutic strategies aimed at stabilizing endothelial function and maintaining BBB integrity are therefore considered promising approaches for improving neurological outcomes [8,9]. Recent experimental studies further demonstrate that astrocytes actively participate in vascular repair and neurovascular remodeling following ischemic injury [90]. In addition, modulation of astrocytic AQP4 dynamics has been proposed as a potential therapeutic strategy for reducing cytotoxic edema and stabilizing astrocyte–vascular interactions during IR injury [92]. Further evidence suggests that astrocytic signaling mechanisms contribute directly to BBB regulation. A recent experimental study demonstrated that astrocytic Slc4a4 regulates BBB integrity through a C-C motif chemokine ligand 2/C-C motif chemokine receptor 2 signaling pathway and nitric oxide–dependent mechanisms, highlighting the importance of astrocyte–vascular communication in ischemic brain injury [96]. Consistent with these findings, recent reviews increasingly recognize astrocytes as promising therapeutic targets for stroke because they regulate glutamate clearance, ion homeostasis, neurovascular coupling, and post-ischemic tissue repair processes [97].

Combination neuroprotection strategies are also increasingly recognized as a promising approach for ischemic brain injury. Because multiple injury pathways—including excitotoxicity, oxidative stress, mitochondrial dysfunction, and inflammation—interact during IR injury, therapeutic approaches that simultaneously target several mechanisms are likely to be more effective than single-target interventions. Recent advances in nanoparticle-based drug delivery systems further support this concept by enabling simultaneous targeting of multiple ischemic injury pathways, including oxidative stress, excitotoxicity, and inflammatory signaling [98].

Another emerging strategy involves regenerative and cell-free therapies. Recent studies suggest that extracellular

vesicles derived from stem cells may promote neuronal survival and functional recovery following cerebral ischemia by reducing inflammation, stabilizing BBB integrity, and enhancing neurovascular remodeling [99].

7.2 Limitations and Future Directions in Neuroprotective Therapy

Despite decades of experimental research, successful translation of neuroprotective strategies into clinical stroke therapies has remained limited. Many agents that demonstrate robust efficacy in experimental models of cerebral ischemia have failed to show consistent benefits in clinical trials [2,3]. In particular, it is now widely recognized that strategies targeting single pathological mechanisms—such as excitotoxicity or oxidative stress—have not consistently achieved clinical efficacy, likely due to the complex and multifactorial nature of ischemic injury [100]. Although several region-specific vulnerability patterns have been observed in human ischemic brain tissue, detailed mechanistic validation in clinical settings remains limited.

Several factors contribute to this translational gap. First, experimental stroke models often differ substantially from human ischemic stroke in terms of age, comorbidities, and vascular risk factors. Most preclinical studies are conducted in young and otherwise healthy animals, whereas patients with ischemic stroke frequently present with advanced age and multiple systemic conditions such as hypertension, diabetes, and atherosclerosis [1]. Second, the temporal dynamics of ischemic injury impose significant therapeutic constraints. Many neuroprotective interventions are effective only when administered within a limited therapeutic window, whereas clinical treatment is often delayed due to diagnostic and logistical factors [3]. Recent studies further emphasize that different pathological mechanisms dominate at different stages of ischemic injury, suggesting that time-dependent therapeutic strategies aligned with the progression of stroke pathology may improve treatment efficacy [101]. Third, ischemic brain injury involves complex interactions among multiple molecular and cellular pathways, and the relative contribution of these mechanisms varies across neuronal populations and brain regions. The concept of selective neuronal vulnerability further implies that therapeutic responses are likely to differ depending on region-specific differences in metabolic demand, synaptic activity, and neurovascular organization. Consequently, interventions targeting a single molecular pathway are unlikely to achieve robust and consistent neuroprotection.

Future research should therefore emphasize integrative and multi-target therapeutic approaches that account for both the multifactorial and region-specific nature of ischemic brain injury. Promising strategies may include modulation of neurovascular unit function, enhancement of mitochondrial resilience and antioxidant capacity, and approaches aimed at strengthening intrinsic neuronal resistance mechanisms. In addition, advances in high-resolution

neuroimaging, single-cell transcriptomics, and multi-omics technologies are expected to provide deeper insights into the cellular determinants of neuronal survival and degeneration, thereby facilitating the development of precision neuroprotective strategies tailored to distinct neuronal populations.

