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REVIEW

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Effect and mechanism of Dichloroacetate in the treatment of stroke and the resolution strategy for side effect

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Abstract

Stroke is a serious disease that leads to high morbidity and mortality, and ischemic stroke accounts for more than 80% of strokes. At present, the only effective drug recombinant tissue plasminogen activator is limited by its indications, and its clinical application rate is not high. Therefore, it is urgent to develop effective new drugs according to the pathological mechanism. In the hypoxic state after ischemic stroke, anaerobic glycolysis has become the main way to provide energy to the brain. This process is essential for the maintenance of important brain functions and has important implications for recovery after stroke. However, acidosis caused by anaerobic glycolysis and lactic acid accumulation is an important pathological process after ischemic stroke. Dichloroacetate (DCA) is an orphan drug that has been used for decades to treat children with genetic mitochondrial diseases. Some studies have confirmed the role of DCA in stroke, but the conclusions are conflicting because some believe that DCA is not effective for ischemic stroke and may aggravate hemorrhagic stroke. This study reviews these studies and finds that DCA has a good effect on ischemic stroke. DCA can protect ischemic stroke by improving oxidative stress, reducing neuroinflammation, inhibiting apoptosis, protecting blood–brain barrier, and regulating metabolism. We also describe the differences in the outcomes of DCA in the treatment of ischemic stroke and the reasons why DCA aggravate hemorrhagic stroke. In addition, DCA, as a water disinfection byproduct, has been concerned about its toxicity. We describe the causes and solutions of peripheral neuropathy caused by DCA. In summary, this study analyzes the neuroprotective mechanism of DCA in ischemic stroke and the contradiction of the different research results, and discusses the causes and solutions of its adverse effects.

Keywords Dichloroacetate, Stroke, Neurotoxicity, Energy metabolism

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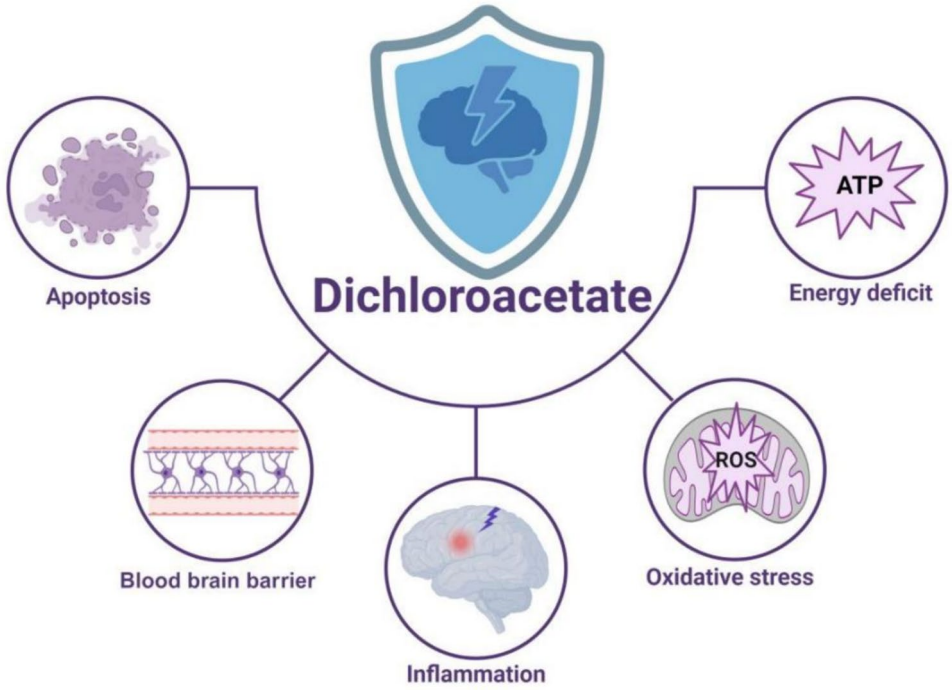
Graphical Abstract



Introduction

Stroke is a prevalent condition characterized by a significant incidence, elevated mortality, and a considerable rate of disability, placing its disease burden as the second highest globally [1]. Stroke comprises two types: hemorrhagic stroke (HS) and ischemic stroke (IS), with IS representing over 80% of cases [2].

IS is a prevalent condition among the elderly, but there has been a noticeable increase in its occurrence among younger individuals in recent years. Presently, approximately 80 million individuals around the globe are affected by IS [3]. As the demographic shifts with an aging population, projections indicate that over a quarter of the world's populace will be over 65 years old by 2050, which is expected to lead to a rise in the number of IS cases [4]. Consequently, the aftereffects of IS place a significant strain on patients, their families, and society as a whole. At this time, effective treatment options for IS include thrombolysis and mechanical thrombolysis; however, their clinical use is restricted due to strict contraindications, a limited treatment time frame, and severe adverse reactions, resulting in only a minority of patients reaping benefits from these interventions [5]. Moreover, the likelihood of hemorrhagic transformation following thrombolytic and mechanical thrombolytic treatments is nearly 10% [6]. Hypertension (HT) is a critical factor contributing to the worsening of brain injury and mortality among IS patients. Implementing secondary prevention measures for IS can significantly lower the risk of occurrences; nevertheless, a substantial number of patients continue to face risk factors such as smoking, alcohol dependence, diabetes, and hypertension, with a particular emphasis on developing nations that struggle with inadequate public health. Thus, it is vital to advance the development of cost-effective medications for IS management.

Dichloroacetate (DCA), known for its role as an inhibitor of pyruvate dehydrogenase kinase (PDK), has been utilized as a therapeutic option for various inherited mitochondrial disorders [7, 8]. Recent research indicates that DCA offers protective effects against IS. IS commonly occur alongside anaerobic glycolysis. In contrast to typical conditions, the cell's cytoplasm is capable of generating and releasing lactic acid under normal circumstances [9]. Due to insufficient oxygen supply in tissues and organs, lactic acid cannot be converted back into pyruvate via oxidative phosphorylation for ATP production. This leads to the buildup of lactic acid, which cannot be eliminated, resulting in lactic acidosis [10]. The pathological process

encompasses inadequate oxygen delivery to brain tissue, as well as damage and dysfunction of mitochondria. Additionally, oxidative phosphorylation, the tricarboxylic acid (TCA) cycle, and the electron transport chain face inhibition, significantly reducing ATP synthesis and impairing energy metabolism [11]. The excess lactate results in an imbalance in the intracellular and extracellular environments, which can disrupt cellular function and initiate an inflammatory response. Extended hypoxia contributes to the accumulation of byproducts from anaerobic glycolysis, worsening the inflammatory response and ultimately resulting in the demise of brain cells. Nonetheless, when PDH is activated, pyruvate can undergo decarboxylation to form acetyl-CoA, enter the TCA cycle, and yield 36 molecules of ATP per glucose unit within the mitochondria. PDH activity diminishes during ischemic conditions [12]. PDK decreases the activity of PDH by phosphorylating three specific serine residues (Ser232, Ser293, and Ser300) on the α subunit of PDH [13]. PDH functions as the "gatekeeper" enzyme, bridging anaerobic glycolysis and aerobic metabolism (Krebs cycle) [14, 15]. Its primary role is to irreversibly convert pyruvate into acetyl coenzyme A (AcCoA), which subsequently enters the TCA cycle for energy generation [16]. DCA offers protection against IS by inhibiting PDK and stimulating PDH, thereby decreasing anaerobic glycolysis, enhancing the TCA cycle, and lowering lactate concentrations in brain tissue. This compound is capable of inhibiting all four subtypes of PDK present in the body [17]. Consequently, DCA enhances the mitochondrial oxidation of pyruvate and elevates the glucose oxidation rate, thus facilitating improved energy metabolism within tissues.

