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Neuroinflammation and energy metabolism: a dual perspective on ischemic stroke

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Abstract

Ischemic stroke is a prevalent form of cerebrovascular accident, with its pathogenesis involving the intricate interplay between neuroinflammation and energy metabolism. Cerebral ischemia disrupts oxygen and energy supply, triggering metabolic dysregulation and activating neuroinflammatory responses, ultimately resulting in cellular damage. This review provides an exhaustive analysis of the complex mechanisms of ischemic stroke, with a particular focus on the interaction between neuroinflammation and energy metabolism. The interruption of oxygen and energy supply due to cerebral ischemia initiates metabolic dysregulation and activates neuroinflammatory responses, including the release of inflammatory cytokines and the activation of immune cells, contributing to cellular damage and further metabolic disturbances. Studies indicate that dysregulation of energy metabolism significantly impairs neural cell function and interacts with neuroinflammation, exacerbating ischemic brain injury. Therapeutic strategies primarily concentrate on modulating energy metabolism and suppressing neuroinflammatory responses, emphasizing the importance of in-depth research into their interaction to provide a theoretical foundation for new treatment strategies for ischemic stroke. Future research should focus on how to balance anti-inflammatory treatment with energy regulation to minimize neural damage and promote recovery.

Keywords Ischemic stroke, Neuroinflammation, Energy metabolism, Cytokines, Microglia, Astrocytes

Introduction

Ischemic stroke is a primary type of stroke, characterized by obstruction of cerebral blood vessels leading to local brain tissue hypoxia and nutrient deprivation [1, 2]. This type of vascular brain injury imposes a significant health burden globally, with high incidence and mortality rates [3]. Strokes are mainly categorized into ischemic and hemorrhagic types, with ischemic stroke constituting the majority. Following acute stroke, secondary neuroinflammation is a critical pathological process that can both exacerbate brain injury leading to cell death and promote brain tissue repair and functional recovery [2, 4, 5].

In the pathological process of ischemic stroke, neuroinflammation and disruption of energy metabolism play key roles. The acute occurrence of stroke rapidly triggers a neuroinflammatory response, including the activation of microglia and macrophages, as well as leukocyte infiltration [6, 7]. These immune cells exacerbate local inflammation by releasing pro-inflammatory cytokines and chemokines. The inflammatory response has a dual role in brain injury. While it can worsen damage by releasing pro-inflammatory cytokines that cause neuronal death, it also helps clear necrotic tissue and promote repair [5, 8]. Concurrently, the interruption of oxygen and energy supply caused by cerebral ischemia triggers metabolic dysregulation, particularly mitochondrial dysfunction, leading to a reduction in adenosine triphosphate (ATP)

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production and subsequently affecting the stability of the intracellular environment [9, 10]. Mitochondrial dysfunction not only reduces cellular energy supply but also leads to excessive production of reactive oxygen species (ROS), which further damage cell membranes and organelles, inducing apoptosis and apoptotic and necrotic cell death. This energy metabolism imbalance severely affects neural cell function and interacts with neuroinflammation, accelerating ischemic brain injury [11, 12].

Despite progress in understanding these mechanisms, the multifactorial mechanisms of ischemic stroke, especially the interaction between neuroinflammation and energy metabolism, require further exploration. This review aims to integrate the current understanding of these mechanisms, with a particular focus on their interplay. We will analyze in detail the development of neuroinflammation following cerebral ischemia, including the release of inflammatory cytokines, activation of immune cells, and disruption of the blood–brain barrier (BBB) as key elements. Additionally, we will discuss the impact of energy metabolism dysregulation on neural cell function and how this dysregulation interacts with neuroinflammation to advance the progression of ischemic brain injury.

By exploring the interaction between neuroinflammation and energy metabolism, we aim to provide a theoretical basis for new IS treatments and guide future research. This will not only help elucidate the complex interplay between inflammation and energy metabolism but also provide a theoretical basis for the development of new therapeutic strategies and drugs.

Neuroinflammatory response in ischemic stroke

Ischemic stroke, a severe form of brain disease, involves a complex neuroinflammatory response in its pathophysiological process. Brain tissue under IS conditions suffers from hypoxia and nutrient deprivation, leading to cellular damage and death. This injury triggers the release of damage-associated molecular patterns (DAMPs), which, similar to pathogen-associated molecular patterns, can be recognized by pattern recognition receptors such as Toll-like receptors and inflammasomes, thereby activating the innate immune system and initiating a local inflammatory response. This response includes the activation of microglia and astrocytes, as well as the recruitment of peripheral immune cells. In the pathophysiology of ischemic stroke, the inflammatory response has a dual role: it may exacerbate brain injury or participate in the repair and functional recovery of brain tissue [13, 14]. Furthermore, the pathophysiological changes in ischemic stroke are a continuous and complex dynamic process involving energy impairment and ion imbalance, excitotoxicity of amino acids, oxidative stress, inflammatory responses, apoptosis and necrosis, reperfusion injury, and neuroregeneration and repair. The inflammatory response at the BBB and endothelial interface is particularly crucial, as it represents a core mechanism of ischemic tissue injury, involving the collective participation of adhesion molecules, cytokines, chemokines, and leukocytes, which is of significant importance to the pathogenesis of cerebral infarction tissue injury [15]. Neuroinflammation is triggered by immune cells like microglia, astrocytes, peripheral immune cells, and endothelial cells. These cells respond to injuries such as infection, ischemia, stress, and trauma by releasing inflammatory mediators, initiating neuroimmune responses [16] (Fig. 1).