8. Conclusions

Selective neuronal vulnerability represents a defining feature of ischemic injury in the CNS. Although ischemia affects the brain and spinal cord globally, neuronal degeneration occurs in distinct regional patterns. Neuronal populations such as hippocampal CA1 pyramidal neurons, cortical neurons, and spinal motor neurons exhibit marked susceptibility, whereas others—including CA3 pyramidal neurons, olfactory bulb mitral cells, and dorsal horn neurons—display relative resistance to ischemic stress. Accumulating evidence indicates that this regional heterogeneity arises from the interaction of multiple molecular and cellular mechanisms. Excitotoxic signaling, mitochondrial dysfunction, oxidative stress, neurovascular impairment, and neuroinflammatory responses interact within the neurovascular unit to determine neuronal fate during IR injury. In addition, differences in synaptic connectivity, mitochondrial resilience, antioxidant defenses, and astrocyte–vascular interactions are likely to shape regional vulnerability across the CNS. These insights have important therapeutic implications. Traditional neuroprotective strategies targeting single molecular pathways have not consistently demonstrated clinical efficacy, suggesting that effective therapies will likely require integrative approaches addressing multiple injury mechanisms. Preservation of neurovascular unit integrity, modulation of glial responses, stabilization of mitochondrial function, and regulation of oxidative stress are considered complementary therapeutic strategies. Despite substantial experimental progress, translation of neuroprotective therapies to clinical practice remains challenging due to differences between experimental models and human stroke as well as the complex temporal dynamics of ischemic injury. Future research should therefore emphasize integrative and translational approaches that consider regional neuronal vulnerability and cellular heterogeneity within the CNS. A deeper understanding of the mechanisms underlying neuronal vulnerability and resistance will be essential for the development of more effective neuroprotective strategies for IR injury.

Author Contributions

JHP conceived the study and wrote the manuscript. JHA and DWK, KYY assisted with literature collection and analysis. JM and MCS prepared the figures and organized the references. JHC and MHW contributed to the conceptualization and design of the review framework, interpretation of the findings, and supervision of the study. All authors contributed to editorial changes in the manuscript. All au-

thors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT-5.3 in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

