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Review

Ketone Bodies in Ischemic Stroke: A Review of Neuroprotective Mechanisms and Therapeutic Implications

Jun Tan[1,†], He Li[1,2,†], Minghao Song[1], Haoyu Cheng[1], Mengyu Zhao[1], Nan Zhang[1], Hongyu Ma[1], Xiaoxi Zhang[1], Pengfei Yang[1,*], Jianmin Liu[1,*]

[1]Neurovascular Center, Changhai Hospital, Naval Medical University, 200433 Shanghai, China
[2]Naval Medical Center of PLA, Naval Medical University, 200433 Shanghai, China
*Correspondence: chyangpf@163.com (Pengfei Yang); chstroke@163.com (Jianmin Liu)
[†]These authors contributed equally.
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Abstract

Ischemic stroke disrupts cerebral metabolism and initiates a cascade of pathological events, including excitotoxicity, mitochondrial dysfunction, and neuroinflammation. These interconnected processes drive neuronal apoptosis, necrosis, and synaptic loss, ultimately leading to irreversible brain injury, persistent neurological deficits, and high rates of long-term disability and mortality. Ketone bodies, including β-hydroxybutyrate, acetoacetate, and acetone, have demonstrated neuroprotective properties through multiple mechanisms. These include sustaining cerebral energy supply and mitochondrial stability, attenuating excitotoxicity and calcium overload, suppressing inflammatory responses, and promoting neural remodeling and functional recovery. Accordingly, ketone bodies are increasingly recognized as a promising therapeutic strategy for ischemic stroke. However, evidence supporting their clinical application and systematic implementation in humans remains limited. In this review we summarize ketone body metabolism and the mechanisms underlying its neuroprotective effects, evaluate the evidence supporting translation from preclinical studies to clinical application, and highlight key challenges that must be addressed in future investigations. Based on the current evidence, we also propose priorities for short-term clinical research and outline future perspectives.

Keywords: ketone bodies; ischemic stroke; 3-hydroxybutyric acid; metabolism; neuroprotective agents

1. Introduction

Acute ischemic stroke represents a major public health challenge because of its high morbidity, disability, and mortality [1]. The pathological cascade is initiated by interruption of local cerebral blood flow due to cerebrovascular occlusion, triggering a series of injury responses centered on the collapse of energy metabolism [2]. Impaired energy production disrupts the Na^+/K^+-ATPase pump, leading to membrane depolarization, excessive glutamate release, and overactivation of N-methyl-D-aspartate (NMDA) receptors [2,3]. The resulting excitotoxicity, together with calcium overload, reactive oxygen species (ROS) generation, mitochondrial dysfunction, neuroinflammation, and neuronal apoptosis, further compromises brain structure and function [4,5,6,7,8]. Metabolic dysfunction and these pathological processes reinforce one another through shared mediators, such as ROS and Ca^{2+}, thereby forming a self-perpetuating cycle. Consequently, metabolic dysfunction has attracted increasing attention as a key initiating event in ischemic stroke–induced injury.

Ketone bodies are water-soluble metabolites, including β-hydroxybutyrate (BHB), acetoacetate, and acetone. They are transported into the brain interstitial fluid via monocarboxylate transporters (MCTs) expressed at the blood–brain barrier (BBB). This transport is significantly upregulated when ketone bodies serve as alternative energy substrates [9]. Since the introduction of the ketogenic diet (KD) for refractory epilepsy in the 1920s [10], ketone bodies have been regarded as high-efficiency fuels, as their oxidation yields adenosine triphosphate (ATP) more efficiently than glucose [11]. Their uptake is insulin-independent, allowing maintenance of cerebral energy homeostasis during impaired glucose metabolism [12,13,14]. Over the past two decades, however, accumulating evidence has shown that ketone bodies, particularly BHB, which accounts for more than 70% of circulating ketone bodies, function not only as energy substrates but also as signaling molecules and epigenetic modulators [15,16]. Under different conditions, they exert anti-inflammatory and anti-excitotoxic effects, preserve mitochondrial function, and protect BBB integrity, thereby attenuating cerebral ischemia–reperfusion injury and promoting neuroregeneration [17,18,19,20]. These properties position ketone bodies as a promising metabolic intervention for brain disorders. Accordingly, the therapeutic scope of ketogenic strategies has expanded beyond epilepsy to ischemic stroke and neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, highlighting their translational potential [21,22]. This review summarizes the neuroprotective roles of ketone bod-

ies in ischemic stroke and provides a framework for future investigation.

2. Materials and Methods

We performed a narrative review based on PubMed searches using combinations of MeSH terms and keywords related to "Ketone Bodies", "3-Hydroxybutyric Acid", "Acetoacetates", "Brain Ischemia", "Ischemic Stroke", and "Cerebral Infarction". We did not limit the timespan of the literature search to include as many relevant publications as possible. The retrieved literature was screened by two senior researchers, and the review finally included 122 articles.

3. Metabolic Dysregulations and Pathological Changes in Ischemic Stroke

3.1 Metabolism Crisis, Excitotoxicity, and Compensatory Metabolic Shift

The brain consumes approximately 20% of the body's total glucose to meet its metabolic demands, a process critically dependent on uninterrupted cerebral blood flow [23]. During ischemic stroke, interruption of blood flow causes localized deprivation of glucose and oxygen, resulting in a profound energy crisis within ischemic regions. The decline in ATP production initially impairs Na^+/K^+-ATPase activity, leading to influx of Na^+ and Ca^{2+} and efflux of K^+ [24], which in turn causes cellular edema and membrane depolarization. Membrane depolarization promotes excessive glutamate release and subsequent excitotoxicity. Elevated glutamate levels overactivate NMDA receptors, inducing calcium overload and activating excitotoxic signaling pathways that trigger downstream cascades culminating in neuronal dysfunction [25].

In the event of an imbalance in energy metabolism, various compensatory energy diversion mechanisms are activated, albeit with certain limitations. The γ-aminobutyric acid (GABA) shunt serves as an alternative pathway for converting α-ketoglutarate to succinate within the citric acid cycle, bypassing succinate-coenzyme A (CoA) ligase activity [26]. However, research has indicated that the GABA shunt inhibits mitochondrial substrate-level phosphorylation [27]. The malate-aspartate shunt (MAS) employs malate as an intermediate electron carrier to facilitate the transfer of electrons from cytosolic nicotinamide adenine dinucleotide (reduced form) (NADH) to mitochondrial NADH, thereby producing ATP [28]. This process is crucial for maintaining an efficient cerebral energy metabolism. Nonetheless, its functionality is highly contingent on the supply of upstream substrates and the operational integrity of the downstream electron transport chain. Furthermore, calcium overload under ischemic pathological conditions impairs MAS function, leading to functional instability [29,30]. The succinate oxidation shunt, mediated by succinate dehydrogenase (SDH, mitochondrial complex II), plays a central role in reperfusion injury [31]. During ischemia, the tricarboxylic acid (TCA) cycle is stalled, resulting in succinate accumulation via anaerobic pathways. Upon reoxygenation or reperfusion, SDH rapidly oxidizes the accumulated succinates. Although this process generates energy, it also results in substantial electron influx and the production of large quantities of ROS via reverse electron transport (RET) at complex I, thereby paradoxically exacerbating injury [31,32].

In response to energy failure, the brain engages multiple compensatory metabolic pathways, including anaerobic glycolysis [33], the pentose phosphate pathway [34], ketone body metabolism [35], amino acid metabolism [36], and fatty acid metabolism [37]. Neurons primarily compensate by shifting toward anaerobic glycolysis, characterized by increased activity of lactate dehydrogenase A (LDHA) and conversion of pyruvate to lactate. This metabolic shift leads to rapid intracellular acidification [38], which suppresses residual mitochondrial function, activates acid-sensing ion channels (ASICs), and exacerbates calcium influx and glutamate release [39]. Metabolomic studies have shown that patients with stroke exhibit significantly reduced serum levels of glycolytic intermediates and TCA cycle metabolites, reflecting a systemic shift from aerobic to anaerobic metabolism [12,40]. Concurrently, hepatic gluconeogenesis is enhanced, and lipolysis in adipose tissue releases free fatty acids (FFAs), providing substrates for ketone body synthesis [39,41] (Fig. 1). Clinically, plasma BHB levels increase two- to fourfold during the acute phase of stroke, a phenomenon termed "stress ketosis" [12,40,41]. This endogenous ketosis represents a physiological countermeasure to cerebral energy failure. However, its magnitude and duration are generally insufficient to fully compensate for impaired glucose metabolism [12], highlighting the therapeutic potential of exogenous ketone supplementation.

