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Myozyme Exhibits Neuroprotection by Reinforcing Astrocytic Antioxidant Defense during Cerebral Ischemia/Reperfusion Injury

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ABSTRACT

Acute ischemic stroke remains a leading cause of death and long-term disability worldwide. Although vascular recanalization restores cerebral blood flow, reperfusion can provoke excessive oxidative stress and secondary neuronal injury. Our previous study indicated lysosomal glycogen degradation was dysfunctional in astrocyte after reperfusion. However, whether pharmacological enhancement of lysosomal glycogen degradation can strengthen astrocytic antioxidant capacity during reperfusion remains unknown. Here, we investigated the neuroprotective potential of Myozyme, a recombinant acid α-glucosidase (GAA), in experimental cerebral ischemia/reperfusion. In mice subjected to middle cerebral artery occlusion/reperfusion (MCAO/R), intravenous Myozyme administration reduced cerebral infarct volume and improved sensorimotor performance after reperfusion. In primary astrocytes subjected to oxygen-glucose deprivation/reoxygenation (OGD/R), Myozyme increased GAA activity and intracellular glucose content. These changes were accompanied by increased G6PD activity, elevated NADPH and GSH levels, and ROS accumulation. In an astrocyte-neuron coculture system, Myozyme-treated astrocytes increased extracellular GSH availability and were associated with higher neuronal GSH and NADPH levels, lower neuronal ROS accumulation, and improved neuronal viability. Collectively, these findings identify Myozyme as a potential therapeutic candidate for cerebral ischemia/reperfusion injury and support a model in which increased astrocytic GAA expression is associated with enhanced PPP-related antioxidant capacity and improved redox support for neighboring neurons.

Keywords

Ischemia/reperfusion, Myozyme, Astrocyte, Neuron, Antioxidant.

Introduction

Acute ischemic stroke remains a leading cause of death and long-term disability worldwide [1]. Intravenous thrombolysis and mechanical thrombectomy restore cerebral blood flow and improve clinical outcomes in eligible patients [2]; however, successful recanalization does not completely prevent secondary tissue injury. During early reperfusion, the rapid re-entry of oxygen into metabolically compromised tissue triggers mitochondrial dysfunction, redox imbalance, excitotoxicity, and inflammation [3]. Ischemic accumulation of metabolites such as succinate contributes to the burst of mitochondrial reactive oxygen species (ROS) after reperfusion, providing a metabolic basis for oxidative injury following blood-flow restoration [4]. Because neurons have limited capacity to withstand sustained oxidative stress, reinforcing endogenous metabolic and antioxidant defenses may provide a useful complement to vascular recanalization therapies [5].

Astrocytes are central to these endogenous defenses, serving as the primary regulators of cerebral energy metabolism and redox homeostasis [6]. They contain most of the readily mobilizable glycogen in the adult brain and support neighboring neurons during increased energetic demand and glucose deprivation [7]. Glycogen-derived carbon can enter the glucose-6-phosphate pool and be distributed between glycolysis and the pentose phosphate pathway (PPP) [8]. In the oxidative branch of the PPP, glucose-6-phosphate dehydrogenase (G6PD) generates NADPH, which is required for glutathione reductase-dependent regeneration of reduced

glutathione (GSH) [9]. This NADPH-dependent antioxidant regeneration is particularly critical during early reperfusion, when the sudden restoration of oxygen rapidly depletes cellular reducing capacity [10]. Astrocytes possess a robust glutathione system and support neuronal antioxidant defense by increasing extracellular availability of GSH and glutathione-related precursors [11]. Thus, astrocytic glucose mobilization influences neuronal resistance to reperfusion injury not only by sustaining energy production, but also by maintaining NADPH- and GSH-dependent redox buffering.

Studies of brain glycogen metabolism have predominantly focused on cytosolic glycogenolysis mediated by glycogen phosphorylase [12]. A distinct fraction of glycogen can, however, be routed to lysosomes for degradation by lysosomal acid α-glucosidase (GAA), a process related to glycophagy that has been characterized primarily in non-neural tissues [13]. While pharmacological activation of glycogen phosphorylase has been explored in other contexts, targeting lysosomal GAA offers the unique advantage of leveraging a clinically approved enzyme with established lysosomal delivery mechanisms [14]. Cerebral ischemia/reperfusion markedly remodels autophagic and lysosomal pathways, although the consequences of this response vary with cell type, injury severity, and time after reperfusion [15]. Whether lysosomal glycogen degradation contributes to astrocytic metabolic and antioxidant adaptation during reperfusion therefore remains an important unanswered question.