This review integrates recent research on the use of DCA for stroke therapy and explores the molecular pathways through which DCA reduces neuronal death in ischemic stroke within the framework of related metabolic disorders. Additionally, we examine the molecular mechanism by which DCA may worsen hemorrhagic stroke. We also evaluated the varying conclusions regarding the effectiveness of DCA in treating ischemic stroke. Moreover, we investigated the mechanisms contributing to DCA's neurotoxicity and potential strategies to mitigate this issue. Our findings offer insights for future research and the clinical application of DCA.

DCA protects against ischemic stroke by improving energy metabolism through multiple mechanisms

Glucose metabolism primarily encompasses the pentose phosphate pathway, aerobic oxidation, and anaerobic glycolysis. Generally, the brain utilizes a substantial amount of aerobic energy metabolism to generate necessary energy. Following an IS, the delivery of glucose and oxygen to the brain is significantly impaired, resulting in considerable disruption of oxidative phosphorylation. This disruption hampers the brain's capacity to effectively produce ATP through its standard metabolic processes. Consequently, the brain is compelled to adjust to this energy deficit by swiftly reallocating its energy mechanisms. IS is frequently linked to a rise in anaerobic glycolysis. The underlying mechanism is as follows: oxidative phosphorylation, the TCA cycle, and the electron transport chain face inhibition due to an inadequate oxygen supply to brain tissue, alongside mitochondrial damage and dysfunction, leading to a marked decrease in ATP synthesis and overall energy metabolism impairment. Acting as a short-term compensatory metabolic pathway for glucose, anaerobic glycolysis emerges as the primary means of producing ATP and nicotinamide adenine dinucleotide (NAD+) in the brain. Glycolysis transforms pyruvate into lactate, yielding 2 mol of ATP for each molecule of glucose. Thus, after IS, anaerobic glycolysis becomes the predominant method for supplying energy to the brain. This mechanism is crucial for sustaining vital brain functions and holds significant importance for recovery post-stroke. Nonetheless, the acidosis resulting from lactic acid buildup, which occurs during anaerobic glycolysis, is a major contributing factor to neuronal cell death following IS. Interestingly, DCA treatment has the potential to reverse this process, involving several key actions.

DCA inhibits PDK4 after IS

In neurons, the generation of ATP primarily relies on glucose or lactic acid via the action of PDH)complexes, which feed into the TCA cycle [18]. During IS, PDH activity in neurons within the ischemic and vulnerable areas is compromised. This impairment can be observed as early as 30 min post-ischemia, leading to subsequent energy deficits and neuronal damage [19]. PDK decreases the activity of PDH by phosphorylating three specific serine residues (Ser232, Ser293, and Ser300) on the α subunit of PDH [13]. The PDK-PDH axis plays a pivotal role in neuronal energy production. Research has indicated that DCA reduced PDK4 expression in IS [20]. The key enzymes in glucose metabolism include PDKs and lactate dehydrogenase A [21]. PDK4 is one of the isoforms among PDKs 1−4. The PDK 1−4, alongside the pyruvate dehydrogenase complex (PDHC) and PDH, are crucial for the function of mitochondria and are located within the mitochondrial matrix, consisting of mitochondrial proteins that exhibit about 70% internal homology [22, 23]. PDK4 leads to a reduction in PDH activity through PDH phosphate. Both PDK and PDH are

vital for the energy regulation within IS [24]. PDK4 can phosphorylate several sites on PDH, facilitating the entry of pyruvate into the lactic acid metabolic pathway, thus enhancing cellular energy metabolism to produce lactic acid, instead of progressing into the TCA cycle [25].

DCA increased the expression of PDH after IS

The expression of phosphorylated PDH (p-PDH) was reduced by DCA, which also led to increased activities of PDHC and PDH [8, 26–29]. The activity of PDH is crucial in connecting anaerobic and aerobic metabolic processes, and the impairment of PDH following a stroke is particularly detrimental [30]. PDH serves as a primary regulatory element that influences whether pyruvate proceeds into the citric acid cycle or undergoes anaerobic glycolysis. When PDH undergoes phosphorylation, it loses its activity, resulting in a metabolic shift toward anaerobic glycolysis [31]. PDK reduces PDH activity via three serine residues located in the α subunit of PDH (Ser232, Ser293, and Ser300) [13]. Comprising three enzymes (PDH, dihydrolipoamide transacetylase, and dihydrolipoamide dehydrogenase) along with six cofactors (TPP, lipoic acid, FAD, NAD+, HSCoA, and Mg ion), PDHC functions synergistically to convert pyruvate into AcCoA and CO_2. Both PDH and the PDH complex, PDHC, play essential roles in mitochondrial functionality [11].

Consequently, DCA diminishes the phosphorylation of PDH while enhancing both PDHC and PDH activities through the suppression of PDK4 expression. PDH is responsible for the oxidative decarboxylation of pyruvate, producing AcCoA, NADH, and CO_2. Following ischemia, DCA promotes the TCA cycle, leading to several advantages.

DCA increased the Ac-CoA levels in IS [8]

PDH is responsible for the irreversible transformation of pyruvate into AcCoA, which subsequently engages in the TCA cycle to produce energy [16].

DCA decreased the pyruvate levels in IS [26]

As the expression of PDK4 and p-PDH mediated by DCA decreased, the activity of PDH and PDHC increased, and pyruvate levels decreased as pyruvate was promoted to enter TCA.

DCA decreased the lactic acid levels in IS

Multiple studies have found that DCA reduces not only brain lactate but also blood lactate [26, 28, 29, 32–35]. Clinical studies have found that the level of lactic acid in the cerebrospinal fluid of patients is related to the severity of stroke [36].

DCA improve the pH levels in IS

Lactic acid is reduced, so that the acidosis after DCA treatment recovers, and the pH returns to normal [37].

DCA improve Brain energy metabolism

DCA increased TCA after IS, increased ATP recovery of nerve cells, and decreased blood glucose levels [26, 34, 35, 37]. In addition, the phosphocreatine (PCr) levels in brain were also increased [27, 37]. PCr can supply energy to the brain and is also a protective agent for IS [38, 39].

DCA regulates autophagy after IS

DCA treatment increased the expression of Pgc-1α, Tfam, Mfn1, Drp1 and SQSTM1. PGC-1α is a key regulator of energy metabolism that synergistically activates many nuclear receptor- and non-nuclear receptor-transcription factors associated with metabolism, such as nuclear respiratory factor (Nrf), mitofusion-1 (Mfn1), and mitochondrial transcription factor A (Tfam) [40].

Mitochondrial function and cell survival are critical processes. Highly fused mitochondria are formed under nutrient deprivation conditions to optimize mitochondrial function and maximize ATP synthesis. Maintenance of mitochondrial fusion plays a protective role in the pathological state of ischemia and hypoxia. In contrast, mitochondrial fission is activated under conditions of excess nutrition [41]. The mechanism of mitochondrial fusion regulates autophagy induced by energy deprivation through maintaining mitochondrial respiration [42, 43]. While DCA can influence autophagy, it does not affect mitochondrial fusion. Ischemia-hypoxia injury reduced the expression of mitochondrial fusion gene Optic Atrophy 1 (Opa1), accompanied by a decrease in Opa1 protein expression and an increase in mitochondrial fission. DCA treatment increased the expression of Opa1 in brain tissue after ischemia and hypoxia, but the difference was not statistically significant [8]. Since phosphorylation of dynamin-related protein 1 (DRP1) at Ser637 inhibits mitochondrial division, the downregulation of P-DRP1 after hypoxic–ischemic injury suggests that hypoxic–ischemic injury results in increased mitochondrial division. Although DCA treatment altered the expression of mitochondrial fusion and fission-related genes, specifically P-DRP1 and OPA1, these changes were not statistically significant when compared to the control group [8]. These results suggest that the neuroprotective effect of DCA treatment is not related to mitochondrial fusion or fission.