When the brain suffers ischemic injury, DAMPs signals activate local microglia and peripheral leukocytes, triggering the release of a large amount of pro-inflammatory cytokines. This activation also enhances the expression of leukocyte adhesion molecules and stimulates the production of chemokines. The permeability of the BBB is increased, facilitating the infiltration of leukocytes into the brain parenchyma to clear the substantial debris generated by cellular death [17]. Cytokines are crucial in this process. These pleiotropic polypeptides regulate cell activation, proliferation, and differentiation in the central nervous system [18]. Under normal brain conditions, cytokines are barely detectable due to their low

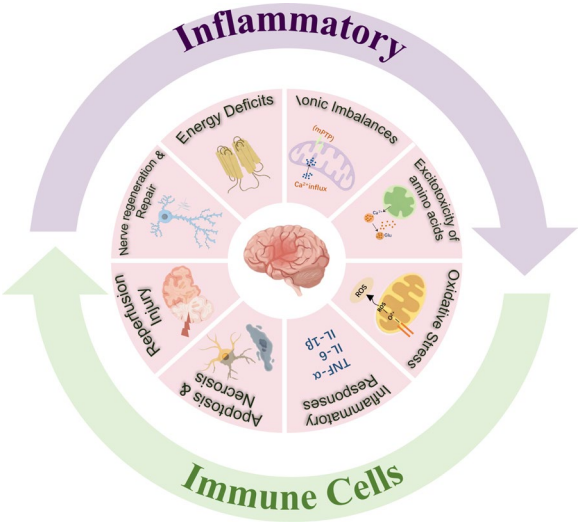

Fig. 1 Multidimensional interactions of pathological and physiological changes following ischemic stroke. This includes energy deficits and ionic imbalances, excitotoxicity of amino acids, oxidative stress, inflammatory responses, inducing both apoptotic and necrotic cell death, reperfusion injury, and nerve regeneration and repair. *mPTP* mitochondrial permeability transition pore. *Glu*: Glucose. *ROS*: reactive oxygen species

expression levels, and their receptors are also expressed at minimal levels. Nonetheless, in the context of brain ischemic injury, these cytokines are rapidly and extensively upregulated [19], playing roles in both pro-inflammatory and anti-inflammatory mechanisms. Specifically, pro-inflammatory cytokines like interleukin- 1β(IL-1β), tumor necrosis factor (TNF-α), and interleukin- 6 play a key role in stroke by stimulating inflammatory responses that can worsen brain injury. Anti-inflammatory cytokines, on the other hand, reduce inflammation by inhibiting the expression of these pro-inflammatory cytokines and modulating immune cell activity. However, Cytokine functions are not strictly pro-inflammatory or anti-inflammatory. Some cytokines can be neurotoxic in certain conditions, while others may have neuroprotective effects. Therefore, the balance between the beneficial and detrimental effects of cytokines depends heavily on the brain's physiological and biochemical environment [20].

It is noteworthy that the IL- 1 receptor antagonist plays a significant role in mitigating neuronal damage caused by stroke. Additionally, other cytokine blockers have also proven effective in reducing cerebral edema, shrinking infarct size, and promoting recovery after experimental stroke. These research findings further substantiate the pivotal role of cytokines in the pathophysiology of stroke. In particular, TNF-α is expressed in ischemic tissue and surrounding neuronal cells at the onset of the disease and continues to be expressed in macrophages within the infarcted tissue, potentially acting as a key mediator of toxic reactions [21]. In early ischemia, inflammatory mediators like tumor necrosis factor and interleukins rapidly increase, attracting neutrophils, monocytes, lymphocytes, and other immune cells to the ischemic area [22].

Following the occurrence of ischemic stroke, the central nervous system's primary immune cells—microglia—swiftly respond to local damage signals. As ischemia persists, these cells become activated by recognizing DAMPs and can be classified into pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes. M1 microglia release pro-inflammatory cytokines and neurotoxic mediators, worsening neuronal damage, while M2 microglia promote repair and anti-inflammatory responses [23]. Subsequently, these cells then produce more ROS and TNF-α [24], increasing C-X-C motif chemokine ligand 10 release by endothelial cells, leading to blood–brain barrier disruption and peripheral T lymphocyte infiltration that exacerbates brain injury [25]. However, during stroke recovery, microglia can promote tissue repair and functional recovery by releasing anti-inflammatory factors like transforming growth factor-beta(TGF-β) and interleukin- 10 (IL- 10), and by stimulating angiogenesis [26]. Concurrently, astrocytes actively participate in the immune response following stroke; cytokines, DAMPs, and ROS released by damaged cells stimulate astrocytes and alter their phenotype, inducing"reactive astrogliosis"[27]. Research shows that the P2Y1 receptor in astrocytes plays a key role after ischemic stroke. Damaged cells promote pro-inflammatory cytokine and chemokine production via the nuclear factor kappa B (NF-κB) pathway, mediated by p65 subunit phosphorylation. These molecular events worsen local inflammation and may also impact the brain's recovery process after infarction [28]. Furthermore, Astrocyte-derived exosomes can regulate neuronal responses by transferring microRNAs like miR- 378a- 5p, reducing neuronal damage and neuroinflammation [29].