- [1] Campbell BCV, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, et al. Ischaemic stroke. *Nature Reviews. Disease Primers*. 2019; 5: 70. <https://doi.org/10.1038/s41572-019-0118-8>
- [2] Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. *Trends in Neurosciences*. 1999; 22: 391–397. [https://doi.org/10.1016/s0166-2236\(99\)01401-0](https://doi.org/10.1016/s0166-2236(99)01401-0)
- [3] Chamorro Á, Dirnagl U, Urra X, Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. *The Lancet. Neurology*. 2016; 15: 869–881. [https://doi.org/10.1016/S1474-4422\(16\)00114-9](https://doi.org/10.1016/S1474-4422(16)00114-9)
- [4] Kirino T. Delayed neuronal death in the gerbil hippocampus following ischemia. *Brain Research*. 1982; 239: 57–69. [https://doi.org/10.1016/0006-8993\(82\)90833-2](https://doi.org/10.1016/0006-8993(82)90833-2)
- [5] Pulsinelli WA, Brierley JB, Plum F. Temporal profile of neuronal damage in a model of transient forebrain ischemia. *Annals of Neurology*. 1982; 11: 491–498. <https://doi.org/10.1002/ana.410110509>
- [6] Moskowitz MA, Lo EH, Iadecola C. The science of stroke: mechanisms in search of treatments. *Neuron*. 2010; 67: 181–198. <https://doi.org/10.1016/j.neuron.2010.07.002>
- [7] Petito CK, Pulsinelli WA. Sequential development of reversible and irreversible neuronal damage following cerebral ischemia. *Journal of Neuropathology and Experimental Neurology*. 1984; 43: 141–153. <https://doi.org/10.1097/00005072-198403000-00004>
- [8] Iadecola C. The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. *Neuron*. 2017; 96: 17–42. <https://doi.org/10.1016/j.neuron.2017.07.030>
- [9] Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-Brain Barrier: From Physiology to Disease and Back. *Physiological Reviews*. 2019; 99: 21–78. <https://doi.org/10.1152/physrev.00050.2017>
- [10] Tiedt S, Buchan AM, Dichgans M, Lizasoain I, Moro MA, Lo EH. The neurovascular unit and systemic biology in stroke - implications for translation and treatment. *Nature Reviews. Neurology*. 2022; 18: 597–612. <https://doi.org/10.1038/s41582-022-00703-z>
- [11] Lo EH, Dalkara T, Moskowitz MA. Mechanisms, challenges and opportunities in stroke. *Nature Reviews. Neuroscience*. 2003; 4: 399–415. <https://doi.org/10.1038/nrn1106>
- [12] Rajput P, Brookshier A, Kothari S, Eckstein L, Chang H, Liska S, et al. Differential Vulnerability and Response to Injury among Brain Cell Types Comprising the Neurovascular Unit. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2024; 44: e1093222024. <https://doi.org/10.1523/JNEUROSCI.1093-22.2024>
- [13] Thaysen M, Westi E, Clarkson AN, Wellendorph P, Kristensen M. Rodent ischemic stroke models and their relevance in pre-clinical research. *Neuroprotection (Chichester, England)*. 2024; 2: 296–309. <https://doi.org/10.1002/nep3.62>
- [14] Qin C, Yang S, Chu YH, Zhang H, Pang XW, Chen L, et al. Signaling pathways involved in ischemic stroke: molecular mechanisms and therapeutic interventions. *Signal Transduction and Targeted Therapy*. 2022; 7: 215. <https://doi.org/10.1038/s41392-022-01064-1>
- [15] Aarts M, Liu Y, Liu L, Besshoh S, Arundine M, Gurd JW, et al. Treatment of ischemic brain damage by perturbing NMDA receptor- PSD-95 protein interactions. *Science (New York, N.Y.)*. 2002; 298: 846–850. <https://doi.org/10.1126/science.1072873>
- [16] Martinez-Arizala A, Rigamonti DD, Long JB, Kraimer JM, Holaday JW. Effects of NMDA receptor antagonists following spinal ischemia in the rabbit. *Experimental Neurology*. 1990; 108: 232–240. [https://doi.org/10.1016/0014-4886\(90\)90128-F](https://doi.org/10.1016/0014-4886(90)90128-F)
- [17] Belov Kirdajova D, Kriska J, Tureckova J, Anderova M. Ischemia-Triggered Glutamate Excitotoxicity From the Perspective of Glial Cells. *Frontiers in Cellular Neuroscience*. 2020; 14: 51. <https://doi.org/10.3389/fncel.2020.00051>
- [18] Shen XY, Gao ZK, Han Y, Yuan M, Guo YS, Bi X. Activation and Role of Astrocytes in Ischemic Stroke. *Frontiers in Cellular Neuroscience*. 2021; 15: 755955. <https://doi.org/10.3389/fncel.2021.755955>
- [19] Lipton SA, Rosenberg PA. Excitatory amino acids as a final common pathway for neurologic disorders. *The New England Journal of Medicine*. 1994; 330: 613–622. <https://doi.org/10.1056/NEJM199403033300907>
- [20] Nicholls DG, Budd SL. Mitochondria and neuronal survival. *Physiological Reviews*. 2000; 80: 315–360. <https://doi.org/10.1152/physrev.2000.80.1.315>
- [21] Schmidt-Kastner R, Freund TF. Selective vulnerability of the hippocampus in brain ischemia. *Neuroscience*. 1991; 40: 599–636. [https://doi.org/10.1016/0306-4522\(91\)90001-5](https://doi.org/10.1016/0306-4522(91)90001-5)
- [22] Starkov AA, Polster BM, Fiskum G. Regulation of hydrogen peroxide production by brain mitochondria by calcium and Bax. *Journal of Neurochemistry*. 2002; 83: 220–228. <https://doi.org/10.1046/j.1471-4159.2002.01153.x>
- [23] Abramov AY, Scorziello A, Duchen MR. Three distinct mechanisms generate oxygen free radicals in neurons and contribute to cell death during anoxia and reoxygenation. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2007; 27: 1129–1138. <https://doi.org/10.1523/JNEUROSCI.4468-06.2007>