Autophagy serves as a vital physiological process essential for maintaining cell homeostasis and survival [44]. Consequently, basal autophagy is pivotal for cell survival in physiological environments. The activation of

autophagy is enhanced by IS [45]. When faced with starvation or nutrient scarcity, there is a depletion of intracellular AcCoA, which acts as a physiological signal for autophagy to mobilize amino acids and fatty acids for energy generation and to remove damaged organelles. DCA was observed to boost AcCoA production and elevate the expression of Sequestosome 1 (SQSTM1), indicating that DCA might safeguard against blood damage by inhibiting autophagy [8]. Consequently, the protective effect of DCA on mitochondria is attributed to its ability to inhibit autophagy and regulate energy metabolism, rather than to its influence on mitochondrial fusion. The specific mechanism by which DCA regulates energy metabolism after IS is shown in Fig. 1.

Anti-oxidative stress effects of DCA after IS

The core concept of oxidative stress revolves around the disruption of the balance between oxidants and antioxidants within the body. This imbalance occurs when antioxidants are insufficient to effectively neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS) in a timely fashion, leading to the buildup of free radicals. The primary types of ROS and RNS consist of superoxide anions, hydrogen peroxide, nitric oxide (NO), and peroxynitrite anions, among others. Antioxidant defense mechanisms prominently feature superoxide dismutase (SOD), glutathione peroxidase, and catalase, among others [46]. In contrast to other tissues, the brain exhibits heightened vulnerability to oxidative injury, primarily due to its increased oxygen demand, rich lipid composition, and a relative scarcity of antioxidant enzymes. Furthermore, the brain's high energy consumption and limited energy reserves rely heavily on a steady intake of oxygen and glucose provided by the vascular system [47]. Following IS, the disruption of ion balance triggers an overproduction of free radicals from the mitochondria, which has been linked to neuronal cell death. Thus, antioxidant therapy is recognized as a potential avenue for treating IS.

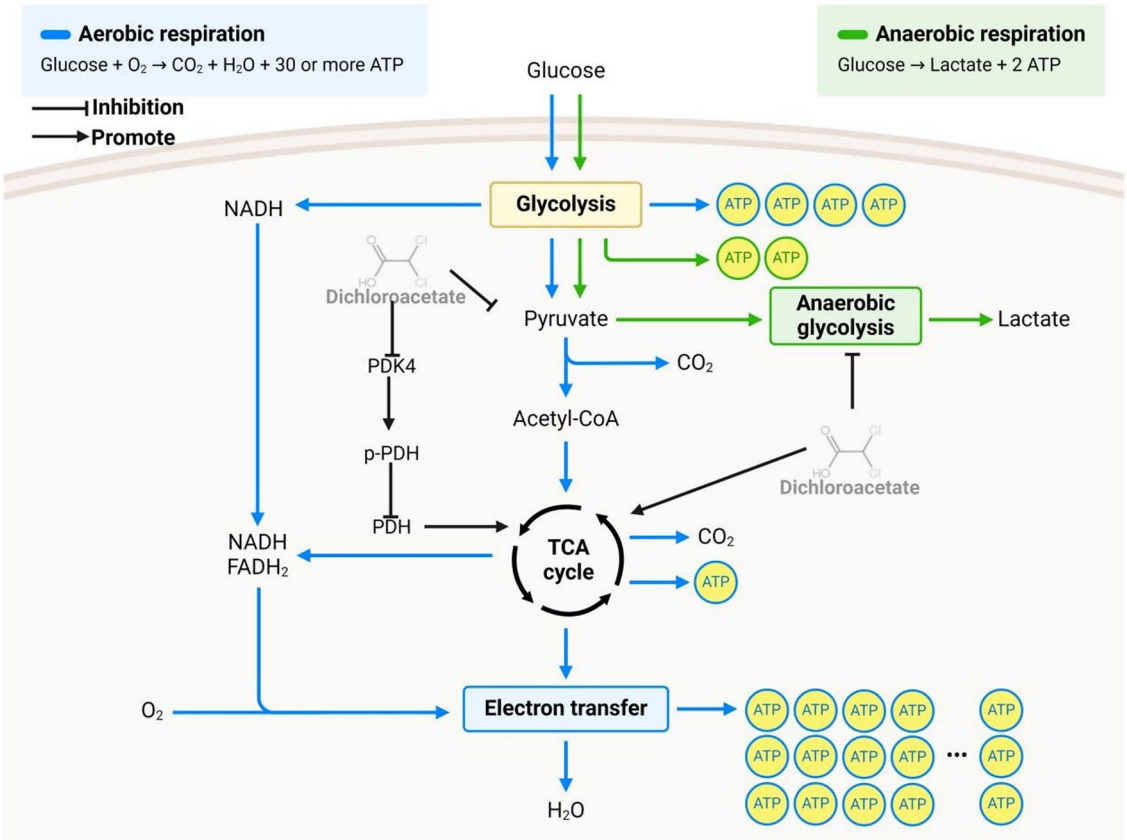


Fig. 1 Schematic illustration of the DCA regulating energy metabolism after ischemic stroke from anaerobic glycolysis to TCA cycle. DCA reduced the expression of phosphorylated PDH while enhancing the activities of both PDHC and PDH. Furthermore, DCA elevated the levels of Ac-CoA in the IS. PDH is responsible for the irreversible conversion of pyruvate into Ac-CoA, which subsequently enters the TCA cycle to generate energy, thereby facilitating the conversion of pyruvate into ATP. Additionally, levels of lactate in both the brain and blood were reduced, and brain pH returned to normal

The expression of inducible nitric oxide synthase (iNOS) was found to decrease following treatment with 40 mg/kg DCA [48]. Moreover, after treatment with 200 mg/kg DCA, the level of SOD in brain tissue rose, while MDA levels decreased [49]. However, one study indicated that DCA does not exhibit antioxidant properties [50]. The potential mechanism may involve the upregulation of nuclear respiratory factor 2 (Nrf2) and Heme Oxygenase-1 (HO-1) due to DCA. Serving as a transcription factor that combats oxidative stress, Nrf2 regulates the expression of a variety of cytoprotective genes [51]. HO-1, acting as a target protein downstream of Nrf2, aids in the breakdown of heme to generate biliverdin, carbon monoxide, and ferrous ions, which all contribute to cellular defenses against oxidative injury [52]. Furthermore, in IS mice treated with a 200 mg/kg dose of DCA, the expression of Nrf1 and the Cytochrome c oxidase IV(COX-IV) gene was observed to increase [8]. Both Nrf1 and Nrf2 play cooperative and distinct roles within the regulatory network to battle oxidation. Nrf1 exerts a regulatory function, thus limiting the activity of Nrf2 to a specific range, with its transcription also being modulated by Nrf2 [53]. In primary human myotubes with COX-IV overexpression, H_2O_2 production was diminished, resulting in enhanced resistance to oxidative stress and extreme hypoxia. This indicates that COX-IV is crucial for managing energy expenditure, tolerance to hypoxia, and the maintenance of mitochondrial ROS levels in humans [54]. It is suggested that the antioxidant properties of DCA in treating IS may operate via the Nrf2/HO-1 signaling pathway.

