QUALITY IN SPORT
eISSN 2450-3118 · Open Access · Peer-reviewed
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BIAŁOWĄS, Patrycja, BIAŁOWĄS, Wojciech, MICHALIK, Zuzanna, JABŁOŃSKI, Wiktor and RASZEWSKA, Julia. Neuroprotection in acute ischemic stroke: promising pharmacological strategies beyond thrombolysis and thrombectomy. Quality in Sport. 2026;65:74110. https://doi.org/10.12775/QS.2026.65.74110

ARTICLE TIMELINE
Received: 07.07.2026. Revised: 02.08.2026. Accepted: 02.08.2026. Published: 10.08.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

Neuroprotection in acute ischemic stroke: promising pharmacological strategies beyond thrombolysis and thrombectomy

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Abstract

Background

Acute ischemic stroke (AIS) remains one of the leading causes of mortality and long-term disability worldwide. Although intravenous thrombolysis and mechanical thrombectomy have substantially improved clinical outcomes, their effectiveness is limited by narrow therapeutic windows, restricted accessibility, contraindications, and the risk of reperfusion injury. Consequently, increasing attention has been directed toward pharmacological neuroprotection targeting the ischemic cascade, including excitotoxicity, calcium overload, oxidative stress, apoptosis, and neuroinflammation.

Aim

This review aimed to evaluate emerging pharmacological neuroprotective strategies in AIS beyond established reperfusion therapies, with particular emphasis on the ischemic cascade as a therapeutic target and on selected pharmacological agents with potential neuroprotective efficacy.

Materials and Methods

A narrative literature review was conducted focusing on the pathophysiology of ischemic brain injury and the current evidence regarding the neuroprotective potential of fingolimod, citicoline, and Cerestat (aptiganel). The analysis included randomized clinical trials, meta-analyses, and experimental studies investigating their neuroprotective and neuroreparative mechanisms of action and clinical efficacy.

Results

The ischemic cascade represents a promising target for adjunctive therapeutic interventions in AIS. Fingolimod demonstrated beneficial immunomodulatory effects and stabilization of the blood–brain barrier, particularly when administered in combination with reperfusion therapies. Citicoline exhibited pleiotropic neuroprotective and neuroreparative properties, with the greatest clinical benefit observed among patients who did not receive thrombolytic therapy; however, its efficacy appears less pronounced in the context of contemporary stroke management. In contrast, Cerestat, despite a strong theoretical rationale as an N-methyl-D-

aspartate (NMDA) receptor antagonist, failed to demonstrate significant clinical benefit and was associated with a substantial incidence of adverse effects.
Conclusion
Effective neuroprotection in AIS is likely to require a multimodal, individualized therapeutic strategy targeting multiple components of the ischemic cascade. Future research should focus on optimizing patient selection, integrating neuroprotective agents with reperfusion therapies, and developing selective combination approaches to improve functional outcomes following ischemic stroke.

Key words: Acute ischemic stroke, Neuroprotection, Ischemic cascade, Reperfusion injury

1. Introduction

Acute ischemic stroke (AIS) is defined as a sudden focal brain injury resulting from critical reduction of blood flow within a specific vascular territory, leading to the development of neurological deficits persisting for more than 24 hours. The direct underlying cause is most commonly arterial vessel occlusion by a thrombus, which initiates a cascade of pathobiochemical events at the cellular level, referred to as the ischemic cascade [1,2].

1.1 Public Health Burden

Stroke remains one of the most serious global health challenges and is currently the second leading cause of death worldwide. Its burden is enormous, accounting for approximately 5.5 million deaths annually, which clearly illustrates its profound impact on mortality and long-term disability [3]. Particularly concerning is the unequal distribution of this burden. Approximately 70% of all strokes occur in low- and middle-income countries, which account for more than 85% of global stroke-related mortality [3–6]. International epidemiological data demonstrate up to a tenfold difference in standardized mortality rates between regions, with the highest rates reported in Eastern Europe, Asia, and Africa [7]. This situation also generates substantial economic pressure, the mitigation of which requires increased attention and a more proportionate allocation of resources within global health policy frameworks [3,5].

Table 1.

Scientific description	Category
Epidemiological significance	Stroke remains one of the leading causes of death in the world, ranking second in the global mortality structure.
Global scale	It is estimated that every year, stroke is responsible for about 5.5 million deaths, significantly affecting the burden on healthcare systems.
Socioeconomic inequalities	The greatest disease burden is observed in low- and middle-income countries, where most cases occur.
Regional mortality	There are significant regional differences in standardized mortality rates, reaching even multiples between regions of the world.
High-risk regions	The highest mortality rates are recorded in Eastern Europe, Asia, and Africa.
Economic implications	High costs of treatment and rehabilitation generate significant economic pressure and indicate the need for a more proportional allocation of health resources.

1.3 Current Standard of Care

The cornerstone of contemporary treatment for acute ischemic stroke (AIS) consists of two complementary reperfusion strategies regarded as the current “gold standard”: intravenous thrombolysis (IVT) and mechanical thrombectomy (MT). Intravenous administration of recombinant tissue plasminogen activator (rtPA, alteplase) within 4.5 hours from the last

known well time (LKW) represents the primary and effective therapeutic approach, with clinical benefit being strongly time-dependent [8,9].