- [24] Chan PH. Reactive oxygen radicals in signaling and damage in the ischemic brain. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*. 2001; 21: 2–14. <https://doi.org/10.1097/00004647-200101000-00002>
- [25] Flippo KH, Strack S. Mitochondrial dynamics in neuronal injury, development and plasticity. *Journal of Cell Science*. 2017; 130: 671–681. <https://doi.org/10.1242/jcs.171017>
- [26] Shao Z, Dou S, Zhu J, Wang H, Xu D, Wang C, et al. The Role of Mitophagy in Ischemic Stroke. *Frontiers in Neurology*. 2020; 11: 608610. <https://doi.org/10.3389/fneur.2020.608610>
- [27] Kann O, Kovács R. Mitochondria and neuronal activity. *American Journal of Physiology. Cell Physiology*. 2007; 292: C641–C657. <https://doi.org/10.1152/ajpcell.00222.2006>
- [28] Pathak D, Berthet A, Nakamura K. Energy failure: does it contribute to neurodegeneration? *Annals of Neurology*. 2013; 74: 506–516. <https://doi.org/10.1002/ana.24014>
- [29] Halliwell B. Oxidative stress and neurodegeneration: where are we now? *Journal of Neurochemistry*. 2006; 97: 1634–1658. <https://doi.org/10.1111/j.1471-4159.2006.03907.x>
- [30] Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *The International Journal of Biochemistry & Cell Biology*. 2007; 39: 44–84. <https://doi.org/10.1016/j.biocel.2006.07.001>
- [31] Orellana-Urzúa S, Rojas I, Libano L, Rodrigo R. Pathophysiology of Ischemic Stroke: Role of Oxidative Stress. *Current Pharmaceutical Design*. 2020; 26: 4246–4260. <https://doi.org/10.2174/1381612826666200708133912>
- [32] Su Z, Ye Y, Shen C, Qiu S, Sun Y, Hu S, et al. Pathophysiology of Ischemic Stroke: Noncoding RNA Role in Oxidative Stress. *Oxidative Medicine and Cellular Longevity*. 2022; 2022: 5815843. <https://doi.org/10.1155/2022/5815843>
- [33] Chen H, Yoshioka H, Kim GS, Jung JE, Okami N, Sakata H, et al. Oxidative stress in ischemic brain damage: mechanisms of cell death and potential molecular targets for neuroprotection. *Antioxidants & Redox Signaling*. 2011; 14: 1505–1517. <https://doi.org/10.1089/ars.2010.3576>
- [34] Dringen R. Metabolism and functions of glutathione in brain. *Progress in Neurobiology*. 2000; 62: 649–671. [https://doi.org/10.1016/s0301-0082\(99\)00060-x](https://doi.org/10.1016/s0301-0082(99)00060-x)
- [35] Jomova K, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M. Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Archives of Toxicology*. 2024; 98: 1323–1367. <https://doi.org/10.1007/s00204-024-03696-4>
- [36] Pawluk H, Tafelska-Kaczmarek A, Sopońska M, Porzycz M, Modrzejewska M, Pawluk M, et al. The Influence of Oxidative Stress Markers in Patients with Ischemic Stroke. *Biomolecules*. 2024; 14: 1130. <https://doi.org/10.3390/biom14091130>
- [37] Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. *Nature Medicine*. 2011; 17: 796–808. <https://doi.org/10.1038/nm.2399>
- [38] Lombardozi G, Castelli V, Giorgi C, Cimini A, d'Angelo M. Neuroinflammation strokes the brain: A double-edged sword in ischemic stroke. *Neural Regeneration Research*. 2026; 21: 1715–1722. <https://doi.org/10.4103/NRR.NRR-D-24-01456>
- [39] Escartin C, Galea E, Lakatos A, O'Callaghan JP, Petzold GC, Serrano-Pozo A, et al. Reactive astrocyte nomenclature, definitions, and future directions. *Nature Neuroscience*. 2021; 24: 312–325. <https://doi.org/10.1038/s41593-020-00783-4>