DCA inhibits inflammation after IS

Following IS, inflammation serves as a crucial pathological factor contributing to brain tissue damage. Neuroinflammation is instrumental in the development of IS, and the inflammatory response that occurs post-IS is triggered by microglial activation. In this sequence of events, neutrophils, monocytes, and macrophages become activated and move toward the injury site. These immune cells further exacerbate tissue injury by secreting excessive inflammatory mediators, which lead to increased brain edema and compromise the integrity of the BBB. The levels of Matrix metalloproteinase 9 (MMP9), Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), and iNOS showed an increase, whereas mannose receptor (CD206) and Interleukin-10 (IL-10) demonstrated a decline in ischemic brain tissue following IS [26, 48]. After treatment with DCA, these changes of indicator levels were reversed.

Following a stroke, levels of MMP-9 rise, which correlates with the breakdown of the BBB, heightened risks of HT and HS, and a poorer prognosis [55]. TNF-α, an inflammatory cytokine typically not found in healthy tissues, sees an increase following IS [56]. IL-6 represents a distinctive cytokine that operates within both pro-inflammatory and homeostatic signaling pathways. These pathways play a role in the neuroinflammatory response post-stroke, where the initial inflammatory response offers protection, yet excessive production intensifies inflammation [57].

CD206 serves as a significant marker for M2 glial cells and is crucial for immune defense and regulation [58]. IL-10, recognized for its multifaceted anti-inflammatory effects, is primarily produced by antigen-presenting cells, including activated T cells, macrophages, monocytes, and B cells. This cytokine functions to inhibit the production of inflammatory cytokines such as TNF-α, IL-6, and Interleukin-1beta (IL-1β) by stimulating macrophages [59]. On the other hand, iNOS is identified as a marker for M1 microglia [60]. Treatment with DCA has been shown to lower levels of inflammatory markers while enhancing anti-inflammatory markers within the brain tissue of individuals with IS. The anti-inflammatory properties of DCA are linked to its influence on the classification of microglia into M1 and M2 types. Nevertheless, the precise molecular mechanisms underlying anti-inflammatory effects of DCA are not yet fully understood. Additionally, the presence of excessive inflammation contributes to the disruption of the BBB.

DCA protects the integrity of the BBB after IS

The BBB serves as a protective barrier, blocking toxic and harmful substances from infiltrating and harming brain tissue, highlighting its critical importance [61]. A significant aspect of this process involves MMP9, which predominantly appears following IS and compromises the integrity of the BBB, resulting in heightened permeability. Various factors contribute to the disruption of the BBB, leading to severe consequences, including escalated brain damage and potentially fatal outcomes. Inflammatory responses and oxidative damage are principal contributors to the deterioration of the BBB.

The processes involved in the disruption of the BBB encompass, but are not confined to factors such as inflammation and oxidative stress. These factors result in the compromise of tight and adherent junctions, which serve as fundamental components of the BBB [62]. When the BBB is compromised, it permits the ingress of water molecules and blood constituents into the brain, leading to significant repercussions such as cerebral edema and hypertension [6]. During the initial week following an IS, cerebral edema emerges as an independent risk factor for mortality and adverse outcomes in IS patients [6]. Furthermore, the enhanced permeability of the BBB facilitates the entry of peripheral immune cells into the

brain parenchyma, exacerbating neuroinflammatory responses and inflicting greater brain damage [6]. Thus, maintaining BBB integrity is not only crucial as a therapeutic objective to avert additional brain injury, but also serves as a vital indicator for the prognosis of IS.

The volume of brain edema reduced, and the integrity of BBB improved following DCA treatment [48, 49]. Additionally, DCA treatment led to elevated levels of ZO-1, Occludin, Arginase 1 (Arg1), Nrf2, and HO-1 within the ischemic brain tissues [48, 49]. Conversely, the levels of Rho-associated protein kinase (ROCK) and Myosin phosphatase target subunit 1 (MYPT1) diminished [48, 49].

Arg1 plays a crucial role in maintaining the integrity of the BBB. A deficiency in Arg1 can lead to decreased cell proliferation, a blockade of the cell cycle at the G1 phase, enhanced permeability of the BBB, and an increase in brain water content [63]. Furthermore, Arg1 serves as a marker for M2 macrophage activation that specifically targets astrocytes. It inhibits inflammatory responses, participates in the clearance of cellular debris and apoptotic cells, and functions as a competitor enzyme to iNOS [64].

Matrix metalloproteinases (MMPs), a class of endopeptidases responsible for the breakdown of the extracellular matrix, have been identified as a primary factor in the disruption of the BBB following IS. Under normal physiological conditions, the expression of MMPs remains low; however, it experiences a significant increase in patients suffering from IS. The activation of MMPs contributes to BBB impairment by degrading the perivascular basal lamina and proteins associated with tight junctions [65]. Specifically, MMP-9 is critical in the process of BBB disruption [66]. Typically, the expression levels of MMP-9 rise after a period of 12 h. Once activated, MMP-9 inflicts severe and irreversible damage to the integrity of the BBB [67].

ZO-1, a crucial cell connexin, primarily resides in the closely linked band area between cells and serves as the primary regulator of tight junction activity. This protein interacts with other tight junction components, including claudin and occludin, to create complexes that facilitate tight junctions and intercellular signaling [68]. ZO-1 effectively seals cellular pathways and establishes the foundation for tight junctions. Occludin's physiological roles mainly encompass its fence and paracellular barrier functions, with its diminished expression potentially resulting in the disruption of the BBB [68].

Astrocytes serve as crucial regulators of the immune response in the brain following IS and are significant components of the BBB. In healthy physiological circumstances, astrocytes outnumber neurons by fivefold and perform various functions including neurotransmitter production, regulation of cerebral blood flow, maintenance of water balance, and modulation of immune reactions [69]. The activation of astrocytes is prompted by several cytokines, such as IL-1 and IL-6, released by activated microglia shortly after the onset of IS [70]. A substantial number of astrocytes perish within 4 to 24 h post-IS, contributing to the disruption of the BBB [71]. Like microglia, the activated forms of astrocytes are categorized into A1 and A2 phenotypes. A2 astrocytes help form glial scars that limit injury spread [72]. Conversely, interactions between M1 microglia and A1 astrocytes lead to the production of excitatory amino acids, which trigger the expression of MMPs in ischemic brain regions, compromising BBB integrity. Moreover, astrocytes are vital for neurogenesis and vascular regeneration through the RhoA/ROCK signaling pathway [73]. Suppressing the RhoA/ROCK signaling pathway has been identified as an effective strategy to protect the BBB from damage [74]. Research indicates that the inflammatory response of astrocytes could worsen IS injury by enhancing the RhoA/ROCK pathway activation. While inhibiting this pathway may encourage astrocyte participation in angiogenesis and neurogenesis, the precise mechanisms remain inadequately understood [75].

MYPT1, which serves as the regulatory subunit of myosin light chain phosphatase, is crucial for smooth muscle contraction through its modulation of the phosphorylation process of the Ca^{2+}-dependent myosin regulatory light chain. A growing body of evidence indicates that MYPT1 is also significant in various non-contractile functions, such as cell adhesion and migration, cell division, cell proliferation, neurotransmitter release, embryonic development, and the regulation of both endothelial and epithelial barrier functions [76, 77].