Myozyme is a recombinant human GAA that restores lysosomal glycogen degradation in Pompe disease, an inherited disorder caused by GAA deficiency [16]. Following receptor-mediated internalization, the enzyme is delivered to lysosomes, where it supplements endogenous GAA activity [17]. Given that astrocytes harbor the brain's principal glycogen reservoir and ischemia/reperfusion remodels lysosomal pathways in a manner that may increase glycogen substrate availability as well as Myozyme has established clinical safety and manufacturing profiles, pharmacological GAA supplementation represents a mechanistically grounded candidate for acute neuroprotection [18]. Nevertheless, whether pharmacological GAA supplementation enhances astrocytic glucose availability and PPP-dependent antioxidant defense during cerebral ischemia/reperfusion has not been investigated.

In the present study, we tested the hypothesis that Myozyme confers protection against cerebral ischemia/reperfusion injury by enhancing astrocytic GAA expression and increasing glucose availability for PPP-dependent NADPH and GSH generation. We first established in vivo efficacy by evaluating infarct burden and sensorimotor function in a mouse model of middle cerebral artery occlusion/reperfusion. We then dissected the cellular mechanism using astrocytic oxygen-glucose deprivation/reoxygenation to determine whether Myozyme increased GAA expression and was associated with coordinated changes in glucose availability, G6PD activity, NADPH, GSH, and ROS. Finally, we tested functional intercellular transmission in an astrocyte-neuron coculture model to examine whether Myozyme-treated astrocytes improved neuronal redox homeostasis and viability. This study therefore repurposes a clinically available lysosomal enzyme for acute ischemic brain injury and identifies a candidate GAA-centered lysosomal-redox pathway linking astrocytic glycogen metabolism to intercellular antioxidant defense.

Materials and Methods

Animals

Four-week-old male C57BL/6J mice, one-day-old neonatal C57BL/6J pups, and embryonic Day 15-16 female C57BL/6J mice were purchased from the Experimental Animal Center of the Fourth Military Medical University. The moyzyme (alglucosidase alfa, rhGAA) was bought from the Sanofi (France).

Primary astrocyte and neuron culture

Primary astrocyte was obtained from the one-day-old neonatal C57BL/6J pups. Primary neuron was obtained from the embryonic Day 15-16 female C57BL/6J mice. The procedures for the primary astrocyte and neuron culture were performed according to our previous study [19].

Astrocyte-neuron coculture

An astrocyte-neuron coculture system was established using hanging inserts with porous membranes (3 μm, Millipore, PTSP24H48). The coculture medium contained a glucose-free neurobasal medium (Thermo Fisher Scientific, A2477501) supplemented with fetal bovine serum (15%, Thermo Fisher Scientific, 16140071), B27 (2%, Thermo Fisher Scientific, 17504044), glucose (5.56 mM, Thermo Fisher Scientific, A2494001), and glutamine (1%, Thermo Fisher Scientific, 35050061).

I/R model in mice

A middle cerebral artery occlusion/reperfusion (MCAO/R) model was established to mimic I/R injury in mice as our previous study reported [19].

I/R model for cultured neural cells

An oxygen-glucose deprivation/reoxygenation (OGD/R) model was established to mimic I/R for the cultured neural cells as our previous study reported [19].

TTC staining

The TTC staining was performed according to our previous study [19].

Neurobehavioral test

The corner test and grid-walking test were performed according to our previous study [20].

Immunoblotting

The immunoblotting was performed according to our previous study [20]. The primary antibodies were as follows: rabbit anti-GAA (Proteintech, 14367-1-AP, 1:1000) and rabbit anti-GAPDH (Proteintech, 10494-1-AP, 1:1000).

Glucose detection
Glucose level in the cultured astrocytes was measured using a Glucose Assay Kit (Abcam, ab65333).

Glycogen detection
Glycogen level in the cultured astrocytes was measured using a Glycogen Assay Kit (Abcam, ab169558).

Glucose-6-phosphate dehydrogenase activity
G6PD activity was determined using a Glucose-6-phosphate Dehydrogenase Activity Assay Kit (Abcam, ab102529).

NADPH detection
NADPH level in the cultured astrocytes and cocultured neurons was measured using an NADPH Assay Kit (Abcam, ab176724).