- [40] Feng X, Tang L, Chen H, Wu J, Wei L, Liu Y, et al. Taohong Siwu Decoction switches the detrimental/reparative phenotypes of astrocytes via RhoA/ROCK2/Profilin-1 axis to bolster oligodendrogenesis and remyelination after ischemic stroke. *Journal of Ethnopharmacology*. 2026; 366: 121669. <https://doi.org/10.1016/j.jep.2026.121669>
- [41] Allan SM, Tyrrell PJ, Rothwell NJ. Interleukin-1 and neuronal injury. *Nature Reviews. Immunology*. 2005; 5: 629–640. <https://doi.org/10.1038/nri1664>
- [42] Li Z, Zhou B, Chen G, Yang X, Su H, Li B. Blocking of Tim-3 Ameliorates Spinal Cord Ischemia-Reperfusion Injury Through Inhibiting Neuroinflammation and Promoting M1-to-M2 Phenotypic Polarization of Microglia. *Immunity, Inflammation and Disease*. 2024; 12: e70084. <https://doi.org/10.1002/iid3.70084>
- [43] Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nature Reviews. Neuroscience*. 2007; 8: 57–69. <https://doi.org/10.1038/nrn2038>
- [44] Ransohoff RM. How neuroinflammation contributes to neurodegeneration. *Science (New York, N.Y.)*. 2016; 353: 777–783. <https://doi.org/10.1126/science.aag2590>
- [45] Hanisch UK, Kettenmann H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nature Neuroscience*. 2007; 10: 1387–1394. <https://doi.org/10.1038/nn1997>
- [46] Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. *Nature Reviews. Neuroscience*. 2006; 7: 41–53. <https://doi.org/10.1038/nrn1824>
- [47] Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron*. 2008; 57: 178–201. <https://doi.org/10.1016/j.neuron.2008.01.003>
- [48] Sandoval KE, Witt KA. Blood-brain barrier tight junction permeability and ischemic stroke. *Neurobiology of Disease*. 2008; 32: 200–219. <https://doi.org/10.1016/j.nbd.2008.08.005>
- [49] Sharma HS. Pathophysiology of blood-spinal cord barrier in traumatic injury and repair. *Current Pharmaceutical Design*. 2005; 11: 1353–1389. <https://doi.org/10.2174/1381612053507837>
- [50] Blase A, di Giasole CG, Benjamin L, Turowski P. Phased blood-brain barrier disruption in ischaemic stroke: implications for therapy? *Fluids and Barriers of the CNS*. 2025; 22: 90. <https://doi.org/10.1186/s12987-025-00701-5>
- [51] Sarvari S, Moakedi F, Hone E, Simpkins JW, Ren X. Mechanisms in blood-brain barrier opening and metabolism-challenged cerebrovascular ischemia with emphasis on ischemic stroke. *Metabolic Brain Disease*. 2020; 35: 851–868. <https://doi.org/10.1007/s11011-020-00573-8>
- [52] Zhu J, Mo J, Liu K, Chen Q, Li Z, He Y, et al. Glymphatic System Impairment Contributes to the Formation of Brain Edema After Ischemic Stroke. *Stroke*. 2024; 55: 1393–1404. <https://doi.org/10.1161/STROKEAHA.123.045941>
- [53] Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. *Nature Medicine*. 2013; 19: 1584–1596. <https://doi.org/10.1038/nm.3407>
- [54] Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. *Neurobiology of Disease*. 2010; 37: 13–25. <https://doi.org/10.1016/j.nbd.2009.07.030>
- [55] Hossmann KA. Viability thresholds and the penumbra of focal ischemia. *Annals of Neurology*. 1994; 36: 557–565. <https://doi.org/10.1002/ana.410360404>
- [56] Choi JH, Yoo KY, Park OK, Lee CH, Kim SK, Hwang IK, et al. Relation among neuronal death, cell proliferation and neuronal differentiation in the gerbil main olfactory bulb after transient cerebral ischemia. *Cellular and Molecular Neurobiology*. 2010; 30: 929–938. <https://doi.org/10.1007/s10571-010-9522-z>
- [57] Lee CH, Ahn JH, Won MH. Factors Contributing to Resistance to Ischemia-Reperfusion Injury in Olfactory Mitral Cells. *International Journal of Molecular Sciences*. 2025; 26: 5079. <https://doi.org/10.3390/ijms26115079>