Damage to the BBB can impact the health and functionality of the central nervous system. Research has indicated that Nrf2 plays a crucial protective role in maintaining BBB integrity [78]. Furthermore, elevated levels of HO-1 have been associated with enhanced BBB integrity following brain injury [79]. DCA offers protection against IS is illustrated in Fig. 2.

DCA reduces nerve cell apoptosis after IS

Nerves treated with DCA exhibited a lower number of apoptotic cells, and the levels of P38 mitogen-activated protein kinase (p38 MAPK), C-Jun N-terminal kinases (JNK), Apoptosis-inducing factor (AIF), and Caspase 3 in brain tissue showed a decline [8, 48]. Conversely, the expression of Nrf2 and HO-1 increased [49].

Apoptosis is a key process in IS and is influenced by various signaling pathways. One significant pathway is the JNK pathway. During the pathological changes that

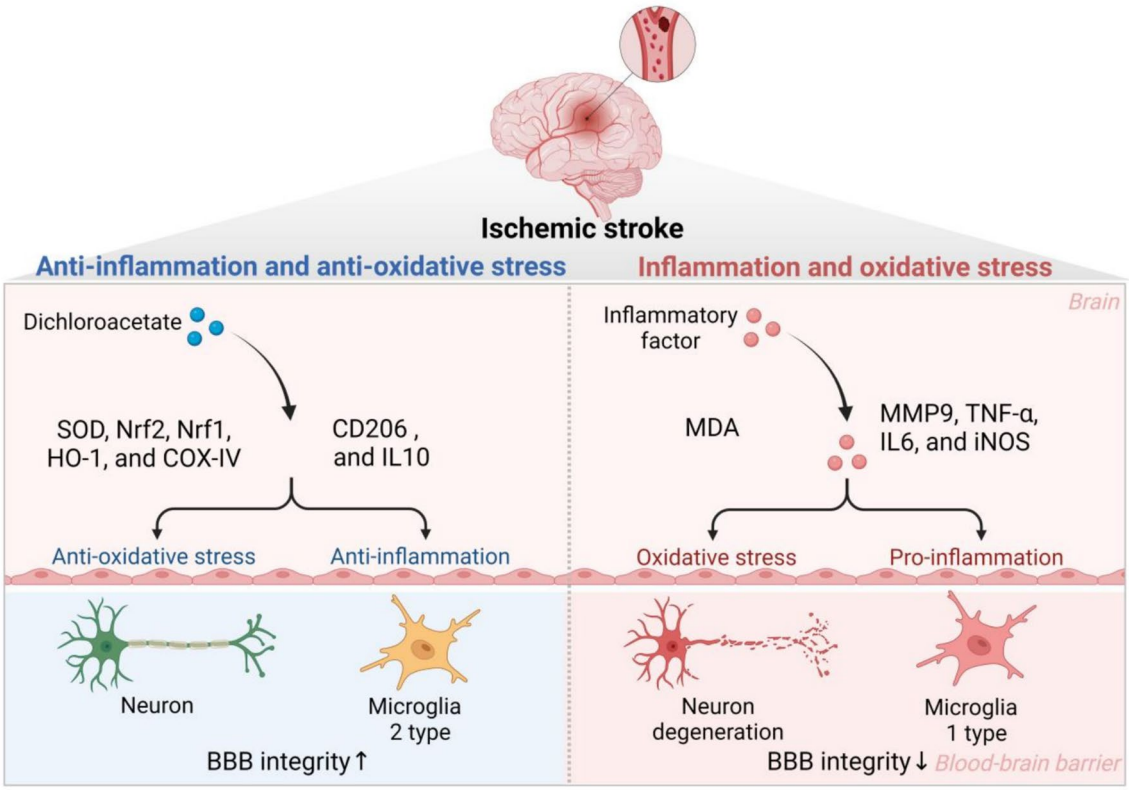


Fig. 2 Schematic illustration of the BBB disruption by IS and the mechanism of DCA protection against ischemic stroke. Increased inflammation and immune response following IS contribute to BBB disruption. Treatment with DCA enhances the expression of anti-inflammatory factors such as IL-10 and CD206, while simultaneously reducing the levels of pro-inflammatory markers including MMP9, TNF-α, IL-6, and iNOS. This suggests that DCA promotes the polarization of small glial cells from the M1 pro-inflammatory phenotype to the M2 anti-inflammatory phenotype. Furthermore, the observed improvement in the expression of BBB-related proteins, such as ZO-1 and occludin, indicates a restoration of the integrity of the BBB

occur following IS, JNK gets activated, which in turn enhances the aggregation of pro-apoptotic proteins Bax and Bak, leading to the activation of Caspase-9 and Caspase-3, ultimately resulting in neuronal apoptosis [80, 81]. Another apoptotic pathway is the p38 MAPK pathway, activated by MAPK proteins, which induces apoptosis by affecting specific transcription factors including cAMP response element-binding protein (CREB), p53, and other associated proteins [82]. The p38 MAPK pathway is implicated in a range of signaling cascades triggered by different stimuli, highlighting its crucial role in eliciting various cellular responses, while also exhibiting regulatory effects on apoptosis [83].

Furthermore, apoptosis encompasses both Caspase-dependent and independent pathways. The Apoptosis Inducing Factor (AIF), known to operate through a caspase-independent mechanism, has been proposed as a key mediator in cell apoptosis [84]. Treatment with DCA has the potential to inhibit the mitochondrial release of AIF; however, the precise mechanism remains unclear. It may be connected to an enhancement of mitochondrial energy metabolism and a decrease in mitochondrial membrane permeability during the initial phase following injury. This reduction in permeability results in a lower release of pro-apoptotic proteins, including AIF and cytochrome c, from the mitochondrial membrane space post-injury. The efflux of cytochrome c from the mitochondria into the cytoplasm triggers the activation of pro-caspase-9, which in turn activates pro-caspase-3, ultimately leading to apoptosis [85].

Caspase-3, which is a type of cysteine-aspartate protease, is crucial for the apoptosis process and is frequently utilized as an apoptosis biomarker [86]. The neuroprotective properties of DCA in cases of ischemia and hypoxia may engage multiple anti-apoptotic pathways. The mechanisms through which nerve cell apoptosis is inhibited following IS encompass the p38 MAPK/JNK pathways, AIF/Caspase-3, and the Nrf2/HO-1 signaling pathways. The specific mechanism of the DCA protects nerve cell apoptosis is shown in Fig. 3.