Oligodendrocytes, crucial for maintaining myelin sheath integrity, play a significant role in inflammation and neurorestoration after ischemic brain injury [30]. Cerebral ischemia not only leads to the injury and death of oligodendrocytes but also triggers demyelination, further exacerbating neurological dysfunction [31]. During stroke recovery, the proliferation and differentiation of oligodendrocyte precursor cells (OPCs) are essential for remyelination. These OPCs migrate to damaged areas, differentiate into mature oligodendrocytes, and promote axon remyelination [32].

Myeloid immune cells also play a key role in the inflammatory response after ischemic stroke. Macrophages and neutrophils are recruited from the blood to damaged brain tissue, guided by DAMPs and chemokines, where they actively contribute to the inflammatory response. Microglia and myeloid immune cells are closely linked. Microglia release inflammatory mediators that recruit and activate myeloid immune cells, while myeloid immune cells release mediators that affect microglia function. This complex interplay collectively drives the progression of inflammation after ischemic stroke [33], making brain tissue injury more complex and difficult to control. This type of immune cell interaction is not unique to ischemic stroke. In oncology, tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) play key roles in tumor immune evasion. TAMs can be polarized by tumor cells to promote tumor growth and immune escape, while MDSCs suppress effector immune cell function [34]. Similarly, in ischemic stroke, the interaction between microglia and myeloid immune cells significantly affects disease outcomes. Understanding these similarities can provide new perspectives for studying ischemic stroke.

After ischemic stroke, significant changes occur in TGF-β signaling in astrocytes and microglia/macrophages [35]. Research shows that during the subacute phase of stroke, inhibiting astrocyte TGF-β

signaling prevents TGF-β upregulation in the peri-infarct cortex and increases innate immune cell infiltration and activation [36]. Previous studies indicate that extracellular vesicles from microglia preconditioned with oxygen–glucose deprivation (OGD) regulate the TGF-β/Smad 2/3 pathway, promoting tissue regeneration and neurorestoration in stroke mice. This mechanism provides anti-apoptotic and neuroprotective effects and may help reduce ischemic brain injury [37, 38]. This finding suggests a new therapeutic strategy: regulating TGF-β signaling to influence the immune response and neurorestoration after stroke.

Furthermore, the release of numerous cytokines and growth factors after ischemic stroke can activate the JAK/STAT3 signaling pathway [39]. Activating this pathway is crucial for regulating neuroinflammation. Resveratrol and tetrandrine can modulate the STAT3 pathway, reducing neuroinflammation [40, 41]. At the same time, the Notch signaling pathway also plays a key role in ischemic stroke, influencing astrocyte behavior and promoting neurorestoration by regulating neural stem cell proliferation and differentiation [42]. In addition, NF-κB activation is a key factor in neuronal loss after ischemic stroke. As a crucial transcription factor, NF-κB regulates many inflammation-related genes, playing a central role in the inflammatory response [43]. In recent years, increasing evidence has shown that triggering receptor expressed on myeloid cells 2 (TREM 2), an important immune receptor expressed on myeloid cells, exerts a strong neuroprotective effect in experimental ischemic stroke. TREM2, an immunoglobulin-like receptor [44], is mainly expressed on microglia in the central nervous system and protects neurons by reducing neuroinflammation caused by OGD-induced injury [45, 46]. These complex molecular signaling pathways work together to regulate neuroinflammation and repair processes after ischemic stroke.

The neuroinflammatory response following ischemic stroke is a complex and dynamic process with dual roles: it can exacerbate brain injury while also promoting repair and protection. As mentioned earlier, the protective effects of neuroinflammation are primarily observed during the recovery phase, where it aids in tissue repair and functional recovery by clearing necrotic tissue, promoting angiogenesis, and facilitating neural regeneration. For example, M2 microglia and anti-inflammatory cytokines like TGF-β and IL- 10 play a key role in later stroke stages by reducing excessive inflammation and promoting tissue repair. However, the contradiction between the protective and damaging effects of neuroinflammation persists. On one hand, early inflammation can worsen neuronal damage by releasing pro-inflammatory cytokines like IL- 1β and TNF-α, and ROS. On the other hand, moderate inflammation in the later stages may help mitigate damage by clearing dead cells and promoting repair. This contradiction may stem from the temporal dynamics, cell-type specificity, and local microenvironment of the inflammatory response [47]. Future research should focus on the temporal and spatial dynamics of neuroinflammation to clarify the specific mechanisms at different stages. For instance, shifting microglia from M1 to M2 or using anti-inflammatory drugs like IL- 1 receptor antagonists could reduce early inflammation while promoting later repair. Additionally, integrating multi-omics and single-cell sequencing technologies to investigate the roles of different cell types in the inflammatory response may provide new insights to resolve this contradiction. In summary, precise regulation of the spatiotemporal dynamics of neuroinflammation holds promise for achieving better neuroprotection and functional recovery in stroke treatment.