GSH detection
GSH level in the cultured astrocytes and cocultured neurons was determined using a GSH Assay Kit (Abcam, ab65332).

ROS detection
ROS level in the cultured astrocytes and cocultured neurons was determined using a ROS Detection Assay Kit (Abcam, ab287839).

Neuronal viability
A Cell Counting Kit-8 (CCK-8, Sigma-Aldrich, 96992) was used to measure the viability of cocultured neurons.

Statistical analysis
All data are presented as the means ± standard deviations (SDs) and were analyzed using Prism software (GraphPad). Independent t-tests were used to analyze the differences between two groups. Statistical significance was set at $P < 0.05$.

Results
Myozyme can alleviate reperfusion injury after ischemic stroke
First, we intended to investigate whether Myozyme can exhibit neuroprotective effects on the reperfusion injury after ischemic stroke. To solve this problem, we used the MCAO/R model in the mouse and injected the Myozyme (40 mg/kg) into the tail vein (Figure 1A). We found that the infarct volume was declined at 72 h after MCAO/R with Myozyme treatment (Figure 1B). We also performed the cornet test to detect the sensory function of the mouse and observed that the sensory dysfunction was improved after MCAO/R with Myozyme treatment (Figure 1C). In addition, the motor dysfunction was ameliorated after MCAO/R with Myozyme treatment, as analyzed by grid-walking test (Figure 1D).