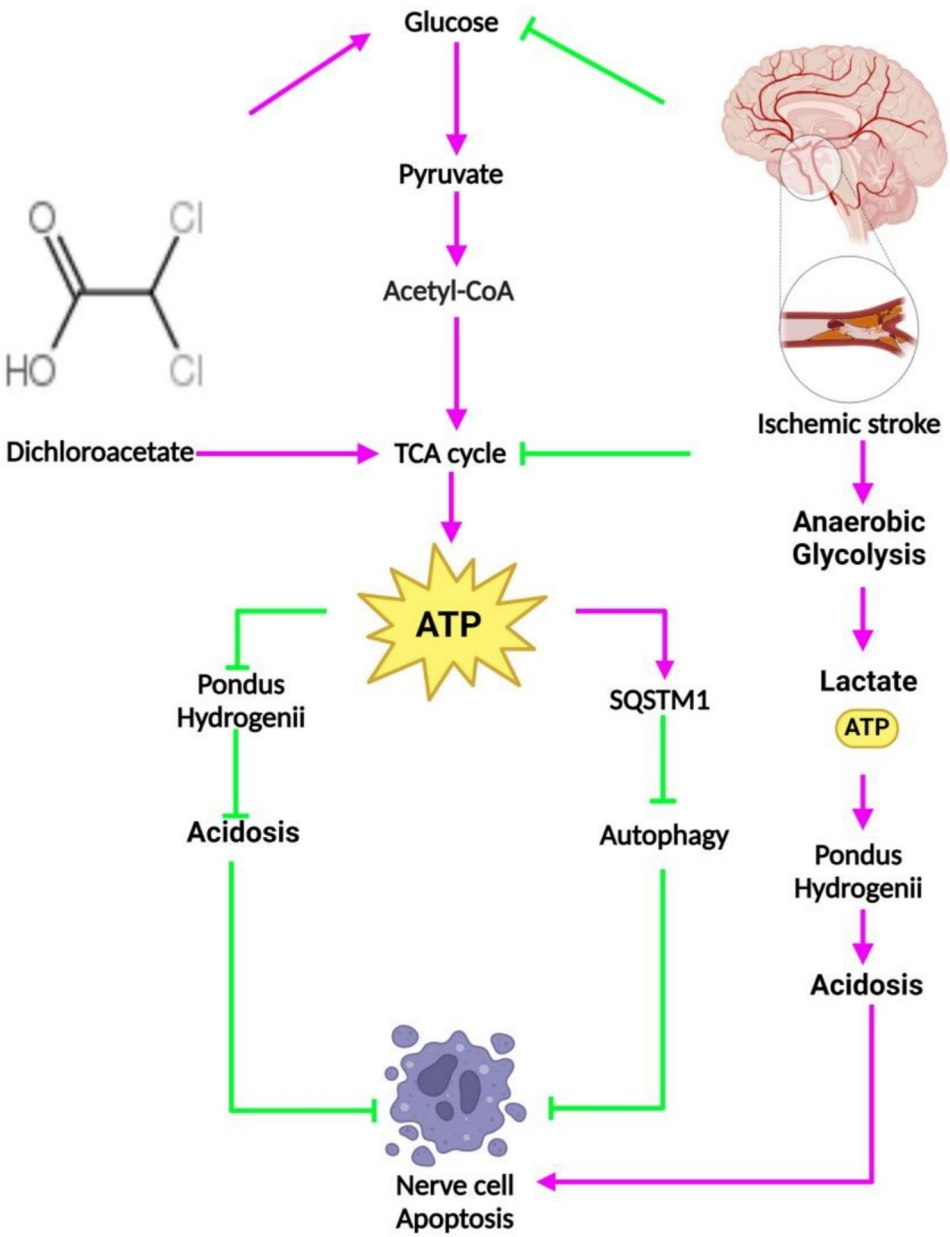


Fig. 3 Schematic illustration of the DCA protects nerve cell apoptosis in IS

The role of DCA in promoting myelin and angiogenesis after IS

Myelin is a membrane that encases the axons of nerve cells, composed of Schwann cells and myelin cell membranes. Its primary function is to insulate, thereby preventing the transmission of electrical impulses between the axons of different neurons. DCA exhibits a protective effect on myelin following an IS. After such a stroke, there is an increase in the positive volume of myelin basic protein, and the subcortical white matter displays abnormalities in myelin structure, specifically within the myelin sheath. Subsequent to DCA treatment, the positive volume of myelin basic protein is observed to decrease within the myelin sheath.

Angiogenesis can enhance collateral circulation, facilitate the restoration of blood supply to ischemic regions, and mitigate ischemic necrosis following an ischemic injury. Strategies aimed at improving angiogenesis may support functional recovery after

a stroke [87, 88]. DCA treatment has been shown to increase angiogenesis in brain tissue subsequent to IS [89]. The mechanism underlying angiogenesis involves DCA's up-regulation of the expression of NO, AKT, Nrf2, endothelial nitric oxide synthase (eNOS), and glycogen synthase kinase 3 beta (GSK-3β) [89].

Protective Effect of DCA on Risk Factors of IS

Risk factors for ischemic stroke include diabetes, hypertension, hyperlipidemia, and atrial fibrillation [90]. Hyperglycemia induces excessive production of ROS within the mitochondrial electron transport chain, leading to oxidative stress and subsequent damage. Vascular endothelial injury resulting from oxidative stress is a critical pathological factor in the development of atherosclerosis and ischemic stroke. Studies have demonstrated that DCA can reduce the levels of pyruvate, a product of glycolysis, in plasma, and it specifically lowers plasma glucose levels in the fasting state [91]. Furthermore, DCA inhibits the conversion of glucose to pyruvate and lactate in cells [91]. Consequently, the supply of gluconeogenesis substrates mediated by DCA from muscle to liver is limited, and the direct inhibition of gluconeogenesis may contribute to its hypoglycemic effect [91].

Hyperlipidemia and atherosclerosis are closely interconnected. Abnormally elevated lipid levels can deposit beneath the intima of blood vessels, leading to the formation of atherosclerotic plaques. The accumulation of these plaques within the arterial walls can narrow the arterial lumen, consequently obstructing blood flow to the brain and resulting in IS. Given that hypercholesterolemia can cause severe cardiovascular disease, managing cholesterol levels presents a significant challenge to human health. Additionally, drugs that target carbohydrate metabolism may also influence lipid metabolism, thereby affecting plasma cholesterol levels. In certain animal models, DCA has been shown to reduce plasma cholesterol and triglyceride levels. As a result, in the 1970s, DCA was employed to treat diabetes, hyperlipoproteinemia, and hypercholesterolemia with promising outcomes. DCA induces the expression of the MAPK ERK5, which activates the transcription factor MEF2. Furthermore, DCA promotes the activation of the ERK5/MEF2 pathway by inducing oxidative phosphorylation (OXPHOS), leading to the expression of LDLR and exerting a hypolipidemic effect [92].

Hypertension is a recognized risk factor for IS, as it exacerbates inflammation and oxidative stress in vascular endothelial cells. DCA has been shown to effectively alleviate pulmonary hypertension. The underlying mechanism involves DCA's ability to inhibit the upregulation of PDK4 induced by FOXO1, thereby providing protection against pulmonary hypertension [93, 94]. Furthermore, DCA also offers protection against pulmonary arterial hypertension by inhibiting the Ca^{2+}/CaMK and Rho kinase signaling pathways, which helps maintain mitochondrial homeostasis [95]. Additionally, hyperlipidemia, diabetes, and hypertension collectively contribute to the progression of atherosclerosis. The progression of atherosclerosis can be mitigated through metabolic activation linked to mitochondrial function. DCA protects the liver from atherosclerosis by enhancing glucose oxidation through the induction of hepatic FGF21 expression and activation of brown adipose tissue (BAT), which in turn increases energy expenditure for thermogenesis [96].

Atrial fibrillation is a significant risk factor for IS, with approximately one-quarter of IS patients exhibiting this condition. Additionally, alcohol consumption, hypertension, obesity, and diabetes are important risk factors associated with the development of atrial fibrillation. DCA has a therapeutic effect on atrial fibrillation [97]. Studies have shown that atrial fibrillation (AF) increases metabolic stress related to the Warburg effect and promotes myocardial fibrosis remodeling by elevating the expression and activity of PDK-1, PDK-4, and LDHA, as well as increasing the content of AMP and lactic acid, and the AMP/ATP ratio. Concurrently, there is a decrease in the expression of PDH, citrate synthase, and isocitrate dehydrogenase, along with reduced glycogen content [98]. Notably, these conditions were reversed following DCA treatment [98]. Details of included studies and results of DCA are shown in Table 1.