Energy metabolism dysregulation induced by ischemic stroke

Cerebral energy metabolism is crucial for maintaining overall body function. Despite the brain's lack of significant energy reserves, its activity relies on a delicate regulation between neurotransmission and energy metabolism. The brain meets the high energy demand during neurotransmission through a continuous supply of metabolic fuels, ensuring the efficient operation of the organism's functions. This precision in energy management guarantees that the brain can maintain efficient energy utilization and stable functional output across different activities and physiological states [48]. Based on this, brain energy metabolism exhibits a unique characteristic of high metabolic rate compared to other tissues. Further research indicates that this high metabolic rate is primarily attributed to the activity of plasma membrane ion pumps and postsynaptic receptors. Moreover, a key observation is that increased local brain activity directly correlates with higher glucose use in that brain region, showing how sensitive and adaptable brain energy metabolism is to local neural activity [49].

Glucose assumes a pivotal role in energy metabolism within the adult brain, acting as the main source of energy for the nervous system. Under specific conditions, although the brain can use other energy sources under certain conditions, glucose enters cells via GLUTs and is converted into glucose- 6-phosphate, which is then metabolized through glycolysis, the pentose phosphate pathway, and glycogen synthesis. These processes produce carbon dioxide, water, and metabolic intermediates that release energy, supporting neurotransmitter synthesis and other brain functions

[50]. In this metabolic process, the connection between neurotransmitters and energy metabolism presents complex multi-level interactions. Studies have shown that acetylcholine (ACh) and its receptor, the α7 nicotinic acetylcholine receptor (α7nAChR), play a role in the arterial baroreflex and have a protective effect against stroke, possibly by affecting cell death and inflammatory responses [51]. Furthermore, plasma amino acid neurotransmitters, including glutamate, aspartate, γ-aminobutyric acid, and glycine, are associated with poor outcomes in ischemic stroke, and changes in these neurotransmitter levels may play a regulatory role in energy metabolism and neuroprotection after stroke [52]. Further research shows that the α7nAChR agonist GTS- 21 can reduce brain injury and glucose metabolic dysregulation in ischemic stroke, likely by lowering oxidative stress, inflammation, and improving mitochondrial function and energy metabolism [53]. These findings emphasize that neurotransmitters may have a direct impact on the energy metabolic process after stroke, in addition to their role in neural signal transmission.

In the context of cerebral ischemia, the equilibrium of glucose metabolism is disrupted. Local ischemia increases anaerobic glycolysis, rapidly lowering intracellular pH, leading to cellular dysfunction and swelling. To counteract the pH drop, cells expel excess H^+ through faster Na^+/H^+ exchange, increasing Na^+ influx. This ion exchange affects cell volume regulation and is linked to cellular excitability and neuroinflammatory responses, which play a key role in post-ischemic pathology [54]; in global cerebral ischemia, mitochondrial ATP synthesis is hindered, causing rapid ATP depletion. This triggers neuronal membrane depolarization, increased potassium efflux, and sodium influx, disrupting Ca^{2+}-ATPase function and leading to high intracellular calcium levels [12, 55]. Under ischemic conditions, due to the lack of oxygen and nutrient supply, mitochondrial oxidative phosphorylation is impaired [56], resulting in reduced ATP production by mitochondria, affecting ATP-dependent Ca^{2+} channel function, leading to cellular and mitochondrial Ca^{2+} accumulation or overload. Additionally, during ischemia, adenine nucleotides degrade, decreasing their concentration and increasing phosphate levels, making the mitochondrial permeability transition pore (mPTP) more sensitive to Ca^{2+} [57]. Under no-flow conditions, cells rely on anaerobic respiration, leading to lactate accumulation and a decrease in cellular pH, further triggering mPTP closure [58, 59]. These changes collectively affect the metabolic state and mitochondrial function of cells under ischemic conditions.

Under ischemic conditions, reduced cellular energy can impair key functions, including Na^+/K^+ pump maintenance, widespread depolarization, and excessive glutamate release. In this state, the overactivation of N-methyl-D-aspartate receptor-type channels in L-glutamate (L-glu) channels mediates a large influx of Ca^{2+}, leading to cellular excitotoxicity and neuronal death. A significant increase in intracellular free calcium activates a series of calcium-sensitive enzymes, such as calpains, which further activate other molecules and disrupt cellular structures, exacerbating cellular damage [50]. L-glutamate, as the dominant excitatory neurotransmitter in the brain, is widely involved in almost all activities of the nervous system. During ATP depletion, glutamate transport to presynaptic vesicles weakens. However, high extracellular glutamate or excitatory amino acid levels overstimulate glutamate receptors, causing excitotoxicity, a key pathological process in ischemic diseases [60, 61].