3.2 Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction following ischemic stroke is a central pathological mechanism that contributes not only to energy failure but also to the progression of secondary injury [42]. Following the onset of excitotoxicity, a substantial accumulation of Ca^{2+} and ROS within the mitochondria leads to mitochondrial dysfunction [43]. Excessive mitochondrial fission, coupled with impaired fusion, results in severely compromised function of the fragmented mitochondria and a reduction in their self-repair capacity [19]. The opening of the mitochondrial permeability transition pore (mPTP) is often accompanied by the release of cytochrome c and the inhibition of mitochondrial respiration [44]. This process is directly associated with mitochondrial dysfunction and apoptosis, which are critical events leading to cell death. During the ischemic cascade, intracellular calcium overload disrupts ionic homeostasis and activates calcineurin, leading to dephosphorylation of dynamin-related protein 1 (Drp1) at Serine 637. This modification promotes translocation of Drp1 from the cytosol to the mitochondrial

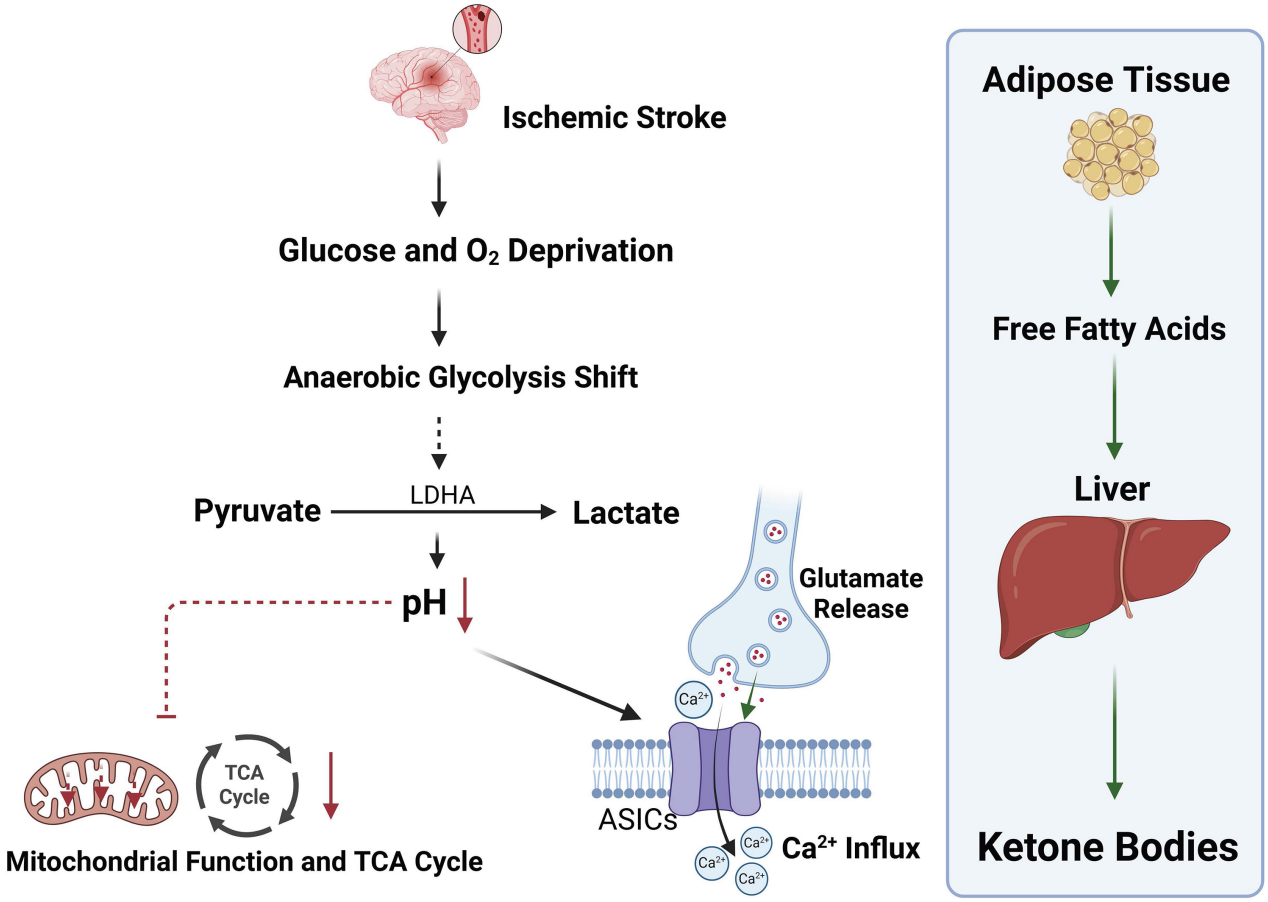

Fig. 1. Metabolic alterations in ischemic stroke and ketone body production. Ischemic stroke induces glucose and oxygen deprivation, leading to a metabolic shift toward anaerobic glycolysis. Concurrently, adipose tissue releases free fatty acids, which are transported to the liver for ketone body synthesis. LDHA, lactate dehydrogenase A; TCA, tricarboxylic acid cycle; ASICs, acid-sensing ion channels. Figure created with BioRender.com (Toronto, ON, Canada; https://www.biorender.com/).

outer membrane (OMM), where it oligomerizes and drives excessive pathological mitochondrial fission [45]. During reperfusion, oxidative stress markedly increases ROS production, which activates the inner mitochondrial membrane protease overlapping with the mitochondrial ATPased associated with diverse cellular activities protease 1 homolog (Oma1). Activated Oma1 mediates proteolytic cleavage of optic atrophy 1 (OPA1), thereby impairing mitochondrial fusion [3,19]. The resulting imbalance between mitochondrial fission and fusion leads to extensive fragmentation of the mitochondrial network and loss of normal mitochondrial morphology. In addition, ischemic injury suppresses key transcriptional regulators of mitochondrial biogenesis, including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), nuclear respiratory factor 1 (Nrf1), and mitochondrial transcription factor A (TFAM) [45,46]. Structural disruption of mitochondria further induces depolarization of the mitochondrial membrane potential (ΔΨm), promoting sustained opening of the mPTP [3,47] (Fig. 2). Cyclophilin D (CypD) within the mitochondrial matrix functions as a crucial regulator of the mPTP opening [48]. Following ischemia, there is a significant increase in its expression level and translocation to the mitochondrial matrix, making it highly susceptible to oxidative stress and calcium overload, which predisposes the mPTP to open [49,50]. Elevated expression and conformational changes in the voltage-dependent anion channel (VDAC) in the outer membrane synergistically interact with mPTP to facilitate outer membrane permeabilization, thereby accelerating the release of apoptotic factors [51]. Concurrently, the expression and activity of the mitochondrial pyruvate carrier (MPC) are markedly reduced, directly impeding the entry of glucose metabolites into the mitochondria [52,53]. This constitutes a fundamental cause of the enforced cessation of aerobic glucose oxidation during ischemia. Collectively, these alterations not only disrupt mitochondrial architecture but also profoundly impair mitochondrial function.