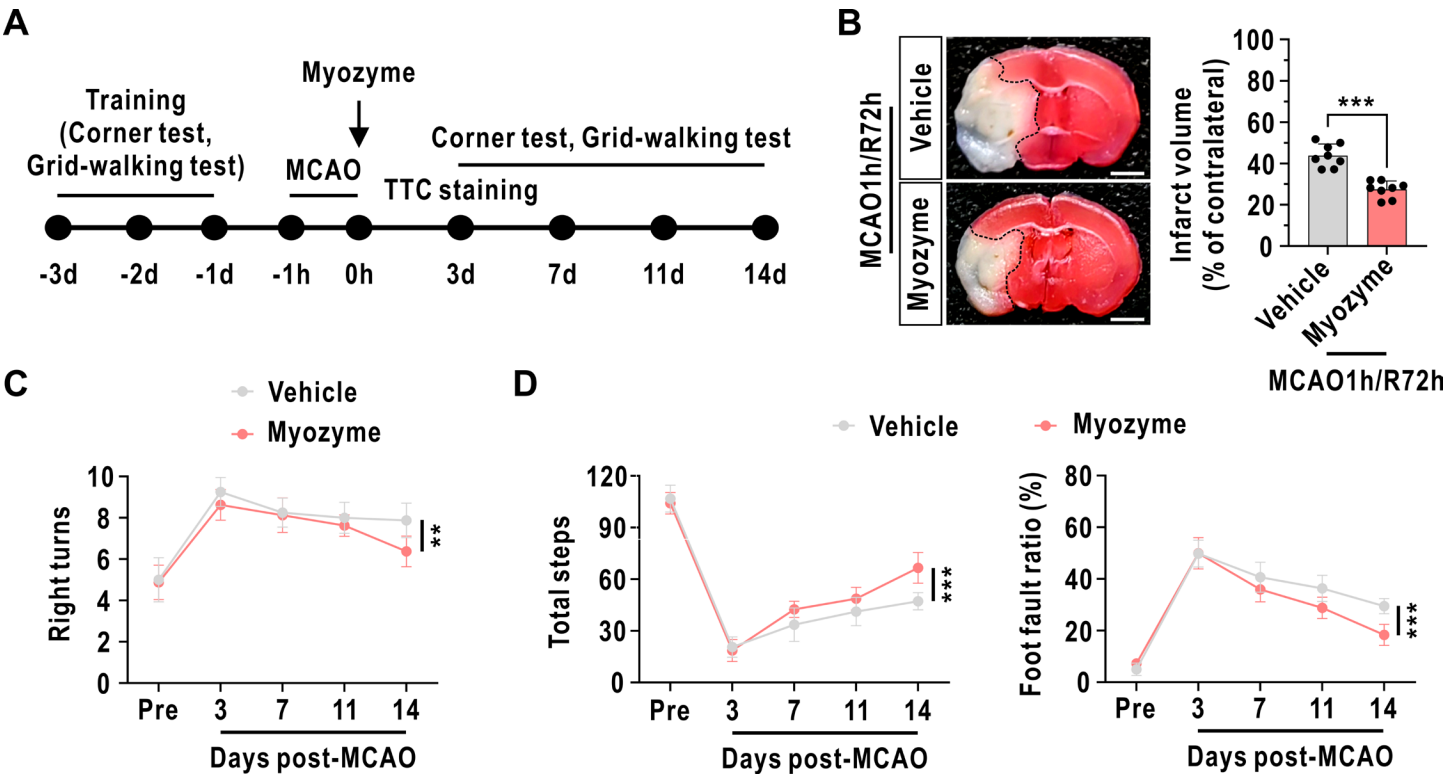

Figure 1: Myozyme alleviates reperfusion injury after ischemic stroke in mice. (A) Timeline schedule for MACO, Myozyme injection, TTC staining and neurobehavioral test. (B) TTC staining showing the infarct volume with the Myozyme injection at 72 h after MCAO/R injury (n = 8). Scale bars = 1 mm. (C) The number of right turns in 10 trials before and after reperfusion in mice, as detected by corner test (n = 8). (D) The total steps (left) and foot fault ratios (right) before and after reperfusion in mice, as detected by grid-walking test (n = 8). The data are presented as the means ± SDs. The statistical analysis was performed using the independent t-tests (B-D). $^{**}P < 0.01$. $^{***}P < 0.001$.

Astrocytic antioxidant ability was accelerated by Myozyme after reperfusion in ischemic stroke

Next, we warranted to discover the underlying mechanism for the Myozyme-induced neuroprotection on the reperfusion injury after ischemic stroke. We used the OGD/R model on the cultured astrocytes and the Myozyme (2 μM) was added into the culture medium immediately after reperfusion. We found that the GAA expression in the cultured astrocytes was upregulated with Myozyme treatment at 12 h after OGD/R (Figure 2A). Accompanied with GAA upregulation, glucose level in the cultured astrocytes was increased with Myozyme treatment at 12 h after OGD/R (Figure 2B). And the glycogen level in the cultured astrocytes was declined with Myozyme treatment at 12 h after OGD/R (Figure 2C). The G6PD activity in the cultured astrocytes, the key enzyme for pentose phosphate pathway (PPP), was activated with Myozyme treatment at 12 h after OGD/R (Figure 2D). The products of PPP, NADPH, was enhanced with Myozyme treatment at 12 h after OGD/R (Figure 2E). And the antioxidants GSH in the cultured astrocytes was increased with Myozyme treatment at 12 h after OGD/R (Figure 2F). Accordingly, the ROS level in the cultured astrocytes was decreased with Myozyme treatment at 12 h after OGD/R (Figure 2G).

Myozyme enhances neuronal viability via astrocyte-neuron GSH shuttle

Previous study indicated there exists an astrocyte-neuron GSH shuttle that astrocytes can transfer antioxidant GSH into surrounding neurons [21]. To further discover the underlying mechanism for the Myozyme-induced neuroprotection on the reperfusion injury after ischemic stroke, we constructed the astrocyte-neuron coculture model (Figure 3A) and the cultured astrocytes were treated with Myozyme for 12 h and then cocultured