- [58] Lipton P. Ischemic cell death in brain neurons. *Physiological Reviews*. 1999; 79: 1431–1568. <https://doi.org/10.1152/physrev.1999.79.4.1431>
- [59] Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*. 2001; 21: 1133–1145. <https://doi.org/10.1097/00004647-200110000-00001>
- [60] Brookshier A, Lyden P. Differential vulnerability among cell types in the neurovascular unit: Description and mechanisms. *Journal of Cerebral Blood Flow & Metabolism*. 2025; 45: 3–12. <https://doi.org/10.1177/0271678X241299960>
- [61] Kleinfeld D, Blinder P, Drew PJ, Driscoll JD, Muller A, Tsai PS, et al. A guide to delineate the logic of neurovascular signaling in the brain. *Frontiers in Neuroenergetics*. 2011; 3: 1. <https://doi.org/10.3389/fnene.2011.00001>
- [62] Nishimura N, Schaffer CB, Friedman B, Lyden PD, Kleinfeld D. Penetrating arterioles are a bottleneck in the perfusion of neocortex. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104: 365–370. <https://doi.org/10.1073/pnas.0609551104>
- [63] Etz CD, Kari FA, Mueller CS, Silovitz D, Brenner RM, Lin HM, et al. The collateral network concept: a reassessment of the anatomy of spinal cord perfusion. *The Journal of Thoracic and Cardiovascular Surgery*. 2011; 141: 1020–1028. <https://doi.org/10.1016/j.jtcvs.2010.06.023>
- [64] Zivin JA, DeGirolami U. Spinal cord infarction: a highly reproducible stroke model. *Stroke*. 1980; 11: 200–202. <https://doi.org/10.1161/01.str.11.2.200>
- [65] Zivin JA, DeGirolami U, Hurwitz EL. Spectrum of neurological deficits in experimental CNS ischemia. A quantitative study. *Archives of Neurology*. 1982; 39: 408–412. <https://doi.org/10.1001/archneur.1982.00510190026008>
- [66] Taira Y, Marsala M. Effect of proximal arterial perfusion pressure on function, spinal cord blood flow, and histopathologic changes after increasing intervals of aortic occlusion in the rat. *Stroke*. 1996; 27: 1850–1858. <https://doi.org/10.1161/01.str.27.10.1850>
- [67] Xing Y, Xiao Y, Zhao M, Zhou J, Zhao K, Xiao C, et al. The role of oxidative stress in spinal cord ischemia reperfusion injury: mechanisms and therapeutic implications. *Frontiers in Cellular Neuroscience*. 2025; 19: 1590493. <https://doi.org/10.3389/fncel.2025.1590493>
- [68] Yadav N, Pendharkar H, Kulkarni GB. Spinal cord infarction: clinical and radiological features. *Journal of Stroke and Cerebrovascular Diseases*. 2018; 27: 2810–2821. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.06.008>
- [69] Gharios M, Stenimahitis V, El-Hajj VG, Mahdi OA, Fletcher-Sandersjö A, Jabbour P, et al. Spontaneous spinal cord infarction: a systematic review. *BMJ Neurology Open*. 2024; 6: e000754. <https://doi.org/10.1136/bmjno-2024-000754>
- [70] Zedde M, De Falco A, Zanferrari C, Guarino M, Pezzella FR, Haggiag S, et al. Spinal Cord Infarction: Clinical and Neuroradiological Clues of a Rare Stroke Subtype. *Journal of Clinical Medicine*. 2025; 14: 1293. <https://doi.org/10.3390/jcm14041293>
- [71] Sandoval JI, De Jesus O. Anterior Spinal Artery Syndrome. *StatPearls: Treasure Island (FL)*. 2026.
- [72] Dokponou YCH, Ontsi Obame FL, Takoutsing B, Mustapha MJ, Nyalundja AD, Elmi Saad M, et al. Spinal cord infarction: A systematic review and meta-analysis of patient's characteristics, diagnosis accuracy, management, and outcome. *Surgical Neurology International*. 2024; 15: 325. https://doi.org/10.25259/SNI_477_2024
- [73] Sobolev VE, Sysoev YI, Vyunova TV, Musienko PE. Animal Models of Spinal Cord Injury. *Biomedicines*. 2025; 13: 1427. <https://doi.org/10.3390/biomedicines13061427>
- [74] Danbolt NC. Glutamate uptake. *Progress in Neurobiology*. 2001; 65: 1–105. [https://doi.org/10.1016/s0301-0082\(00\)00067-8](https://doi.org/10.1016/s0301-0082(00)00067-8)