The effectiveness of numerous neuroprotective agents is contingent on the functional integrity of the mitochon-

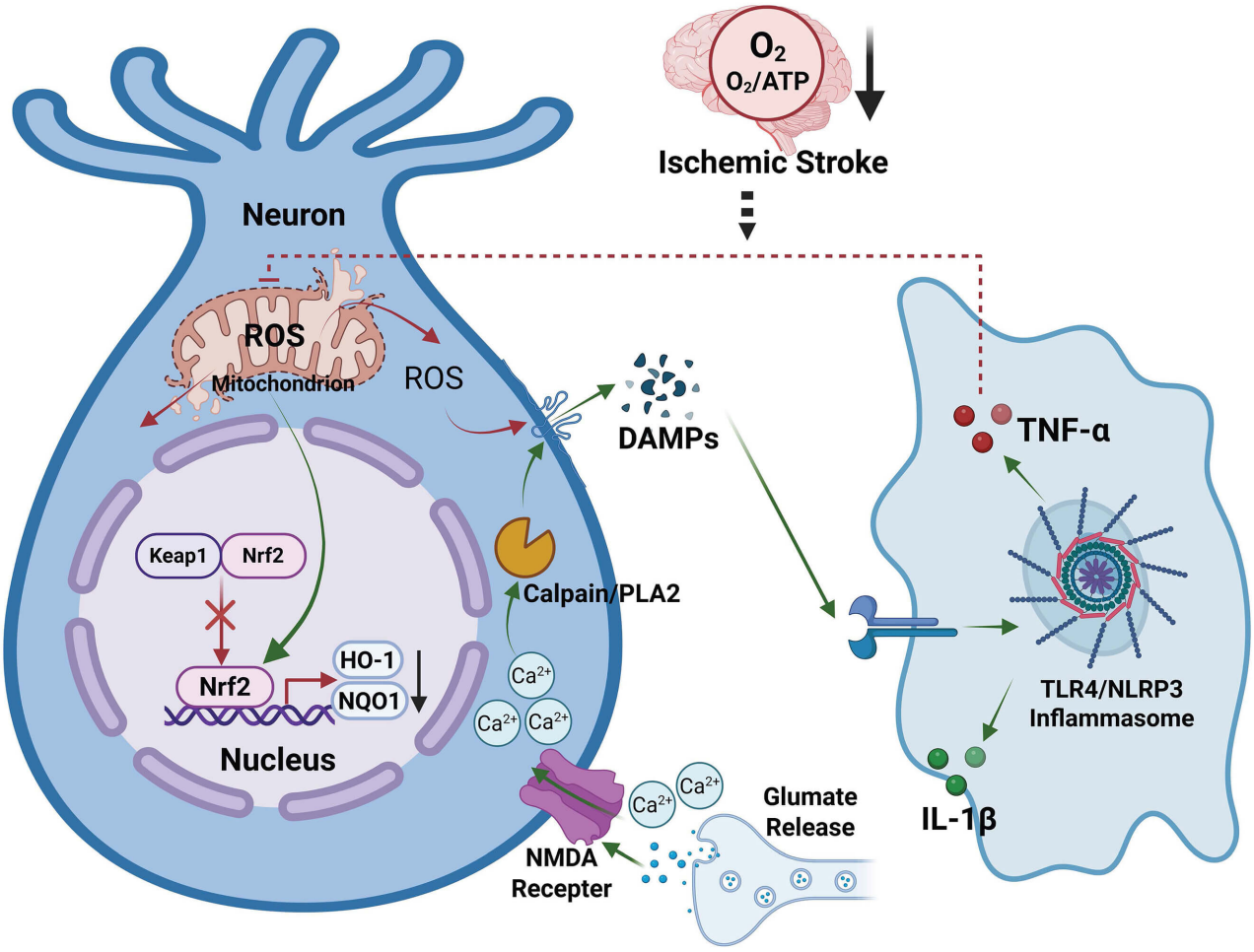

Fig. 2. Mitochondrial dynamics imbalance and apoptosis in ischemia–reperfusion injury. Ischemia induces calcium overload and activates calcineurin, promoting Drp1-mediated mitochondrial fission. Upon reperfusion, excessive ROS activate Oma1, leading to OPA1 cleavage, inhibition of mitochondrial fusion, and fragmentation of the mitochondrial network. Concurrently, reduced mitochondrial biogenesis and impaired self-repair, together with cytochrome c release and Caspase-9/-3 activation, drive apoptotic cell death. Drp1, dynamin-related protein 1; Oma1, Overlapping with the mitochondrial ATPased associated with diverse cellular activities protease 1 homolog; OPA1, optic atrophy 1; ROS, reactive oxygen species; mPTP, mitochondrial permeability transition pore; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; Nrf1, nuclear respiratory factor 1; TFAM, mitochondrial transcription factor A; Caspase-9, cysteine-aspartic protease 9; Caspase-3, cysteine-aspartic protease 3. Figure created with BioRender.com.

dria. In cases of mitochondrial dysfunction, aerobic glucose oxidation is restricted [54]. As this dysfunction progresses, the utilization of substrates necessitating an intact electron transport chain and membrane potential, such as glucose and ketone bodies, becomes further constrained. The uptake and accumulation of many lipophilic cationic drugs targeting mitochondria are dependent on the mitochondrial membrane potential [55]. A decline in the membrane potential results in a significant reduction in the concentration of these drugs within the mitochondria, thereby substantially diminishing their efficacy. In cases where mitochondrial function is severely compromised, cells are entirely deprived of their energy sources, rendering the condition irreversible [56].

Mitochondrial dysfunction is a major source of ROS and reactive nitrogen species (RNS) following ischemic stroke [57]. The mitochondrial electron transport chain (ETC) comprises five enzyme complexes embedded in the inner mitochondrial membrane: NADH-coenzyme Q (CoQ) reductase (complex I), succinate–CoQ reductase (complex II), CoQ–cytochrome c reductase (complex III), cytochrome c oxidase (complex IV), and ATP synthase (complex V) [58]. Under ischemic conditions, impairment of cytochrome c oxidase (complex IV) drives the ETC into a highly reduced state, facilitating electron leakage from complexes I and the quinol oxidation (Qo) site of complex III to residual oxygen. This single-electron transfer generates superoxide anion ($O_2^{\bullet-}$) and initiates a burst of ROS production [59]. Dysfunction of the ETC, together with

activation of NADPH oxidase (NOX), leads to excessive ROS generation, causing oxidative damage to lipids, proteins, and DNA [47,60]. Moreover, inducible nitric oxide synthase (iNOS) is markedly upregulated, resulting in sustained overproduction of nitric oxide (NO). As an RNS, NO rapidly reacts with $O_2^{\bullet-}$ to form the highly reactive peroxynitrite anion ($ONOO^-$), further exacerbating oxidative and nitrosative stress [61].

Concurrently, endogenous antioxidant defenses are impaired after ischemic stroke. The Kelch-like epichlorohydrin (ECH)-associated protein 1 (Keap1)/nuclear factor erythroid 2–related factor 2 (Nrf2) pathway is a key cellular defense mechanism against oxidative stress and mitochondrial dysfunction. Under physiological conditions, Nrf2 is retained in the cytoplasm through binding to Keap1 [47]. Post-ischemic stabilization of the Keap1-Nrf2 complex limits Nrf2 nuclear translocation, thereby suppressing transcription of antioxidant enzymes, including heme oxygenase-1 (HO-1) and NAD(P)H: quinone oxidoreductase 1 (NQO1) [47].

3.3 Vicious Cycle of Metabolic Dysfunction and Neuroinflammation

Pathological changes triggered by disruption of oxygen and energy supply, such as excitotoxicity, mitochondrial dysfunction, and oxidative stress, initiate robust neuroinflammatory responses [62]. Neuroinflammation is characterized by the release of inflammatory mediators and activation of resident and infiltrating immune cells, leading to cellular injury and further metabolic dysregulation. Excessive glutamate release overactivates NMDA receptors [5], causing calcium overload and subsequent activation of calpain and phospholipase A2 (PLA2), which disrupt cytoskeletal organization and plasma membrane integrity [2,3]. In parallel, damage-associated molecular patterns (DAMPs) released from necrotic cells resulting from metabolic dysfunction activate the microglial toll-like receptor 4 (TLR4)/nucleotide-binding and oligomerization domain (NOD)-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome pathway, promoting secretion of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). These mediators exacerbate BBB disruption, enhance neutrophil infiltration, and inhibit mitochondrial respiratory chain complex IV (cytochrome c oxidase) in a TNF-α–dependent manner, thereby increasing ROS production. Elevated ROS levels further aggravate mitochondrial dysfunction, cellular injury, and neuroinflammation. Consequently, metabolic dysfunction and neuroinflammation form a self-amplifying vicious cycle that accelerates ischemic brain injury (Fig. 3).