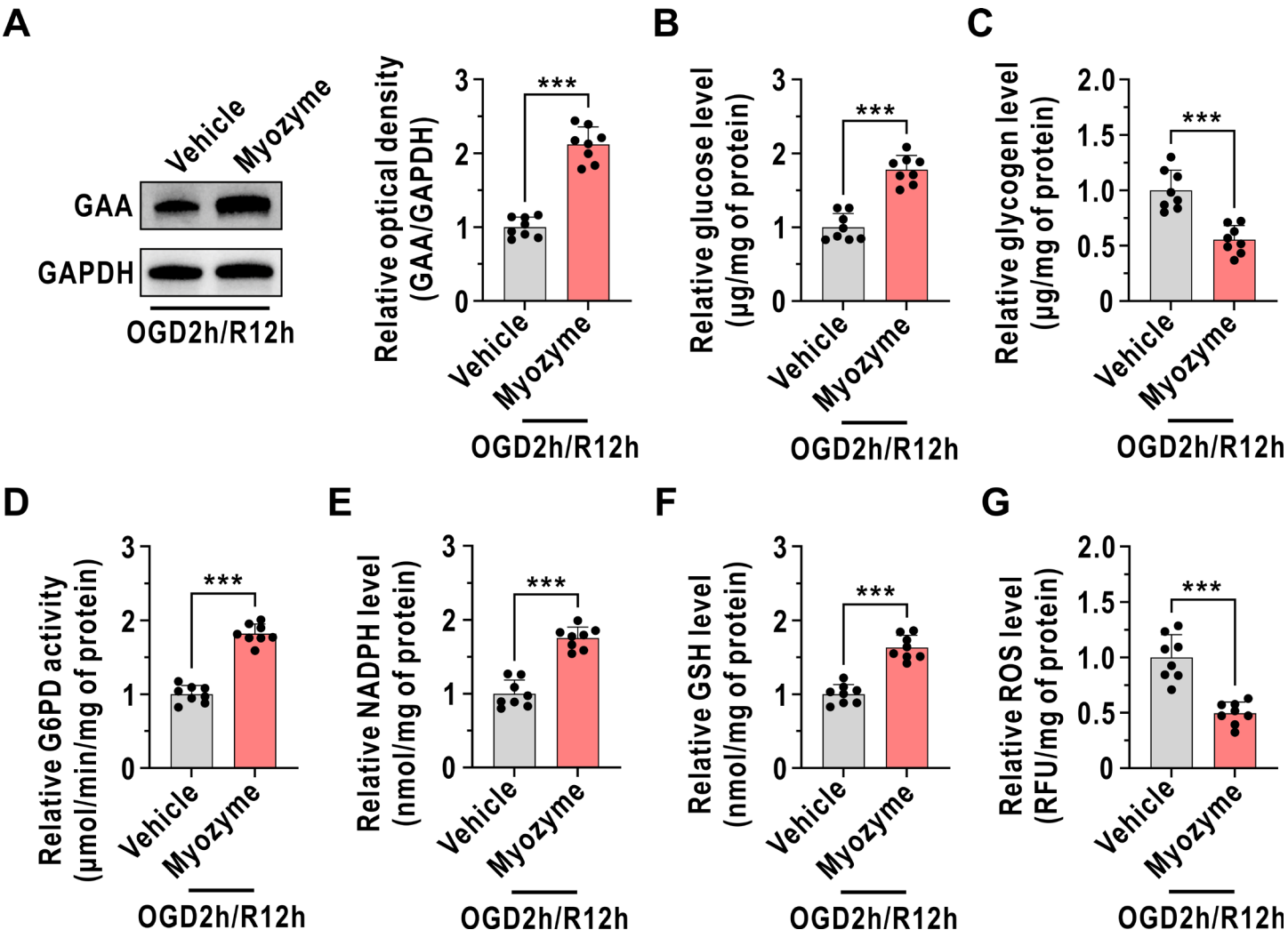

Figure 2: Myozyme enhances astrocytic antioxidant ability after OGD/R. (A) Immunoblotting to detect the expression of GAA in the cultured astrocytes at 12 h after OGD/R (n = 8). The relative optical density was calculated by the optical density of GAA dividing the optical density of GAPDH. (B) Relative glucose level in the cultured astrocytes at 12 h after OGD/R (n = 8). (C) Relative glycogen level in the cultured astrocytes at 12 h after OGD/R (n = 8). (D) Relative G6PD activity in the cultured astrocytes at 12 h after OGD/R (n = 8). (E) Relative NADPH level in the cultured astrocytes at 12 h after OGD/R (n = 8). (F) Relative GSH level in the cultured astrocytes at 12 h after OGD/R (n = 8). (G) Relative ROS level in the cultured astrocytes at 12 h after OGD/R (n = 8). The data are presented as the means ± SDs. The statistical analysis was performed using the independent t-tests (A-G). $^{***}P < 0.001$.

with neurons for another 12 h. As shown in the Figure 3B, the GSH was increased in the coculture medium at 24 h after OGD/R (Figure 3B). And the GSH in the cocultured neurons was enhanced at 24 h after OGD/R (Figure 3C). The NADPH in the cocultured neurons was also upregulated at 24 h after OGD/R (Figure 3D). Accompanied with GSH enhancement, the ROS in the cocultured neurons was downregulated at 24 h after OGD/R (Figure 3E). Accordingly, the cell viability of neurons was accelerated at 24 h after OGD/R when cocultured with Myozyme-treated astrocytes (Figure 3F).