The energy metabolic changes in ischemic stroke underscore the brain's susceptibility to energy deprivation crises. These complex processes show the central role of energy metabolism in the brain and how ischemia disrupts intracellular stability. With in-depth research into the mechanisms of ischemic stroke, we hope to develop more effective therapeutic measures to block or reverse these pathological processes, thereby reducing brain damage and promoting the recovery of neurological functions. Future research should focus on regulating energy metabolism during ischemia and optimizing it through drugs or other interventions, offering new approaches for ischemic stroke treatment.

Energy metabolism dysregulation induced by ischemic stroke is a core mechanism of brain injury. The interruption of oxygen and energy supply due to cerebral ischemia triggers mitochondrial dysfunction, reduced ATP production, and intracellular environmental imbalance, leading to apoptosis and necrotic cell death. Disruptions in glucose metabolism, glutamate excitotoxicity, and excessive ROS production further exacerbate neuronal damage. Dysregulation of energy metabolism not only directly affects neuronal survival and function but also interacts with neuroinflammation, jointly driving the progression of ischemic brain injury. Therefore, future research should focus on how to regulate energy metabolism under ischemic conditions to mitigate brain damage and promote functional recovery.

Interplay between neuroinflammation and energy metabolism dysregulation

The interaction between neuroinflammation and energy metabolism dysregulation is complex in ischemic stroke. The disruption of oxygen and energy supply during cerebral ischemia triggers metabolic disarray [62], with mitochondrial dysfunction leading to a decrease in

ATP production, affecting active transport processes within the cell, causing a decline in the function of ion pumps, and subsequently leading to an imbalance in the intracellular environment [57]; this imbalance activates energy sensors such as 5'-AMP-activated protein kinase (AMPK) [63],and influences signaling pathways like Mammalian/mechanistic target of rapamycin (mTOR) [64]. Research shows that autophagy is activated in HT22 cells treated with Oxygen Glucose Deprivation/Reperfusion (OGD/R). Rapamycin, an autophagy inducer, enhances cell viability, reduces injury, and alleviates apoptosis, suggesting that appropriately enhanced autophagy exerts a protective effect on cells [65]. Further studies have revealed that OGD/R activates the AMPK/DDiT4/mTOR axis, which increases autophagy and reduces cell damage, indicating its significant importance in neuroprotection [66]. Additionally, in a model of cerebral ischemia–reperfusion injury, Nek6 expression is upregulated. Overexpression of Nek6 activates the mTOR signaling pathway, inhibits autophagy, and reduces neuronal damage Moreover, Nek6 mRNA undergoes post-transcriptional regulation through m6 A modification, which affects its expression levels [67]. Moreover, this state of energy deprivation activates Toll-like receptor 4 (TLR4) on astrocytes and microglia, leading to the initiation of an inflammatory response. The activation of TLR4 promotes the production of inflammatory cytokines, ROS, and nitric oxide (NO), all of which contribute to neurodamage associated with stroke [68]. Simultaneously, within the ischemic penumbra, the activation of platelets and the complement system, as well as the release of inflammatory mediators, induce metabolic pathways to overcompensate for ischemic damage, leading to an excessive release of ROS [69, 70]. These ROS activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and inflammasomes involved in the inflammatory response, such as the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, resulting in the release of inflammatory mediators like the cytokine IL-1β. This further exacerbates the neuroinflammatory response, which not only increases brain tissue damage but may also lead to long-term neurological dysfunction [71].

Following the restoration of blood supply after cerebral ischemia, glucose and oxygen levels gradually recover, while the overproduction of ROS triggers oxidative stress responses. Such responses promote the infiltration of leukocytes, the pro-inflammatory effects of neutrophils, and the activation of complement and platelets, leading to the disruption of the BBB [72]. This allows more inflammatory cells and mediators to enter brain tissue [73], activating microglia and astrocytes, which release more inflammatory mediators, creating a positive feedback loop that worsens neuroinflammation [74]. At the same time, increased ROS causes the mPTP to open, which both causes and results from mPTP opening. High levels of tumor necrosis factor TNF-α/MLR can upregulate the production of ROS [75]. Excessive ROS induce the opening of the mitochondrial outer membrane pores, releasing calcium ions, cytochrome C, and apoptosis-inducing factor AIF, leading to apoptosis [76]. These processes can disrupt nutrient and metabolic substance transport, impairing energy metabolism and affecting brain tissue recovery and function [77] (Fig. 2).