3.4 Multiple Pathways of Cell Death

Multiple cell death pathways are activated as a consequence of the pathological changes described above [63], including intrinsic (mitochondrial) apoptosis (such as calpain-mediated apoptosis [64], ROS-mediated apoptosis [65], and DNA damage–mediated apoptosis [66]), extrinsic (death receptor)–mediated apoptosis by the extrinsic/death receptor pathway [67], necroptosis [68,69], autophagy [70], and ferroptosis [71]. Calpain-mediated apoptosis is triggered by calcium overload, which activates calpain proteases and leads to cleavage of substrates such as BH3-interacting domain death agonist (BID), opening of the mPTP, and release of pro-apoptotic factors, including cytochrome c and apoptosis-inducing factor. These events culminate in both caspase-dependent and caspase-independent neuronal death. ROS disrupt plasma membrane integrity [72] and induce DNA strand breaks [73]. DNA damage activates nuclear death pathways through phosphorylation of tumor protein p53 [74], while p53 can also directly promote mitochondrial apoptosis [75]. Inflammatory responses initiated by ischemic stroke further contribute to neuronal death through the extrinsic apoptotic pathway, as activated immune cells release factors such as TNF-α and IL-1β [76,77]. Necroptosis is a regulated form of necrotic cell death dependent on receptor-interacting protein kinase (RIPK)1, RIPK3, and mixed lineage kinase domain-like pseudokinase (MLKL), representing a caspase-independent pathway distinct from apoptosis [68,69]. Autophagy is a lysosome-mediated self-degradation process in which organelles and cytosolic macromolecules are sequestered within autophagosomes and subsequently degraded, serving primarily as an adaptive response to cellular stress [70]. Ferroptosis is an iron-dependent form of regulated cell death characterized by mitochondrial shrinkage and lipid peroxidation of polyunsaturated fatty acids; it is counteracted by glutathione (GSH)–dependent glutathione peroxidase 4 (GPX4) activity and antioxidant systems [71]. Following ischemic stroke, neurons undergo death through multiple overlapping pathways, leading to regional infarction and neurological dysfunction. Current evidence indicates that these mechanisms operate concurrently; however, whether specific pathways predominate under particular conditions remains unclear.

4. Multifaceted Neuroprotection of Ketone Bodies

4.1 Acute-Phase Protection

4.1.1 Energy Supply and Mitochondrial Stabilization

Cerebral ischemia reduces the supply of glucose and oxygen to brain tissue, thereby suppressing mitochondrial oxidative phosphorylation and leading to ATP depletion [78]. BHB is transported into the brain via MCTs, where it is metabolized to acetyl coenzyme A (acetyl-CoA) for entry into the TCA cycle. BHB oxidation yields ATP more efficiently than glucose with reduced ROS production and does not require insulin-mediated transport [21,22,54]. Extracellular signal-regulated kinase (ERK) is a core member of the mitogen-activated protein kinase (MAPK) fam-

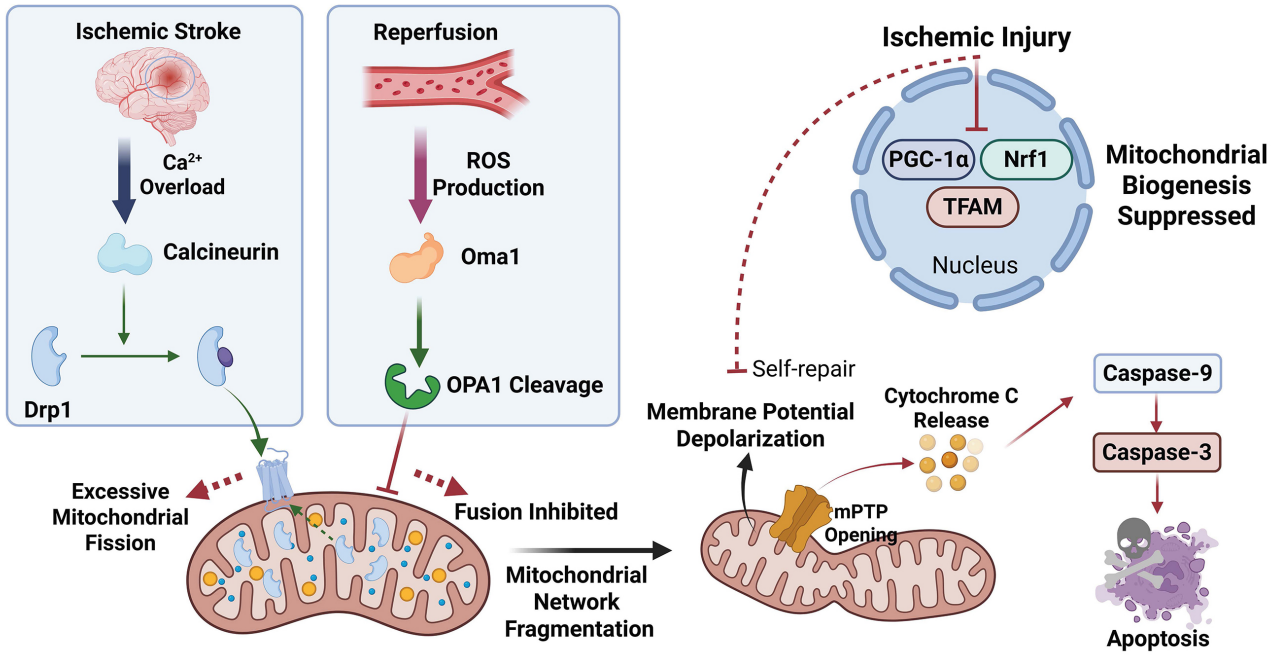

Fig. 3. Neuronal injury and immune activation in ischemic stroke. Ischemic stroke induces mitochondrial ROS overproduction in neurons, inhibits the Keap1–Nrf2 signaling pathway, and promotes calcium influx via NMDA receptors in response to excessive glutamate release. Concurrently, injured neurons release DAMPs, which activate the TLR4/NLRP3 inflammasome in immune cells and promote the secretion of pro-inflammatory cytokines, including TNF-α and IL-1β. NMDA, N-methyl-D-aspartate; DAMPs, damage-associated molecular patterns; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; NQO1, NAD(P)H quinone dehydrogenase 1; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; TLR4, Toll-like receptor 4; NLRP3, NOD-like receptor family pyrin domain-containing 3; PLA2, phospholipase A2. Figure created with BioRender.com.

ily, which plays a critical role in the initiation and progression of ischemic stroke [79]. It can activate downstream cyclic adenosine monophosphate (AMP)-response element-binding protein to promote neuronal survival [80]. Endothelial nitric oxide synthase (eNOS) is a critical enzyme in endothelial cells that generates NO, mediating diverse vascular regulatory functions [81]. Yin et al. [82] reported that BHB increases the NAD^+/NADH ratio, activating mitochondrial sirtuin 3 (SIRT3), which deacetylates forkhead box O3a (FoxO3a) and superoxide dismutase 2 (SOD2), thereby enhancing mitochondrial antioxidant capacity. Li et al. [83] demonstrated that BHB activates the ERK/cAMP response element-binding protein (CREB)/eNOS pathway, leading to improved mitochondrial respiratory chain complex I activity and reduced ROS production. In addition, Holstein et al. [84] showed using oxygen consumption rate (OCR) analysis of isolated brain tissue that BHB increases mitochondrial coupling efficiency from 54.1% to 96.95% under normal glucose conditions and from 64.47% to 89.11% under high-glucose conditions, while enhancing mitochondrial responsiveness to substrates. Furthermore, BHB inhibits Drp1 translocation to mitochondria, thereby suppressing pathological mitochondrial fission and preserving mitochondrial morphology and function [19].

4.1.2 Inhibition of Excitotoxicity and Calcium Overload

Energy failure leads to Na^+/K^+-ATPase dysfunction, membrane depolarization, and excessive glutamate release, which results in overactivation of NMDA receptors and subsequent calcium overload [2,85]. BHB counteracts these processes through complementary mechanisms. First, BHB competitively inhibits vesicular glutamate transporters (VGLUTs), thereby reducing presynaptic glutamate release [86]. Second, BHB activates neuronal ATP-sensitive potassium channels (KATP), inducing membrane hyperpolarization and decreasing neuronal excitability [23,87,88]. In oxygen–glucose deprivation models, pretreatment with 10 mM BHB significantly reduced extracellular glutamate concentrations and mitochondrial calcium loading, effectively blocking downstream apoptotic cascades [83]. These effects not only limit acute neuronal injury but also create a favorable environment for subsequent repair and recovery.