Discussion

The present study identifies Myozyme as a candidate therapeutic intervention for cerebral ischemia/reperfusion injury and implicates astrocytic redox metabolism as a key contributor to its protective effects. In mice subjected to MCAO/R, intravenous Myozyme administration reduced cerebral infarct volume and improved sensorimotor performance after reperfusion. In primary astrocytes exposed to OGD/R, Myozyme increased intracellular GAA exprission and glucose availability, accompanied by higher G6PD activity, increased NADPH and GSH levels, and reduced ROS accumulation. Moreover, Myozyme-treated astrocytes increased extracellular GSH availability and improved neuronal redox status and viability in coculture. Collectively, these findings support a working model in which GAA supplementation enhances astrocytic glucose-dependent antioxidant capacity and creates a

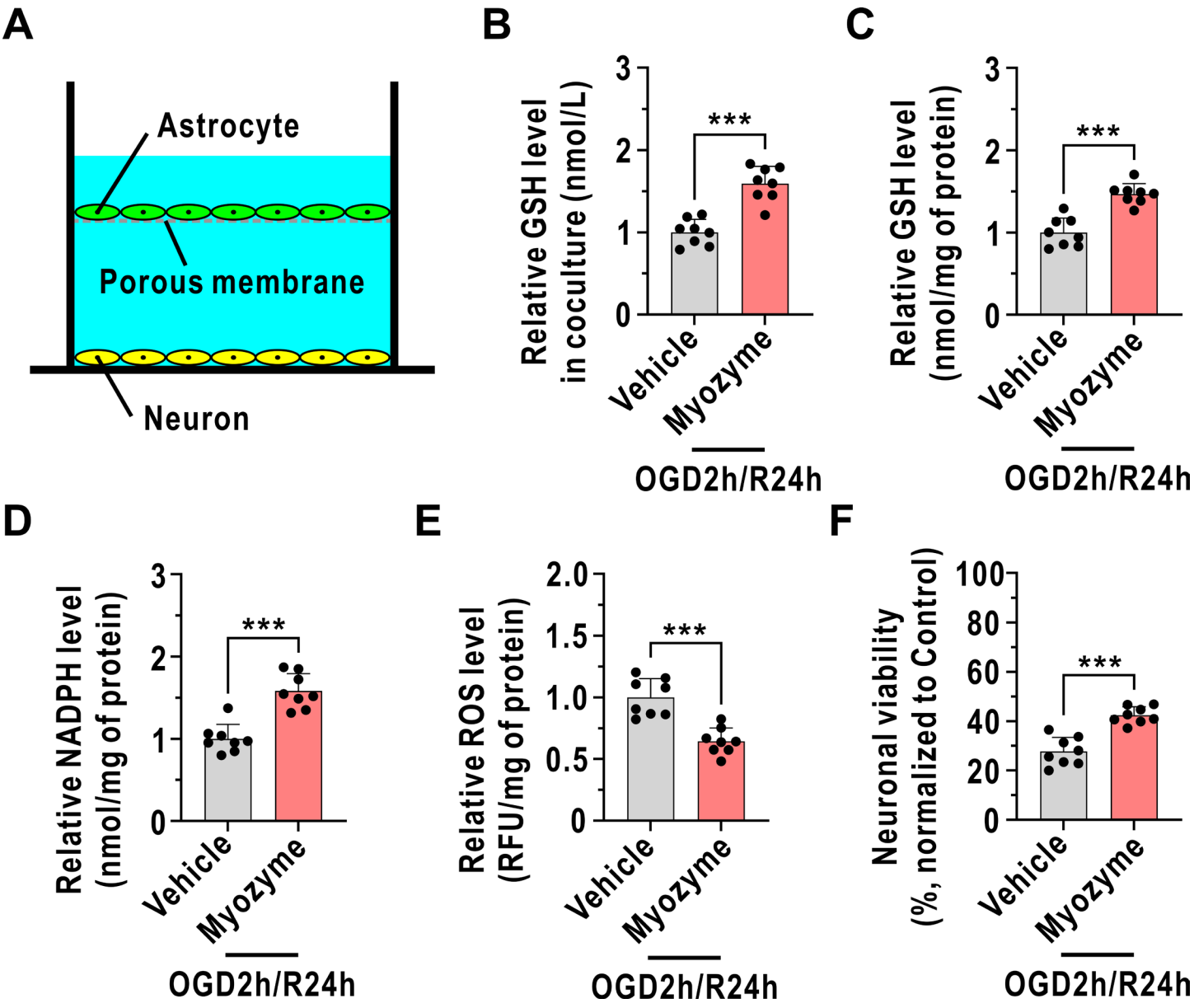

Figure 3: Myozyme enhances cocultured neuronal viability after OGD/R. (A) A schematic picture describing the astrocyte-neuron coculture model. (B) Relative GSH level in the cocultured medium at 24 h after OGD/R (n = 8). (C) Relative GSH level in the cocultured neurons at 24 h after OGD/R (n = 8). (D) Relative NADPH level in the cocultured neurons at 24 h after OGD/R (n = 8). (E) Relative ROS level in the cocultured neurons at 24 h after OGD/R (n = 8). (F) Cell viability of cocultured neurons at 24 h after OGD/R (n = 8). The statistical analysis was performed using the independent t-tests (B-F). $^{***}P < 0.001$.

more favorable metabolic environment for neighboring neurons, thereby contributing to tissue protection after cerebral ischemia/reperfusion.

Oxidative stress is a central driver of secondary injury after the restoration of cerebral blood flow [22]. During ischemia, metabolites such as succinate accumulate and are rapidly oxidized upon reperfusion, triggering mitochondrial ROS generation [23]. Mitochondrial dysfunction, NADPH oxidase activation, excitotoxicity, and inflammatory responses can subsequently sustain oxidative damage, leading to lipid peroxidation and cell death [24,25]. Despite this strong pathological rationale, direct ROS-scavenging strategies have generally provided limited clinical benefit, in part because ROS production is rapid, compartmentalized, and closely coupled to cellular metabolism [26]. Myozyme differs from conventional antioxidants because it does not directly neutralize free radicals. Instead, the present results indicate that it reinforces endogenous systems responsible for generating reducing equivalents and maintaining glutathione-dependent antioxidant defense. Such a metabolic mechanism may be particularly relevant during reperfusion, when the demand for NADPH and GSH increases sharply [27].