- [75] Zhou Y, Danbolt NC. Glutamate as a neurotransmitter in the healthy brain. *Journal of Neural Transmission (Vienna, Austria: 1996)*. 2014; 121: 799–817. <https://doi.org/10.1007/s00702-014-1180-8>
- [76] Choi DW. Excitotoxic cell death. *Journal of Neurobiology*. 1992; 23: 1261–1276. <https://doi.org/10.1002/neu.480230915>
- [77] Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. *Progress in Neurobiology*. 2014; 115: 157–188. <https://doi.org/10.1016/j.pneurobio.2013.11.006>
- [78] Hansen AJ. Effect of anoxia on ion distribution in the brain. *Physiological Reviews*. 1985; 65: 101–148. <https://doi.org/10.1152/physrev.1985.65.1.101>
- [79] Rossi DJ, Oshima T, Attwell D. Glutamate release in severe brain ischaemia is mainly by reversed uptake. *Nature*. 2000; 403: 316–321. <https://doi.org/10.1038/35002090>
- [80] Amaral DG, Witter MP. The three-dimensional organization of the hippocampal formation: a review of anatomical data. *Neuroscience*. 1989; 31: 571–591. [https://doi.org/10.1016/0306-4522\(89\)90424-7](https://doi.org/10.1016/0306-4522(89)90424-7)
- [81] Eichenkel AM, Salameh A. Selective vulnerability of hippocampal CA1 and CA3 pyramidal cells: What are possible pathomechanisms and should more attention be paid to the CA3 region in future studies? *Journal of Neuroscience Research*. 2024; 102: e25276. <https://doi.org/10.1002/jnr.25276>
- [82] Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Cell biology of ischemia/reperfusion injury. *International Review of Cell and Molecular Biology*. 2012; 298: 229–317. <https://doi.org/10.1016/B978-0-12-394309-5.00006-7>
- [83] Tait SWG, Green DR. Mitochondrial regulation of cell death. *Cold Spring Harbor Perspectives in Biology*. 2013; 5: a008706. <https://doi.org/10.1101/cshperspect.a008706>
- [84] Niizuma K, Endo H, Chan PH. Oxidative stress and mitochondrial dysfunction as determinants of ischemic neuronal death and survival. *Journal of Neurochemistry*. 2009; 109 Suppl 1: 133–138. <https://doi.org/10.1111/j.1471-4159.2009.05897.x>
- [85] Sanderson TH, Reynolds CA, Kumar R, Przyklenk K, Hüttemann M. Molecular mechanisms of ischemia-reperfusion injury in brain: pivotal role of the mitochondrial membrane potential in reactive oxygen species generation. *Molecular Neurobiology*. 2013; 47: 9–23. <https://doi.org/10.1007/s12035-012-8344-z>
- [86] Rodrigo R, Fernández-Gajardo R, Gutiérrez R, Matamala JM, Carrasco R, Miranda-Merchak A, et al. Oxidative stress and pathophysiology of ischemic stroke: novel therapeutic opportunities. *CNS & Neurological Disorders Drug Targets*. 2013; 12: 698–714. <https://doi.org/10.2174/1871527311312050015>
- [87] Allen CL, Bayraktutan U. Oxidative stress and its role in the pathogenesis of ischaemic stroke. *International Journal of Stroke: Official Journal of the International Stroke Society*. 2009; 4: 461–470. <https://doi.org/10.1111/j.1747-4949.2009.00387.x>
- [88] Park CW, Ahn JH, Lee TK, Park YE, Kim B, Lee JC, et al. Post-treatment with oxcarbazepine confers potent neuroprotection against transient global cerebral ischemic injury by activating Nrf2 defense pathway. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*. 2020; 124: 109850. <https://doi.org/10.1016/j.biopha.2020.109850>
- [89] Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. *Nature*. 2010; 468: 232–243. <https://doi.org/10.1038/nature09613>
- [90] Williamson MR, Fuentes CJA, Dunn AK, Drew MR, Jones TA. Reactive astrocytes facilitate vascular repair and remodeling after stroke. *Cell Reports*. 2021; 35: 109048. <https://doi.org/10.1016/j.celrep.2021.109048>