4.1.3 Anti-Inflammatory Effects

The post-ischemic release of DAMPs activates the microglial TLR4/NLRP3 inflammasome pathway, leading to the induction of IL-1β and TNF-α release [2]. Offermanns and Schwaninger [89] identified BHB as an en-

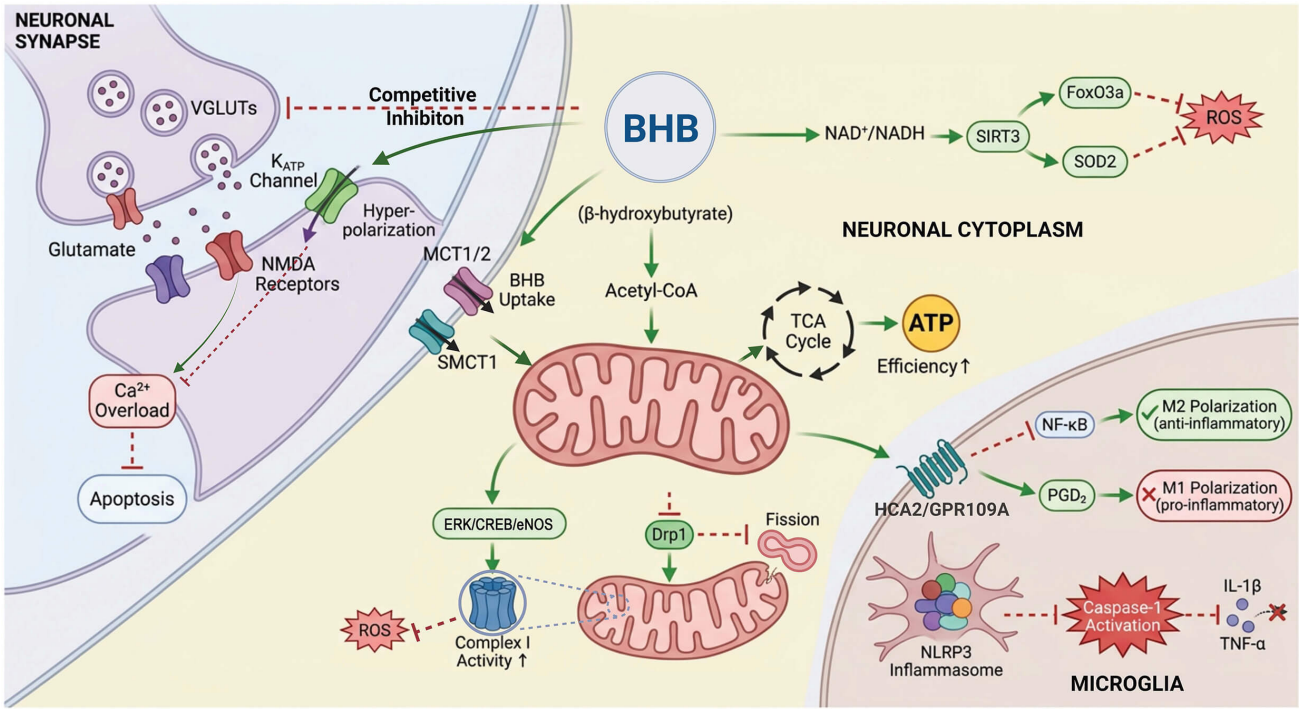

Fig. 4. Neuroprotective mechanisms of BHB. This schematic illustrates the multifaceted roles of BHB in regulating neuronal synaptic function, mitochondrial metabolism, and microglial polarization. At the synapse, BHB modulates KATP channels to promote membrane hyperpolarization, attenuates calcium overload and glutamate excitotoxicity, and suppresses apoptosis. In the cytoplasm, BHB is transported via MCT1/2 and SMCT1, enters mitochondria to enhance TCA cycle efficiency and ATP production, and activates SIRT3 to upregulate the FoxO3a/SOD2 axis. In microglia, BHB activates HCA2/GPR109A, promoting anti-inflammatory M2 polarization and reducing the release of pro-inflammatory cytokines, including IL-1β and TNF-α. BHB, β-hydroxybutyrate; VGLUTs, vesicular glutamate transporters; KATP, ATP-sensitive potassium channels; MCT1/2, monocarboxylate transporter 1/2; SMCT1, sodium-coupled monocarboxylate transporter 1; FoxO3a, forkhead box O3a; SIRT3, sirtuin 3; SOD2, superoxide dismutase 2; ERK, extracellular signal-regulated kinase; CREB, cAMP-response element-binding protein; eNOS, endothelial nitric oxide synthase; HCA2, hydroxycarboxylic acid receptor 2; PGD_2, prostaglandin D_2; TCA, tricarboxylic acid; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain-containing 3; Drp1, dynamin-related protein 1. Figure created with BioRender.com.

dogenous ligand for hydroxycarboxylic acid receptor 2 (HCA2/GPR109A). Activation of HCA2 by BHB suppresses nuclear factor-κB (NF-κB) signaling while promoting prostaglandin D_2 (PGD_2) synthesis, which drives microglial polarization toward the anti-inflammatory M2 phenotype [89]. In addition, BHB directly inhibits NLRP3 inflammasome assembly, thereby reducing cysteine-aspartic protease-1 (caspase-1) activation and IL-1β maturation and release [19,90]. In middle cerebral artery occlusion (MCAO) models, BHB treatment significantly reduced IL-1β and TNF-α expression within the infarct core and attenuated neutrophil infiltration [17,20]. These acute anti-inflammatory effects mitigate secondary injury and facilitate resolution of inflammation during the subacute phase (Fig. 4).

4.1.4 Maintaining the Cerebral Barrier and Clearance Systems

The BBB is a dynamic interface composed of brain capillary endothelial cells with tight junctions, the basement membrane, astrocytic endfeet, and pericytes. It tightly regulates material exchange between the bloodstream and brain parenchyma, thereby maintaining central nervous system homeostasis [91]. Zonula occludens-1 (ZO-1) is a core scaffold protein essential for BBB tight junction integrity. Following ischemic stroke, ZO-1 expression rapidly decreases, leading to increased BBB permeability and facilitating infiltration of peripheral inflammatory cells and mediators into brain tissue, which exacerbates neuroinflammation [20]. BHB has been reported to upregulate histone H3 lysine 9 β-hydroxybutyrylation, thereby inducing ZO-1 expression and preserving BBB function [18]. These findings highlight a protective role for BHB and suggest that β-hydroxybutyrylation may represent a therapeutic target in ischemic stroke, warranting further investigation.

The glymphatic system, also referred to as the brain lymphatic–like clearance pathway, functions as a waste removal mechanism mediated primarily by astrocytes. It operates through convective exchange between cerebrospinal fluid and interstitial fluid within brain tissue [92]. Dys-