Discussion

DCA exacerbates the cause of HS

A research investigation revealed that administering DCA (100 mg/kg) modified the levels of PDK4, PHD, pyruvate, and p-PDH. These findings suggest that DCA enhances energy metabolism in HS. Nevertheless, treatment with DCA resulted in increased production of ROS and elevated cell apoptosis, as evidenced by the heightened expression of p-ASK1, p-P38, and cleaved-caspase3. It is plausible that autophagy serves a protective function in HS by facilitating the elimination of damaged proteins and organelles, which may be used for energy production and cellular defense mechanisms [104]. DCA has the potential to stimulate energy metabolism while simultaneously inhibiting autophagy within hematoma brain tissue, which could lead to a worsening of HS.

Difference in outcomes of IS treated by DCA

One study found that the levels of lactate, ATP, and PCr in the hindbrain of rats with bilateral carotid artery occlusion (15 min) treated with 100 mg/kg DCA were

Table 1 Details of included studies and results of DCA

Model	Species	Dose and Time	Evidence	References
Ischemic stroke	Rat	25 mg/kg, 2 h	Brain temperature↑, Lactate level↓	[32]
Ischemic stroke	Gerbil	225 mg/kg, 72 h	Pyruvate dehydrogenase enzyme↑, Lactate level↓, Neuronal damage↓	[33]
Ischemic stroke	Sprague – Dawley rats	40 mg/kg, 24 h	Ischemic lesion volume↓, Neurological defects, Long-term Functional Recovery↑, Survival Proportions↑, Weight↑, BBB integrity↑, Brain edema volume↓, ZO-1↑, Occludin↑, MMP9↓, TNF-α↓, IL6↓, iNOS↓, CD206↑, IL10↑, Arg1↑, ROCK↓, MYPT1↓, p38 MAPK↓, JNK↓, p-phd↓,	[48]
Ischemic stroke	Sprague – Dawley rats	80 mg/kg, 72 h	Survival time↑, Neurons↑, Apoptotic cells↓, TNF-α↓, IL-1β↓, Blood lactate ↓, Blood glucose levels↓, ATP↑, PDH activity↑, Pyruvate levels↓,	[26]
Ischemic stroke	Wistar rats	100 mg/kg, 105 min	DCA is ineffective in the treatment of ischemic stroke	[99]
Ischemic stroke	Wistar rats	25 mg/kg, 30 min	Brain lactate levels ↓, Brain glycogen↑	[34]
Ischemic stroke	Sprague – Dawley rats	100 mg/kg, 30 min	Brain lactate levels↓, Phosphocreatine↑, PH↑, ATP↑	[37]
Ischemic stroke	Wistar rats	300 mg/kg,30 min	Brain lactate levels↓	[100]
Ischemic stroke	UC-11MG cells	100 mm, 24 h	PDHC activity↑, Brain lactate levels↓	[28]
Ischemic stroke	Macaque monkeys	35 mg / kg, 24 h	Size of Infarct↓	[101]
Ischemic stroke	Wistar rats	25 mg / kg, 45 min	Glycogen levels↑, Brain lactate levels↓	[35]
Ischemic stroke	Mongolian gerbils	2.3 mmol/kg, 4.5 h	PCr↑, ATP↑, PDH activity↑	[27]
Hemorrhagic stroke	Sprague – Dawley rats	100 mg/kg, 2 d	PDK4↑, p-PDH↓, PDH↑, Pyruvate↓, p-ASK1↑, p-P38↑, Cleaved-caspase3↑	[102]
Ischemic stroke	C57BL/6 mice	200 mg/kg, 3 d	PDK4↓, PDH activity↑,p-PDH↓	[103]
Ischemic stroke	C57BL/6 mice	200 mg/kg, 24 h	Occludin↑, ZO-1↑, Neurological deficit score↓, Infarct volume↓, BBB↑, PDK2↓, PDH↑, SOD↑, MDA↓, NRF2↑, HO-1↑, Apoptosis↓	[49]
Ischemic stroke	Sprague – Dawley rats	100 mg/kg, 7 d	PDHC activity↑, Brain lactate levels↓, PCr↑, ATP↑,	[29]
Perinatal Asphyxia induced Hypoxic Ischemic Brain Injury	C57BL/6 mice	200 mg/kg, 3 d	Infarction volume↓, Myelin structure↑, MAP2↑, PDH activity↑, Acetyl-coenzyme A↑, Pgc-1α ↑, Nrf1↑, Tfam↑, COX-IV↑, Mfn1↑, Drp1↑, SQSTM↑, AIF↓, Caspase3↓	[8]
Ischemic stroke	Sprague – Dawley rats	50, 100 and 200 mg/kg, 21 d	Learning capacity↑, Neuronal death↓, Brain atrophy↓,VEGF↑, bFGF↑, Vitro tube forming ability↑, Endothelial progenitor function↑, NO↑, ROS↓, AKT↑, Nrf2↑, eNOS↑, GSK-3β↑	[89]

↑ = increased, ↓ = decreased. blood brain barrier(BBB), pyruvate dehydrogenase (PDH), pyruvate dehydrogenase complex (PDHC), phosphocreatine (PCr), SOD (superoxide dismutase), malondialdehyde (MDA). A total of 17 studies on ischemic stroke and one study on hemorrhagic stroke were included. The specific effects of DCA encompass improvements in energy metabolism, autophagy, oxidative stress, inflammation, the integrity of the blood–brain barrier, apoptosis, and angiogenesis in the context of ischemic stroke

unchanged compared with control rats after intravenous glucose (2 g/kg) [99]. This study contradicts all other studies, all of which demonstrate that DCA has a therapeutic effect on IS. It may be related to the following reasons. ① 2 g/kg glucose may provide sufficient glycogen to the brain. ② The bilateral carotid artery occlusion model is not the standard model of IS, resulting in incomplete occlusion of cerebral vessels. ③ The model time of 15 min is too short, and usually the model time is more than 30 min. ④ The experimental animal was selected with mixed male and female rats, and female rats are more tolerant to IS because of the protective effect of estrogen.

Pharmacokinetics

The pharmacokinetic variability of DCA presents a significant concern that warrants careful consideration [105]. Oral administration of DCA is rapidly absorbed, with bioavailability comparable to that of parenteral administration [106]. Due to its high lipid solubility, DCA is distributed across various tissues and organs, including the liver, muscle, skin, intestine, kidney, lung, heart, and brain [107, 108]. DCA crosses the cell membrane via the monocarboxylic acid transporter and subsequently enters the mitochondrial matrix through the pyruvate transporter, where it exerts its effects [109]. In vivo, DCA is primarily metabolized by the glutathione

transferase zeta-1 family isoform (GSTZ1) [110]. While GSTZ1 is present in several tissues, including the liver, kidney, testis, heart, and brain, with the highest level in the liver, establishing liver as the principal metabolic organ for DCA [111]. Research indicates that DCA exhibits nonlinear kinetics when administered at a single injection dose of ≥ 35 mg/kg [112]. This phenomenon arises from DCA's ability to inhibit GSTZ1, thereby limiting its own metabolism and resulting in a decreased plasma clearance rate following multiple administrations [113].

More importantly, GSTZ1 activity and the recovery time of this activity are related to the time and dose of DCA administration [17]. Following a single intraperitoneal injection of DCA (45 mg/kg) in male rats, GSTZ1 protein and activity were significantly reduced within 12 h, with the lowest value dropping below 40% of the initial level, and recovery did not occur until 10 to 12 days post-administration [113]. Therefore, it is theoretically feasible to adjust DCA doses based on GSTZ1 levels during treatment to achieve a controllable blood concentration. Dunbar et al. concluded that the initial oral dose for patients without the variant should be 5 mg/kg every 12 h, which can be increased appropriately in the absence of peripheral neuropathy. Additionally, subjects carrying the EGT variant should be able to tolerate at least 6.25 mg/kg/h [114].