Astrocytes are well positioned to mediate this response. They represent the principal cellular glycogen reservoir in the adult brain and provide metabolic support to neurons during increased activity, glucose deprivation, and ischemic stress [28]. Previous studies of brain glycogen have focused predominantly on cytosolic glycogenolysis mediated by glycogen phosphorylase [29]. However, a fraction of cellular glycogen can also be delivered to lysosomes and hydrolyzed by GAA through a process associated with glycophagy [30]. This lysosomal arm of glycogen metabolism has been studied primarily in non-neural tissues and in the context of Pompe disease [31]. GAA deficiency causes lysosomal glycogen accumulation and progressive cellular dysfunction, whereas Myozyme, a recombinant human GAA, restores enzyme activity after mannose-6-phosphate receptor-mediated uptake and lysosomal delivery in responsive tissues [32]. The present study extends this biological framework by suggesting that increasing GAA activity may also be beneficial under acute metabolic stress, even in cells without an inherited GAA deficiency.

This link is particularly relevant to the brain because glucose allocation between glycolysis and the PPP strongly influences neural resistance to oxidative stress [33]. Neurons rely heavily on PPP activity to preserve their antioxidant capacity, and disruption of glucose flux toward the PPP increases their susceptibility to oxidative injury [34]. Astrocytes exhibit greater metabolic flexibility and can adjust glucose utilization, NADPH production, and glutathione metabolism in response to neuronal activity and oxidative demand [35]. In the present study, higher G6PD activity in Myozyme-treated astrocytes was accompanied by increased NADPH and GSH levels and decreased ROS accumulation. The coordinated direction of these changes indicates that Myozyme reinforced PPP-associated antioxidant capacity under OGD/R conditions. These findings broaden the potential role of astrocytic glycogen metabolism from emergency energy provision to the maintenance of reducing power during reperfusion stress.

The coculture experiments further connect the astrocytic response to neuronal redox homeostasis. Neurons have limited metabolic flexibility and depend partly on astrocytes for precursors required to maintain their glutathione pool [36]. Astrocytes synthesize and release GSH, which is generally processed extracellularly by γ-glutamyl transpeptidase and related peptidases into cysteine-containing products that can be taken up by neurons and used for de novo GSH synthesis [21]. Consistent with this intercellular support pathway, activation of astrocytic antioxidant programs, including Nrf2-dependent glutathione synthesis and release, has previously been shown to protect neighboring neurons from oxidative injury [37].