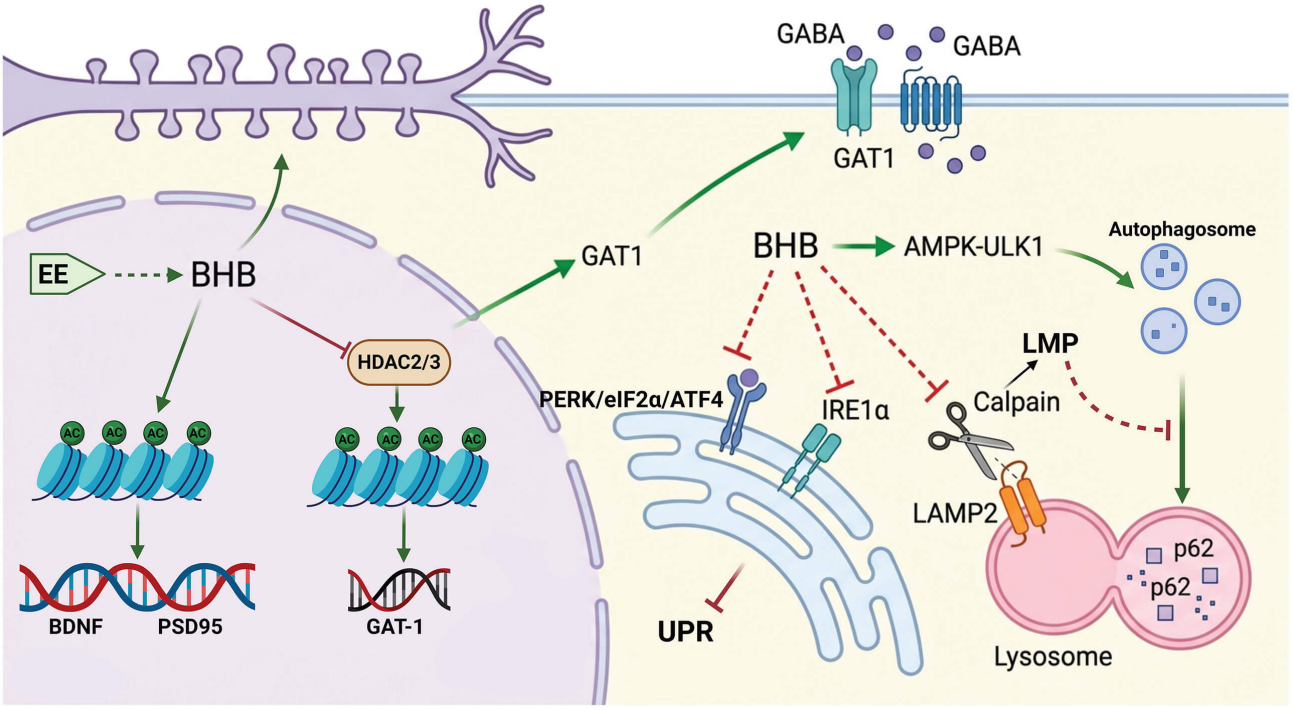

Fig. 5. Role of BHB in neural remodeling and functional recovery. This schematic illustrates that BHB coordinates neuronal synaptic plasticity and cellular homeostasis through multiple mechanisms, including promoting histone acetylation of BDNF and PSD95, upregulating GAT1 expression and modulating GABA transport, suppressing UPR signaling, and activating AMPK–ULK1-dependent autophagy. PSD95, postsynaptic density protein 95; BDNF, brain-derived neurotrophic factor; EE, environmental enrichment; HDAC, histone deacetylase; GAT1, γ-aminobutyric acid transporter 1; AMPK, AMP-activated protein kinase; ULK1, Unc-51-like autophagy activating kinase 1; LAMP2, lysosomal-associated membrane protein 2; LMP, lysosomal membrane permeabilization; UPR, unfolded protein response; PERK, protein kinase RNA-like endoplasmic reticulum kinase; eIF2α, eukaryotic initiation factor 2 alpha; ATF4, activating transcription factor 4; IRE1α, inositol-requiring enzyme 1 alpha; Calpain, calcium-dependent cysteine protease; GABA, gamma-aminobutyric acid; HDAC2/3, histone deacetylase 2/3. Figure created with BioRender.com.

function of the glymphatic system, particularly involving aquaporin-4 (AQP4), contributes to the development of brain edema after ischemic stroke. Yu et al. [93] demonstrated in a mouse MCAO model that BHB enhances glymphatic function and reduces post-ischemic brain edema by upregulating α1-syntrophin and restoring AQP4 polarity through inhibition of histone deacetylase 3 (HDAC3) and increased E1A binding protein p300 (p300) activity.

4.2 Promoting Neural Remodeling and Functional Recovery

4.2.1 Epigenetic Reprogramming

During stroke recovery, synaptic remodeling requires activation of genes associated with neuroplasticity [94]. Lin and colleagues [95] demonstrated that BHB functions as a class I HDAC inhibitor, promoting histone H4 acetylation and derepressing transcription of brain-derived neurotrophic factor (BDNF) and postsynaptic density protein 95 (PSD95). Environmental enrichment (EE), defined as enhancement of the living environment of experimental animals, further promotes stroke recovery through BHB-mediated epigenetic reprogramming [96]. EE increases BHB levels in the peri-infarct cortex, enhancing H4 acetylation at the promoter regions of BDNF and PSD95 and increasing their expression. Chromatin immunoprecipitation (ChIP) assays confirmed enrichment of active chromatin markers (e.g., histone H3 lysine 27 acetylation) at promoters of neuroplasticity-related genes following BHB treatment. This epigenetic remodeling increases dendritic spine density in the peri-infarct cortex and enhances plasticity of long-range circuits connecting the contralateral cortex and spinal cord [95,96].

4.2.2 Regulation of Neural Network Excitability

An imbalance in neuronal excitability in the peri-infarct cortex, characterized by increased tonic GABA inhibition and reduced phasic GABA inhibition, impairs functional recovery after stroke [97,98]. In a mouse photothrombotic stroke model, BHB restored network excitability by modulating the histone deacetylase 2/3 (HDAC2/3)–GABA transporter 1 (GAT1) axis. Specifically, BHB inhibited HDAC2/3 activity, promoting histone acetylation at the GAT1 promoter and upregulating GAT1 expression. This process reduces tonic GABA in-

hibition, thereby enhancing neuronal excitability in the peri-infarct cortex, while simultaneously augmenting phasic GABA inhibition to improve interneuron activity and inhibitory synaptic transmission [95,99,100]. Experimental study demonstrated that BHB treatment significantly increased neuronal excitability in the peri-infarct cortex, restored local field potential amplitude, and promoted axonal sprouting of the contralateral corticospinal tract [95].

4.2.3 Facilitation of Autophagy

Accumulation of damaged organelles and misfolded proteins exacerbates neuronal injury [101], making efficient autophagic–lysosomal function essential for clearance of toxic substrates [102]. Under ischemic conditions, calcium overload activates calpain, which cleaves lysosomal-associated membrane protein 2 (LAMP2), a key lysosomal membrane component [103]. This cleavage induces lysosomal membrane permeabilization (LMP), characterized by loss of the acidic lysosomal pH gradient and reduced enzymatic activity, as demonstrated by acridine orange staining. LMP disrupts autophagosome–lysosome fusion and causes leakage of lysosomal enzymes, thereby blocking autophagic flux. This impairment is reflected by accumulation of the autophagy substrate sequestosome 1 (SQSTM1)/p62 and failure to clear damaged proteins and organelles. Montiel et al. [102] showed that D-β-hydroxybutyrate (D-BHB), the physiological enantiomer, prevents LAMP2 cleavage and preserves lysosomal integrity. Restoration of LAMP2 facilitates autophagosome–lysosome fusion, enabling p62 degradation and mitophagy [102]. BHB also suppresses endoplasmic reticulum (ER) stress pathways, including the protein kinase RNA-like ER kinase (PERK)/eukaryotic initiation factor 2 alpha (eIF2α)/activating transcription factor 4 (ATF4) and inositol-requiring enzyme 1 alpha (IRE1α) signaling axes, thereby reducing ER protein burden and preventing pathological activation of the unfolded protein response (UPR), particularly the pro-apoptotic PERK/ATF4/C/EBP homologous protein (CHOP) and IRE1α pathways, and maintaining proteostasis [102]. In severe hypoglycemia models, D-BHB modulates the AMP-activated protein kinase (AMPK)–Unc-51-like kinase 1 (ULK1) axis to enhance cortical autophagic flux while limiting excessive autophagy initiation in the hippocampus. This bidirectional regulation improves autophagic dynamics and reduces neuronal degeneration [104] (Fig. 5, Table 1).

5. Clinical Translation: Evidence, Challenges, and Directions

5.1 Preclinical Evidence of the Protective Effects of Ketone Bodies

Animal studies provide substantial evidence supporting the neuroprotective effects of ketone bodies. A meta-analysis by Gambardella et al. [105], encompassing 49 experimental murine studies of acute central nervous system (CNS) injury, showed that ketogenic interventions, either dietary or via exogenous ketones, significantly reduced mortality (Hedges' g = 2.45), neuronal injury (g = 1.96), and functional deficits (g = 0.99). The magnitude of protection exhibited a positive linear correlation with blood BHB levels, with each 1 mmol/L increase in BHB corresponding to a 0.07 increase in effect size [105]. Protective effects of KD pretreatment or acute ketone administration have been observed in transient middle cerebral artery occlusion (tMCAO), photothrombotic stroke, and intracerebral hemorrhage models [83,84,106]. In addition, ketone bodies consistently reduce neuronal death in experimental models of cerebral ischemia [107]. Collectively, these findings support ketone body administration as a multifaceted therapeutic strategy for stroke.