DCA has neurotoxicity

DCA, recognized as a byproduct of water disinfection, raises concerns regarding its toxicity. Research on DCA's neurotoxic effects is limited. We have compiled a summary of findings. The functionality and structure of nerve cells are directly affected by DCA [115]. In studies conducted on animals, exposure to DCA led to observed neurological deficits, which included diminished grip strength in the hindlimbs, signs of neuromuscular toxicity, decreased conduction velocities in large myelinated sensory and motor fibers, increased anxiety levels, weight reduction, thermal hypoalgesia, peripheral neuropathy, and lowered nerve conduction velocities in large myelinated fibers [115–119]. DCA prompted an increase in oxidative stress within nerve cells, characterized by decreased levels of SOD, CAT, and GSH, alongside elevated amounts of ROS and NO [117]. Moreover, exposure to DCA resulted in heightened inflammation in nerve cells, as evidenced by increased levels of TNF-α, IL-1β, IL-6, and NF-κB within the brain [117]. Additionally, DCA is associated with causing DNA damage in nerve cells [115, 117].

DCA application and clinical adverse reactions

As a drug designated for rare conditions, DCA has been utilized for many years to aid children suffering from congenital mitochondrial metabolic disorders, demonstrating advantageous effects [120]. Moreover, the therapeutic impact improves with increased dosage of DCA. At doses of 100 mg/kg, DCA exhibited neuroprotective properties, while lower doses of 10 mg/kg did not show the same benefits [29, 37]. It is generally regarded that the prolonged administration of DCA in pediatric cases is safe and well tolerated [121, 122].

Nonetheless, the toxicity of DCA has raised concerns as a by-product of disinfection through water chlorination. The potential carcinogenic effects of DCA have been extensively researched in animal studies [123]. However, current epidemiological data do not establish any direct carcinogenic impact of DCA on humans, and investigations have shown that long-term use of DCA does not result in hematologic, hepatic, or renal toxicity. In one investigation, eight individuals suffering from congenital lactic acidosis received oral DCA (5.12 mg/kg/9 h) and were monitored over a span of 5.1 to 7.16 years, during which their renal, hepatic, electrolyte, and liver functions remained stable [121].

Treatment with DCA at a dosage of 25 mg/kg daily has been linked to reversible neuropathic toxicity; however, it remains unclear if this effect is a result of DCA itself or the advancement of the underlying condition [122, 124]. Despite this, our findings indicate that DCA is connected to neuropathic toxicity only in a limited number of toxicological investigations. Typically, these studies administer higher doses of DCA (as much as 1000 mg/kg for durations reaching 120 days)) [116, 119].

However, DCA may be safe because of its bioaccumulation and intergenerational transmission properties in the treatment of IS. DCA treatment improves mitochondrial metabolism in the short term, unlike inherited mitochondrial metabolism defects that require long-term treatment. The damage to peripheral nerves may be limited and reversible when a large dose of DCA is given within 14 days of the acute phase of IS. However, the protective effects of DCA on IS are more important than its side effects. Therefore, DCA treatment may be an effective treatment strategy to improve the prognosis of IS.

DCA in clinical combination drug strategy and drug dose adjustment

Curcumin has been shown to reverse oxidative stress, DNA damage, inflammation, and neurodevelopmental issues induced by DCA[116]. In addition, curcumin also has therapeutic effects on IS [125].Therefore, the combination of DCA and curcumin may increase the efficacy of IS

and reduce side effects. The physical examination and total neuropathy score can be conducted on patients receiving treatment with DCA [126]. Additionally, DCA levels and GSTZ1 protein were assessed, and the dosage of DCA was adjusted according to the results. Potential protective strategies against DCA, such as curcumin, should be subjected to rigorous randomized controlled trials to evaluate their benefits.

DCA recommendations for IS patients in different regions

Epidemiological evidence does not indicate a direct carcinogenic effect of DCA in humans, and long-term use of DCA has been shown to lack haematological, hepatic, or renal toxicity [17, 127]. For instance, Abdelmalak et al. followed eight patients with congenital lactic acidosis who received oral DCA (5.12 mg/kg every 9 h) for a duration ranging from 5.1 to 7.16 years, during which their renal, liver, electrolyte, and hepatic statuses remained stable [128]. In regions that cannot afford frequent blood biochemistry and other tests, it may be a viable strategy to adjust drug dosage and determine whether to discontinue medication based on the patient's adverse reactions and total neuropathy score.

Recommendations for future clinical trials

The initial oral dose for the clinical trial patient treatment group should be set at 5 mg/kg every 12 h, with the potential for appropriate increases based on the absence of peripheral neuropathy and the patient's ability to tolerate at least 6.25 mg/kg per hour. The treatment group received DCA in conjunction with standard IS treatment medications, while the control group did not receive DCA. Following treatment, total neuropathy score, NIHSS, BI, mRS scores, DCA levels, and GSTZ1 protein will be measured at regular intervals.

Conclusion

In summary, the present animal and cell experiments indicate that DCA is a promising agent for the treatment of IS with multiple pharmacological activities. This review includes data from several studies, but does not include meta-analysis. These deficiencies include statistical tests, confidence intervals, adjustment for age, sex, and comparisons with other treatment effects. This limits the ability to statistically validate the findings. Moreover, there is still a lack of data on the optimal dose and neurotoxicity of this drug in clinical practice, so further preclinical and clinical studies are needed.

Abbreviations

AIF	Apoptosis-inducing factor
BBB	Blood–brain barrier
CREB	CAMP response element-binding protein
JNK	C-Jun-N-terminal kinases
AcCoA	Coenzyme A
COX-IV	Cytochrome c oxidase IV
DCA	Dichloroacetate
NAD +	Dinucleotide
DRP1	Dynamin-Related Protein 1
HO-1	Heme Oxygenase-1
HS	Hemorrhagic stroke
iNOS	Inducible nitric oxide synthase
IL10	Interleukin 10
IL6	Interleukin- 6
IL-1β	Interleukin-1beta
iNOS	Inducible nitric oxide synthase
IS	Ischemic stroke
CD206	Mannose Receptor
MMP9	Matrix metalloproteinase 9
Tfam	Mitochondrial transcription factor A
Mfn1	Mitofusion-1
MYPT1	Myosin phosphatase target subunit 1
NO	Nitric oxide:
Nrf2	Nuclear respiratory factor 2
Nrf-1	Nuclear respiratory factor
Opa1	Optic Atrophy 1
p38 MAPK	P38 mitogen-activated protein kinase
PCr	Phosphocreatine:
PDH	Pyruvate dehydrogenase
PDHC	Pyruvate dehydrogenase complex
PDK	Pyruvate dehydrogenase kinase
PDKs	Pyruvate dehydrogenase kinases
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
ROCK	Rho-associated protein kinase
SQSTM1	Sequestosome 1
SOD	Superoxide dismutase:
TCA	Tricarboxylic acid
TNF-α	Tumor Necrosis Factor-α

Author contributions

Xu Wang and Chunshu Rong contributed to conceptualization, literature search, manuscript writing, and draft preparation. Ping Niu and Wei Leng contributed to literature search and writing. Ziqiao He, Gaihua Wang and Xinqi contributed to software and data curation. Dexi Zhao and Jinhua Li contributed to conceptualization, drafting, guidance, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

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