In addition, Vitamin B12 deficiency can disrupt immune homeostasis, increasing inflammation. For example, homocysteine, a pro-inflammatory amino acid, can promote atherosclerosis and raise the risk of ischemic stroke [78]. The CCL5/CCR5 axis is key in post-stroke neuroinflammation, and CCR5 activation may worsen neuroinflammation via the JAK2/STAT3 pathway, affecting energy metabolism [79]. Ischemic stroke also disrupts the liver's role in lipid metabolism, which is closely tied to glucose and glutathione homeostasis. Lipoproteins produced by the liver, such as very-low-density lipoprotein, may play an important role in lipid supply after cerebral ischemia, affecting cell survival, neurogenesis, and anti-inflammatory pathways [80]. It is noteworthy that PLA2G2E-mediated lipid metabolism triggers an autonomous neural repair process within the brain following cerebral ischemia. This process induces PAD4 expression in neurons via dihomo-g-linolenic acid and 15-hydroxy-eicosatrienoic acid production, promoting gene expression linked to stroke recovery. These lipid metabolic products are not only crucial for preventing additional cell death and subsequent severe inflammation but may also regulate energy metabolism by affecting mitochondrial function and oxidative phosphorylation processes [81].

This bidirectional process worsens brain tissue damage and impairs recovery and function. Accordingly, a deep understanding of this complex interplay network is crucial for the development of effective therapeutic strategies. For instance, Resolvin D1 promotes oxidative phosphorylation and inhibits glycolysis, increasing ATP production in microglia and enhancing their ability to phagocytose neutrophils. This metabolic reprogramming boosts energy production, reduces neutrophil accumulation, and prevents neutrophil extracellular trap formation, alleviating neuroinflammation [82]. By identifying and intervening in the key components of energy metabolism disorders and neuroinflammation, new strategies for the treatment of ischemic stroke can be provided. These strategies may include protecting mitochondrial

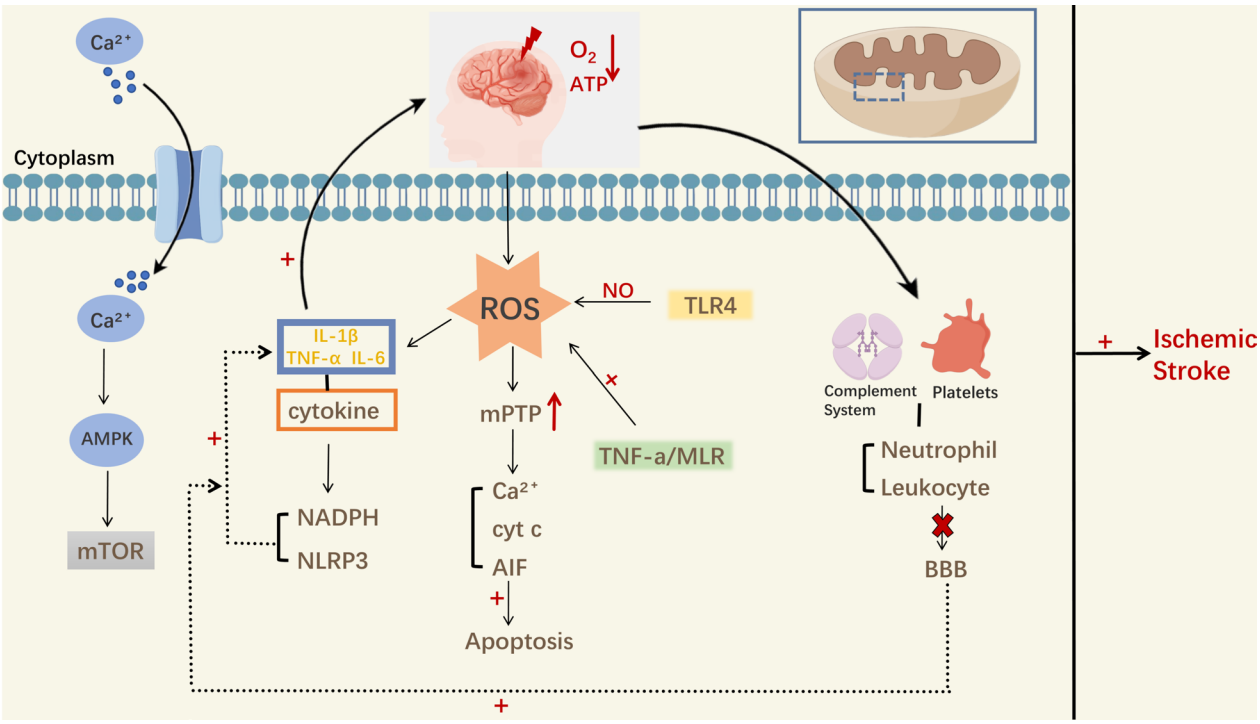

Fig. 2 The interplay between neuroinflammation and energy metabolism dysregulation. In ischemic stroke, oxygen and energy deprivation cause mitochondrial dysfunction, reducing ATP and ion pump function, leading to cellular imbalance. This disruption activates energy sensors such as AMPK and signaling pathways like mTOR and TLR4, triggering inflammation and ROS release. Platelet and complement activation in the penumbra, coupled with the excessive release of inflammatory mediators and ROS, triggers NADPH oxidase and NLRP3 inflammasomes, exacerbating neuroinflammation and brain damage. After blood supply restoration, excessive ROS induce oxidative stress, compromise the blood–brain barrier, and facilitate the entry of inflammatory cells and mediators into the brain tissue, creating a positive feedback loop that intensifies neuroinflammation. The increase in ROS also leads to the opening of mitochondrial permeability transition pores, releasing apoptotic factors and inducing apoptosis, which affects the recovery and function of brain tissue. Dashed lines: Positive feedback."+": Promotion."X": Destruction

function, modulating the release of inflammatory mediators, repairing the BBB, and optimizing metabolic pathways to alleviate brain damage and promote the recovery of brain function.