In the present coculture system, Myozyme-treated astrocytes increased extracellular GSH availability and were associated with higher neuronal GSH and NADPH levels, lower neuronal ROS accumulation, and improved neuronal viability. These results suggest that enhancing astrocytic redox metabolism can generate a more supportive extracellular environment for neurons during astrocytic OGD/R stress. The extracellular GSH measurement should not, however, be interpreted as evidence that intact GSH was transferred directly from astrocytes into neurons. It more likely reflects an increased extracellular glutathione-related pool that can supply precursor substrates for neuronal GSH synthesis. Similarly, because NADPH does not ordinarily undergo direct intercellular transfer, the increase in neuronal NADPH probably reflects preservation or enhancement of neuronal endogenous redox metabolism. The coculture findings therefore support functional astrocyte-to-neuron antioxidant coupling without requiring direct transfer of intact GSH or NADPH.

The cellular observations provide a biologically coherent explanation for the *in vivo* effects of Myozyme. The reduction in infarct burden was accompanied by improved sensorimotor performance, indicating that the treatment effect extended beyond biochemical markers to tissue preservation and neurological function. Astrocytes are integral components of the neurovascular unit and regulate neuronal metabolism, extracellular homeostasis, antioxidant defense, blood-brain barrier integrity, and inflammatory signaling after stroke [38]. Reinforcing astrocytic GAA-associated glucose metabolism may therefore improve the resilience of the ischemic brain during reperfusion. Nevertheless, the *in vivo* effects cannot yet be attributed exclusively to astrocytes. Endothelial cells, perivascular cells, microglia, infiltrating immune cells, and peripheral tissues may also respond directly or indirectly to systemic Myozyme administration. Actions on these compartments could influence vascular permeability, inflammation, and systemic metabolism and thereby contribute to the overall therapeutic effect.

Repurposing Myozyme also has potential translational advantages. As an approved enzyme-replacement therapy for Pompe disease, it has established manufacturing procedures, formulation characteristics, and clinical safety information [39].

These features may reduce some of the developmental barriers encountered by entirely new neuroprotective agents [40]. In ischemic stroke, Myozyme would most plausibly be used as an adjunct to thrombolysis or mechanical thrombectomy rather than as an alternative to vascular recanalization. Administration around the onset of reperfusion may complement recanalization by strengthening endogenous antioxidant defenses during the period in which restored oxygen delivery precipitates oxidative injury. Nevertheless, its approved status in Pompe disease does not establish efficacy, optimal dosing, or safety in acute stroke, and these issues require dedicated evaluation.

Several limitations should be considered. First, the proposed GAA-glucose-PPP-NADPH-GSH pathway is based on coordinated endpoint measurements rather than direct metabolic-flux analysis. Cellular glycogen content, lysosomal glycogen degradation, glucose-6-phosphate abundance, and PPP flux were not directly measured. Stable-isotope tracing of glycogen-derived carbon, combined with measurements of NADPH/$NADP^+$ and GSH/GSSG ratios, would more directly establish whether Myozyme redirects glycogen-derived glucose toward antioxidant metabolism. Second, increased whole-cell GAA expression does not by itself demonstrate astrocytic uptake and lysosomal localization of recombinant GAA. Astrocyte-specific GAA depletion, together with G6PD inhibition or disruption of GSH synthesis, would help determine the causal requirement for individual steps in the proposed pathway. Third, although astrocytes were washed before coculture, neuron-only Myozyme controls and direct measurements of residual extracellular enzyme would be needed to exclude a contribution from neuronal exposure.

In conclusion, the present study demonstrates that Myozyme attenuates acute cerebral ischemia/reperfusion injury and supports astrocytic redox metabolism as a mechanistic contributor to its neuroprotective effects. Myozyme increased astrocytic GAA expression and glucose availability in association with enhanced G6PD activity, higher NADPH and GSH levels, and reduced oxidative stress. These astrocytic changes were accompanied by improved neuronal redox status and viability in coculture. Collectively, the findings identify a candidate astrocytic GAA-glucose-PPP-GSH axis that connects lysosome-associated glycogen metabolism with intercellular antioxidant support. By extending a clinically approved lysosomal enzyme from chronic glycogen storage disease to acute ischemic brain injury, this study establishes a GAA-centered lysosomal-redox pathway as a novel neuroprotective target. Direct demonstration of metabolic flux, astrocyte-specific causality, and in vivo brain target engagement will be the next critical steps toward clinical translation.

Acknowledgments

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