1016/j.celrep.2021.109048

- [91] Nagelhus EA, Ottersen OP. Physiological roles of aquaporin-4 in brain. *Physiological Reviews*. 2013; 93: 1543–1562. <https://doi.org/10.1152/physrev.00011.2013>
- [92] Patabendige A, Chen R. Astrocytic aquaporin 4 subcellular translocation as a therapeutic target for cytotoxic edema in ischemic stroke. *Neural Regeneration Research*. 2022; 17: 2666–2668. <https://doi.org/10.4103/1673-5374.339481>
- [93] Jayaraj RL, Azimullah S, Beiram R, Jalal FY, Rosenberg GA. Neuroinflammation: friend and foe for ischemic stroke. *Journal of Neuroinflammation*. 2019; 16: 142. <https://doi.org/10.1186/s12974-019-1516-2>
- [94] Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathologica*. 2010; 119: 7–35. <https://doi.org/10.1007/s00401-009-0619-8>
- [95] Kwak D, Park JH, Kim YH, Yoo HI. Decoding hippocampal subfield and glial responses in ischemia using single-cell transcriptomics. *Journal of Translational Medicine*. 2025; 23: 671. <https://doi.org/10.1186/s12967-025-06738-2>
- [96] Ye Q, Jo J, Wang CY, Oh H, Zhan J, Choy TJ, et al. Astrocytic Slc4a4 regulates blood-brain barrier integrity in healthy and stroke brains via a CCL2-CCR2 pathway and NO dysregulation. *Cell Reports*. 2024; 43: 114193. <https://doi.org/10.1016/j.celrep.2024.114193>
- [97] Li J, Gao K, Wang L, Wang J, Qin M, Wang X, et al. Astrocytes: Therapeutic targets for stroke. *Neural Regeneration Research*. 2026; 21: 1074–1088. <https://doi.org/10.4103/NRR.NR-R-D-24-01062>
- [98] Liu W, Liu L, Li H, Xie Y, Bai J, Guan J, et al. Targeted pathophysiological treatment of ischemic stroke using nanoparticle-based drug delivery system. *Journal of Nanobiotechnology*. 2024; 22: 499. <https://doi.org/10.1186/s12951-024-02772-2>
- [99] Sun Y, Wan G, Bao X. Extracellular Vesicles as a Potential Therapy for Stroke. *International Journal of Molecular Sciences*. 2025; 26: 3130. <https://doi.org/10.3390/ijms26073130>
- [100] Anderson CS, Song L. Promising Efforts to Define a Novel Approach to Neuroprotection for Acute Ischemic Stroke. *JAMA Neurology*. 2024; 81: 317–318. <https://doi.org/10.1001/jamaneuro.2023.5727>
- [101] Xu A, Zhang H, Zhang Y, Wu J, Huang Z. Ischemic stroke and intervention strategies based on the timeline of stroke progression: Review and prospects. *Acta Pharmaceutica Sinica. B*. 2025; 15: 4543–4581. <https://doi.org/10.1016/j.apsb.2025.07.026>