The interplay between neuroinflammation and energy metabolism dysregulation in ischemic stroke forms a complex pathological network. Energy supply disruption directly causes cellular dysfunction and triggers neuroinflammation by activating pathways like AMPK, mTOR, and TLR4. Excessive ROS and inflammatory mediators worsen brain injury, creating a positive feedback loop that reinforces inflammation and metabolic dysregulation. Therefore, understanding the key nodes of this interaction network, particularly how to modulate mitochondrial function, inhibit inflammatory mediator release, and repair the blood–brain barrier, is crucial for developing effective therapeutic strategies.

Nutrition and pharmacotherapy: improving neuroinflammation and dysregulation of energy metabolism

Neuroinflammation and dysregulation of energy metabolism following stroke are critical pathological processes leading to neuronal damage and functional impairment. Studies have shown that sodium butyrate and Guhong injection alleviate neuroinflammation by modulating the gut-brain axis, inhibiting the TLR4/MyD88/NF-κB signaling pathway, reducing pro-inflammatory microglia, and increasing anti-inflammatory microglia [83]. Additionally, these interventions improve energy metabolism pathways (such as glycerophospholipid metabolism, the tricarboxylic acid cycle, and glycolysis) by regulating the production of short-chain fatty acids (SCFAs), reducing oxidative stress and neuronal apoptosis, thereby promoting post-stroke neurological recovery [84]. Probiotics like Lactobacillus reuteri GMNL- 89 and Lactobacillus paracasei GMNL-133 show potential as stroke adjunctive therapies by modulating the gut-spleen-brain axis, reducing infarct volume, improving neurological function, protecting

the blood–brain and intestinal barriers, and reducing inflammation through immune regulation and gut microbiota balance [85]. Salvianolic acid C (SalC) significantly alleviates post-stroke neuroinflammation and protects neurons from ischemia–reperfusion injury by inhibiting the TLR4-TREM1-NF-κB signaling pathway. Furthermore, SalC improves post-stroke neurological function by regulating microglial inflammatory responses and reducing the release of pro-inflammatory factors, offering a novel pharmacological intervention strategy for neuroinflammation treatment [86]. Retinoic acid significantly suppresses post-stroke neuroinflammation and apoptosis by modulating the PI3 K-Akt signaling pathway and the interaction of Bcl- 2 family proteins [87]. Vitamin D has anti-inflammatory and immunomodulatory effects. While its ability to reduce cardiovascular disease and mortality is limited [88], its potential for treating post-stroke neuroinflammation and energy metabolism dysregulation deserves further study.

In terms of drug delivery systems, Polyamidoamine dendrimers encapsulating curcumin significantly reduce astrocyte reactivity, alleviate neuroinflammation, and promote functional recovery [89]. In particular, the RVG29 peptide-modified Cur@GAR NPs enhance brain targeting, effectively reduce neuroinflammation and neuronal apoptosis, and mitigate oxidative stress by scavenging free radicals, indirectly improving mitochondrial function and energy metabolism [90]. ROS generated during cerebral ischemia–reperfusion activate the AKT/SP1-NFκB pathway, increasing SURI expression and triggering cellular edema and necrosis. Antioxidants such as resveratrol (RSV) alleviate neuroinflammation and cellular damage by inhibiting ROS generation and modulating SURI expression [91]. RSV preconditioning (RPC) reduces post-ischemic cell death and mitigates NAD^+/NADH level loss by downregulating PARP1 protein expression, thereby inhibiting AIF nuclear translocation and reducing neuroinflammation and apoptosis. The long-term neuroprotective effects of RPC may be achieved through energy metabolism regulation and PARP1 overactivation inhibition [92]. Additionally, polyphenolic compounds like quercetin and gallic acid in Moringa oleifera leaf extracts have anti-inflammatory and antioxidant properties, potentially inhibiting inflammatory factor release and modulating energy metabolism-related gene expression [93]. Studies on ω3 and ω6 polyunsaturated fatty acids (PUFAs) indicate that lower ω6 PUFA levels (e.g., arachidonic acid, AA) are associated with increased atrial fibrillation risk, while AA has anti-inflammatory and cardioprotective effects, potentially improving stroke outcomes by suppressing neuroinflammation and reducing atrial fibrosis [94]. Post-stroke, ceramides accumulate in astrocytes, triggering neuroinflammation and energy metabolism dysregulation by disrupting mitochondrial integrity and activating the cGAS/STING pathway. Inhibition of SPTLC2 or the use of antioxidants (e.g., SKQ1) reduces ceramide production and mitochondrial oxidative stress, thereby alleviating inflammation and brain damage [95]. These findings provide new therapeutic strategies for addressing neuroinflammation through nutritional and pharmacological interventions.