5.2 The Paradox of E ndogenous Elevation vs. Exogenous Supplementation

Despite promising preclinical data, a paradox exists between clinical observations and experimental findings. Elevated serum BHB levels in patients with acute stroke have been associated with poorer functional outcomes and increased mortality [12,90,108,109], seemingly contradicting the protective effects observed in preclinical studies. However, current evidence does not indicate that increased ketone levels directly worsen outcomes. Instead, metabolomic analyses suggest that post-stroke endogenous ketogenesis reflects a systemic stress response characterized by acute adipose tissue catabolism and hepatic ketone production, accompanied by hyperglycemia, inflammatory cytokine surges, and increased oxidative stress [12,39,41,110]. These observations imply that ketone elevation is more likely a marker of disease severity rather than a causal factor. Accordingly, it is essential to distinguish between "stress ketosis", a maladaptive response, and "therapeutic ketosis", a targeted metabolic intervention, when interpreting clinical data and designing treatment strategies [12,90].

In contrast, exogenous ketone supplementation allows precise control of circulating ketone levels, potentially avoiding stress-induced metabolic dysregulation while maintaining neuroprotective effects [106,111,112,113]. This controllability highlights the translational potential of exogenous ketone administration. Future preclinical studies should therefore define optimal dosing, routes of administration, delivery strategies, and treatment timing to establish a robust framework for clinical translation.

5.3 The Windows of Timing and Dosage

The timing of ketogenic interventions demonstrates considerable therapeutic flexibility. Benefits have been observed with prolonged KD adaptation (more than seven days before ischemia), acute administration after stroke onset, and delayed treatment initiated up to ten hours after stroke [93,105]. Notably, the mechanisms of ketone bodi-

Table 1. Multifaceted neuroprotective mechanisms of β-hydroxybutyrate in ischemic stroke.

Mechanistic domain	Key molecules/pathways	BHB-mediated regulation	Core biological effects
Energy metabolism	Acetyl-CoA/TCA cycle	Metabolic conversion: BHB is transported into the brain through MCT1/2 and converted into acetyl-CoA, which enters the tricarboxylic acid cycle	Provides an insulin-independent energy substrate and sustains ATP production under conditions of impaired glucose metabolism
Mitochondrial homeostasis	SIRT3-FoxO3a-SOD2	Activation: BHB increases the NAD^+/NADH ratio, thereby activating SIRT3 signaling	Enhances mitochondrial antioxidant capacity and promotes reactive oxygen species clearance
	ERK/CREB/eNOS/respiratory chain complex I	Activation: BHB activates the ERK/CREB/eNOS pathway following cellular uptake	Improves mitochondrial respiratory efficiency and attenuates oxidative stress and apoptosis
	Drp1	Inhibition: BHB prevents Drp1 translocation to the mitochondrial outer membrane	Suppresses pathological mitochondrial fission and preserves mitochondrial morphology and function
Excitotoxicity inhibition	VGLUTs	Competitive inhibition	Reduces presynaptic glutamate release and limits calcium overload
	KATP channels	Activation	Induces membrane hyperpolarization and suppresses neuronal hyperexcitability
Anti-inflammation and immunity	HCA2 (GPR109A)/NF-κB	Receptor-mediated inhibition: BHB activates HCA2 and suppresses NF-κB signaling	Promotes PGD_2 synthesis and drives microglial polarization toward a neuroprotective M2 phenotype
	NLRP3 inflammasome	Direct inhibition of inflammasome assembly	Reduces caspase-1 activation and limits the maturation and release of IL-1β and TNF-α
Barrier and clearance systems	ZO-1/H3K9 β-hydroxybutyrylation	Epigenetic upregulation: BHB enhances H3K9 β-hydroxybutyrylation and induces ZO-1 expression	Preserves blood-brain barrier integrity and facilitates barrier repair after ischemic injury
	AQP4 polarity/α1-syntrophin/HDAC3/p300	Restoration of polarization: BHB inhibits HDAC3 and enhances p300 activity, thereby restoring AQP4 polarity and α1-syntrophin expression	Improves glymphatic clearance and alleviates cerebral edema
Epigenetic reprogramming	Class I HDACs	Enzymatic inhibition: BHB inhibits class I HDACs and promotes histone acetylation	Derepresses neuroplasticity-related genes, including *BDNF* and *DLG4*, and promotes synaptic remodeling
	HDAC2/3-GAT1	Disinhibition: BHB inhibits HDAC2/3, leading to upregulation of GAT1 expression	Reduces tonic GABA inhibition and restores peri-infarct cortical network excitability
Autophagy and proteostasis	LAMP2/calpain	Targeted protection: BHB prevents calpain-mediated cleavage of LAMP2	Preserves lysosomal membrane integrity and restores autophagic flux and p62 degradation
	ER stress (PERK/ATF4/CHOP, IRE1α)	Inhibition: BHB suppresses PERK/ATF4/CHOP and IRE1α signaling	Alleviates endoplasmic reticulum stress and prevents unfolded protein response-associated apoptosis
	AMPK-ULK1	Bidirectional modulation: BHB modulates autophagy dynamics through AMPK-ULK1 signaling	Maintains autophagic homeostasis and reduces neuronal degeneration under metabolic stress

BHB, β-hydroxybutyrate; MCT1/2, monocarboxylate transporter 1/2; Acetyl-CoA, acetyl coenzyme A; TCA cycle, tricarboxylic acid cycle; ATP, adenosine triphosphate; SIRT3, sirtuin 3; FoxO3a, forkhead box O3a; SOD2, superoxide dismutase 2; NAD^+/NADH, nicotinamide adenine dinucleotide (oxidized/reduced form); ERK, extracellular signal-regulated kinase; CREB, cAMP response element-binding protein; eNOS, endothelial nitric oxide synthase; Drp1, dynamin-related protein 1; VGLUTs, vesicular glutamate transporters; KATP channels, ATP-sensitive potassium channels; HCA2 (GPR109A), hydroxycarboxylic acid receptor 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGD_2, prostaglandin D_2; NLRP3 inflammasome, NOD-like receptor family pyrin domain-containing 3 inflammasome; Caspase-1, cysteine-aspartic protease-1; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor alpha; ZO-1, zonula occludens-1; H3K9 β-hydroxybutyrylation, histone H3 lysine 9 β-hydroxybutyrylation; AQP4, aquaporin-4; α1-syntrophin, alpha-1 syntrophin; HDAC3, histone deacetylase 3; p300, E1A binding protein p300; HDACs, histone deacetylases; HDAC2, histone deacetylase 2; GAT1, GABA transporter 1; BDNF, brain-derived neurotrophic factor; PSD95, postsynaptic density protein 95; LAMP2, lysosome-associated membrane protein 2; Calpain, calcium-dependent cysteine protease; ER stress, endoplasmic reticulum stress; PERK, protein kinase RNA-like ER kinase; ATF4, activating transcription factor 4; CHOP, C/EBP homologous protein; IRE1α, inositol-requiring enzyme 1 alpha; AMPK, AMP-activated protein kinase; ULK1, Unc-51 like autophagy activating kinase 1.

Table 2. Dosage, route, and timing of ketone bodies administration.