Nutritional and pharmacological interventions show great potential in improving neuroinflammation and energy metabolism dysregulation after stroke. By modulating the gut-brain axis, inhibiting inflammatory pathways like TLR4/NF-κB, enhancing mitochondrial function, and reducing oxidative stress, various interventions can effectively reduce neuroinflammation and improve energy metabolism. Probiotics, antioxidants like resveratrol, and specific fatty acid supplements not only reduce brain damage but also promote neurological recovery. These studies offer new directions for stroke treatment, and future research should explore the best timing and dosage of these interventions to maximize their effectiveness.

Conclusions and prospects

This review discusses the interplay between neuroinflammation and energy metabolism dysregulation in ischemic stroke, emphasizing their importance in the disease's pathophysiology. Neuroinflammatory responses not only exacerbate brain injury during the acute phase but also profoundly affect brain tissue repair and functional recovery during the recovery phase. At the same time, the disruption of energy metabolism significantly impacts the survival and functional stability of neural cells, further aggravating the extent of ischemic damage.

With the widespread application of advanced technologies such as single-cell RNA sequencing (scRNA-seq), we have gained a more precise understanding of the responses of different cell types following ischemic stroke. Using scRNA-seq, the dynamic changes in microglia and astrocytes post-stroke have been revealed, particularly the role of SLC7 A11 in regulating microglial polarization. Additionally, studies have found that overexpression of CD73 can alleviate astrocyte pyroptosis induced by cerebral ischemia–reperfusion through the A2B/NF-κB signaling pathway [96, 97]. These findings further confirm the critical role of neuroinflammation and energy metabolism in the pathological mechanisms of ischemic stroke and provide potential targets for future precision therapies.

Future research should focus on elucidating the underlying mechanisms of the interaction between

neuroinflammation and energy metabolism dysregulation, as well as exploring new therapeutic targets. By gaining a deeper understanding of these complex biological processes and validating their therapeutic effects through clinical trials, we can develop new treatment modalities aimed at modulating neuroinflammatory responses and improving energy metabolism. These modalities may include inhibitors targeting specific inflammatory mediators, drugs that enhance mitochondrial function, and strategies to protect and repair the BBB. The common goal of these strategies is to mitigate brain injury, promote neurological recovery, and improve long-term patient outcomes. At the same time, the importance of clinical laboratory science in disease diagnosis cannot be overlooked. Establishing comprehensive academic programs to train professionals is crucial for advancing medical innovation in diseases like ischemic stroke [98, 99]. As we better understand these key pathophysiological mechanisms, we expect to provide more effective treatments for ischemic stroke patients.

Abbreviations

ATP	Adenosine triphosphate
ROS	Reactive oxygen species
BBB	Blood–brain barrier
DAMPs	Damage-associated molecular patterns
IL- 1β	Interleukin- 1β
TNF-α	Tumor necrosis factor
TGF-β	Transforming growth factor-beta
IL- 10	Interleukin- 10
NF-κB	Nuclear factor kappa B
OPCs	Oligodendrocyte precursor cells
TAMs	Tumor-associated macrophages
MDSCs	Myeloid-derived suppressor cells
OGD	Oxygen–glucose deprivation
OGD/R	Oxygen-glucose deprivation/reperfusion
JAK/STAT 3	Janus kinase/signal transducer and activator of transcription 3
TREM 2	Triggering receptor expressed on myeloid cells 2
GLUTs	Glucose transporter proteins
ACh	Acetylcholine
α7nAChR	α7 Nicotinic acetylcholine receptor
GTS- 21	α7nAChR agonist
mPTP	Mitochondrial permeability transition pore
L-glu	L-glutamate
AMPK	5′-AMP-activated protein kinase
mTOR	Mammalian/mechanistic target of rapamycin
TLR4	Toll-like receptor 4
NO	Nitric oxide
NADPH	Nicotinamide adenine dinucleotide phosphate
NLRP3	NOD-like receptor family pyrin domain containing 3
SCFA	Short-chain fatty acids
SalC	Salvianolic acid C
RVG29	Rabies virus glycoprotein
Cur@GAR NPs	Cur-loaded gelatin nanoparticles
RSV	Resveratrol
RPC	Resveratrol preconditioning
PARP1	Promotes poly-ADP-ribose polymerase 1
PUFAs	Polyunsaturated fatty acids
AA	Arachidonic acid

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Author contributions
All authors contributed to the conception and design of the study. The first draft of the manuscript was written by Wen Lei, and all authors commented on previous versions of the manuscript. Wen Lei and Hao Zhuang contributed to the creation of figures and the final draft.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
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Consent for publication
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