Ketone type/strategy	Model	Dosage	Route	Timing	Broad mechanism class	Reference
KD	Mice	KD for 3 weeks	Diet (KD);	3 weeks before MCAO/R	Anti-inflammatory; mitochondrial/ER-stress protection	[19]
BHB	Mice	1 g/mL and 8 µL/h for 3 days	Subcutaneous pump infusion	Early post-stroke period (first 3 days)	BBB protection/repair; anti-inflammatory; epigenetic regulation	[20]
BHB	Mice	2 g/kg/day for 2 weeks	Drinking water	Before PT	Anti-inflammatory; anti-oxidative; mitochondrial support; recovery promotion	[60]
BHB	Rats	500 µg/kg (optimal ICV dose)	ICV	1 h after MCAO surgery	Energy/mitochondrial support; anti-oxidative/anti-apoptotic signaling	[83]
BHB	Mice	2.52 g/kg	Subcutaneous injection	Acute setting (metabolic stress/photothrombotic model)	Energy metabolism optimization; mitochondrial function improvement	[84]
BHB/KD comparison arm	Mice	BHB 5 g/kg/day; KD for 4 weeks (preconditioning arm)	Post-MCAO BHB administration; diet for KD	Post-MCAO; delayed-start arm at 10 h also tested	Glymphatic/edema control; BBB-water homeostasis; epigenetic regulation	[93]
BHB; 1,3-butanediol	Mice	Continuous drug delivery during 5–11 days: 1.6 mmol/kg/day; 1 µL/h	Subcutaneous pump infusion	5 days after stroke	Neuroplasticity/network remodeling; epigenetic regulation	[95]
BHB; (R)-3-hydroxybutyl (R)-β-HB	Mice	Continuous drug delivery during 5–11 days: 1.6 mmol/kg/day; 1 µL/h	Subcutaneous pump infusion	5 days after stroke	Neuroplasticity/functional recovery; cortical network remodeling	[96]
D-BHB	Rats	1 M (500 µL) intraperitoneal injection, continuous infusion of 2 M	Intraperitoneal injection/local infusion	After MCAO	Autophagy-lysosomal protection; preventing proteotoxicity	[102]
L-BHB	Rats	1 M (500 µL) intraperitoneal injection, continuous infusion of 2 M	Intraperitoneal injection/local infusion	After MCAO	No significant protective effect	[102]

KD, ketogenic diet; BHB, β-hydroxybutyrate; D-BHB, D-β-hydroxybutyrate; L-BHB, L-β-hydroxybutyrate; (R)-3-hydroxybutyl (R)-β-HB, (R)-3-hydroxybutyl (R)-β-hydroxybutyrate; MCAO/R, middle cerebral artery occlusion/reperfusion; PT, photothrombosis; ICV, intracerebroventricular; BBB, blood-brain barrier.

es differ across temporal phases. During the acute phase, ketone bodies enhance energy supply, inhibit inflammasome activation, and stabilize the BBB [19,20]. During the recovery phase, they promote epigenetic reprogramming, dendritic spine formation, and long-range circuit remodeling [95].

Currently, ketone bodies can be administered through two main approaches. The first induces endogenous ketogenesis via oral nutritional interventions, such as KD or intermittent fasting [13,18]. Although slower in onset, this approach provides sustained elevation of BHB levels and generally favorable tolerability and safety. The second involves exogenous supplementation with ketone bodies or their precursors, including oral ketone esters, intravenous BHB salts, and intracerebroventricular (ICV) or subcutaneous administration [18,20,22,83,102]. This strategy offers rapid onset and precise control of circulating ketone concentrations, making it particularly suitable for time-sensitive interventions in acute brain injury, including ischemic stroke.

Importantly, the neuroprotective effects of BHB appear dose-dependent. Li et al. [83] demonstrated in MCAO rats that intracerebroventricular administration of moderate-dose BHB (500 μg/kg) significantly improved neurological scores and reduced infarct volume, whereas a higher dose (1000 μg/kg) showed diminished efficacy. *In vitro*, 10 mM BHB enhanced neuronal viability, whereas concentrations ≥50 mM induced cytotoxicity, indicating a relatively narrow therapeutic window [83]. These findings underscore the importance of precise dose titration in future translational studies (Table 2, Ref. [19,20,60,83,84,93,95,96,102]).

5.4 The Impact of Individual Heterogeneity and Metabolic Context

The efficacy of exogenous ketone interventions exhibits substantial interindividual variability, influenced by genetic, metabolic, and microbial factors. For example, individuals carrying apolipoprotein E ε4 (ApoE4) show attenuated responses to medium-chain triglyceride supplementation (i.e., exogenous BHB elevation) compared with ApoE4-negative individuals [114]. In addition, a study in Alzheimer's disease has demonstrated that regions of glucose hypometabolism identified by fluorodeoxyglucose positron emission tomography (FDG-PET) are associated with responsiveness to ketone-based interventions [14]. Metabolic conditions such as diabetes and obesity, characterized by insulin resistance and chronic inflammation, may impair ketone utilization efficiency or exacerbate metabolic side effects [22,39]. Hyperhomocysteinemia further aggravates cerebral ischemia by altering plasma amino acid profiles and competitively inhibiting monocarboxylate transporter 1 (MCT1)-mediated ketone transport across the BBB [40]. Age also influences therapeutic efficacy. Meta-analyses demonstrate that the neuroprotective effect of ketosis, as measured by the aggregated advantage (a composite of mortality, neuronal damage, and dysfunction), is markedly stronger in juvenile animals (Hedges' g = 3.99) than in adults (g = 1.50), an effect that correlates with developmental expression patterns of cerebral MCT1/2 isoforms [105]. Moreover, KD alters the gut microbiome, increasing the abundance of *Akkermansia muciniphila* and reducing *Bacteroides fragilis* [21]. These microbial shifts enhance short-chain fatty acid (SCFA) production, which modulates microglial metabolism through G protein–coupled receptor 43/41 (GPR43/41) signaling, promoting a shift from glycolysis-dependent M1-like phenotypes to oxidative phosphorylation-driven M2-like states [115]. Conversely, several studies report that BHB can induce oxidative stress and inflammatory responses in bovine mammary epithelial cells, abomasal smooth muscle cells, hepatocytes, and mouse gastric smooth muscle cells [116,117,118]. These findings underscore that the effects of BHB are highly context-dependent and influenced by cell type and metabolic state. Future precision medicine strategies should therefore incorporate genomic, metabolomic, and microbiomic profiling to establish integrated metabolic stratification systems and enable personalized ketone-based interventions.

5.5 Other Strategies of Increasing BHB Levels

The ketogenic diet and exogenous BHB supplementation remain the primary approaches for elevating systemic BHB levels; however, alternative strategies with translational potential are emerging. As early as the 1980s, animal studies demonstrated that exogenous administration of 1,3-butanediol (BD) markedly increased plasma BHB levels and enhanced cerebral tolerance to ischemia and hypoxia [119,120]. More recently, clinical trials have shown that oral BD induces sustained ketosis in patients with heart failure with reduced ejection fraction, conferring cardiovascular and metabolic benefits and supporting its translational feasibility [121]. Another approach involves modulating expression of MCT genes, including MCT1 (*SLC16A1*: Solute carrier family 16 member 1), MCT2 (*SLC16A7*), MCT3 (*SLC16A8*), and MCT4 (*SLC16A3*), to alter cellular BHB uptake capacity. For example, Shi et al. [122] demonstrated that modulation of endothelial MCT1 expression influences axonal regeneration after spinal cord injury. Yu et al. [123] reported that overexpression of neuronal MCT2 in the hippocampus facilitates recovery of cognitive function following ischemic stroke. With advances in targeted drug delivery technologies, future studies may achieve cell type–specific regulation of MCT expression, potentially opening new therapeutic avenues for ischemic stroke.

6. Conclusion and Future Prospects

Extensive evidence from animal models indicates that moderate elevations of ketone bodies exert protective effects in ischemic stroke. Mechanistically, ketone bodies

target key pathological processes, including metabolic dysfunction, inflammation, mitochondrial injury, and oxidative stress. During the acute phase, ketone bodies act as alternative energy substrates, stabilize mitochondrial function, inhibit excitotoxicity and calcium overload, attenuate inflammatory responses, and preserve the BBB and clearance systems. During the recovery phase, they promote neurological repair through epigenetic reprogramming, regulation of neural network excitability, and enhancement of autophagy. With progressive elucidation of these mechanisms, preclinical investigations of BHB-based therapies for acute ischemic stroke have expanded and demonstrated promising protective effects. To advance clinical translation, future studies should further define mechanistic pathways, optimize delivery strategies, determine safe and effective dosing regimens, and account for individual metabolic variability. These efforts will be essential for developing ketone-based precision therapies for ischemic stroke.

Author Contributions

JT wrote the original draft. HL revised the manuscript, provided critical intellectual input, and supervised the overall project. MS conceptualized the review framework, designed the search strategy, and contributed to the interpretation of the literature. HC participated in the literature acquisition, data extraction, and contributed to the analysis of the findings. MZ and NZ contributed to the interpretation of the included literature and provided critical revisions to the sections on “Metabolic Dysregulations and Pathological Changes in Ischemic Stroke”. HM and XZ participated in the literature screening and data extraction, and contributed to the interpretation of the results. All authors contributed to editorial changes in the manuscript. All authors 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.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

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