A major breakthrough of the past decade has been the introduction of mechanical thrombectomy, which enables direct mechanical removal of thrombi from large intracranial vessels. Owing to landmark trials such as MR CLEAN, followed by DAWN and DEFUSE 3, the therapeutic window for MT in selected patients (e.g., those with basilar artery occlusion or a small ischemic core identified on perfusion imaging) has been extended up to 24 hours [10]. In patients eligible for both therapeutic modalities, a combined approach (so-called bridging therapy) is recommended, as administration of thrombolytic agents prior to MT has been shown to improve procedural efficacy, whereas a strategy based solely on MT has not demonstrated non-inferiority [11-13].

1.4 Limitations of Current Standards

Despite their proven efficacy, reperfusion-based treatment standards are associated with significant limitations. The primary challenge remains the narrow therapeutic time window. For intravenous thrombolysis, the window is limited to only 4.5 hours, and therapeutic benefit declines rapidly with time [8]. Although MT has expanded treatment eligibility up to 24 hours, advanced neuroimaging techniques-such as computed tomography perfusion (CTP) or magnetic resonance diffusion-weighted imaging (MRI-DWI)-are required within this extended time frame for precise patient selection, and such modalities are not universally available [10].

Another major barrier is the limited accessibility of these procedures, particularly mechanical thrombectomy, which requires highly specialized Comprehensive Stroke Centers equipped with neurointerventional specialists and dedicated peri-procedural teams. Within the “drip-and-ship” model, this frequently results in additional transportation-related delays [14].

Numerous contraindications to treatment also remain clinically relevant. In the case of thrombolysis, these include an increased risk of hemorrhage, recent use of anticoagulant therapy, or excessively mild neurological deficits (NIHSS score 0-5), for which IVT has not demonstrated superiority over antiplatelet therapy [15,16]. Even following successful reperfusion, reperfusion injury may occur. This represents a complex pathophysiological process involving, among others, intensified oxidative stress, inflammation, and increased permeability of the blood–brain barrier, all of which may contribute to additional neuronal tissue damage despite restoration of cerebral blood flow [17].

2. The ischemic cascade as a therapeutic target

Brain injury occurring during acute ischemia results from a complex, multistep pathophysiological cascade. Understanding these sequential events is of fundamental importance for the development of effective neuroprotective strategies [18].

The cascade is initiated by disruption of energy homeostasis. Deficiency of oxygen and glucose leads to a rapid decline in mitochondrial ATP production. Due to the absolute dependence of neurons on aerobic energy metabolism, even 5-10 minutes of vascular occlusion may result in irreversible brain damage. The consequent energy crisis leads to failure of ion pumps essential for maintenance of membrane potential, particularly the sodium-potassium pump (Na+/K+-ATPase), resulting in cellular membrane depolarization [19].

A direct consequence of depolarization is excitotoxicity, which is regarded as the key initiating mechanism of neuronal injury. Depolarization stimulates massive glutamate release into the extracellular space. This neurotransmitter excessively activates postsynaptic receptors, predominantly of the NMDA and AMPA subtypes. Activation of NMDA receptors opens calcium channels, leading to massive and uncontrolled influx of calcium ions (Ca^{2+}) into the cell. Sodium influx through AMPA receptors further exacerbates depolarization and cellular edema [20].

Elevated cytoplasmic Ca^{2+} concentrations act as a universal mediator of cell death by triggering activation of degradative enzymes. Calcium ions activate an enzymatic cascade involving lipases (leading to degradation of lipid membranes), proteases (responsible for breakdown of cytoskeletal proteins and enzymes), and endonucleases (causing DNA fragmentation), thereby inducing irreversible structural cellular damage and ultimately resulting in necrotic cell death [20].

Another crucial component of the cascade is oxidative and nitrosative stress, which becomes particularly pronounced following restoration of blood flow (reperfusion). Under conditions of hypoxia and intracellular Ca^{2+} overload, mitochondrial dysfunction and enzymatic activation lead to massive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These free radicals damage lipids, proteins, and DNA, thereby aggravating cellular injury and initiating inflammatory processes [21–23].

The final stages of the cascade, developing over hours to days following the onset of ischemia, include apoptosis and neuroinflammation. Mitochondrial and DNA damage may activate caspases, leading to programmed cell death (apoptosis), which is particularly relevant within the ischemic penumbra [24,25]. Simultaneously, released mediators-including cytokines and adhesion molecules-initiate a local inflammatory response. Leukocytes infiltrate the damaged tissue and, together with activated microglia, release additional toxic mediators, thereby culminating in tissue destruction [21,26].

Each of these interconnected processes constitutes a potential therapeutic target for interventions aimed at interrupting the ischemic cascade and preserving threatened brain tissue.

3. Pharmacological Strategies

3.1 Fingolimod

A key mediator of secondary brain injury in ischemic stroke is activation of the immune system triggered both by the ischemic event itself and by subsequent reperfusion [27-29]. The sudden and massive influx of lymphocytes from the peripheral circulation into the central nervous system intensifies the local inflammatory response, further disrupting blood–brain barrier (BBB) integrity and worsening clinical outcomes. Early BBB damage and an exaggerated inflammatory response play a critical role in infarct expansion, hemorrhagic transformation, and vasogenic edema formation [30,31]. In this context, therapeutic strategies aimed at suppressing the detrimental immune response appear highly attractive not only as standalone interventions but also as ideal adjuncts to reperfusion therapy designed to reduce its complications.

Fingolimod, an oral sphingosine-1-phosphate receptor modulator, exerts pleiotropic therapeutic effects in acute ischemic stroke. Its primary mechanism of action involves induction of transient lymphopenia through sequestration of lymphocytes within lymph nodes [32,33]. However, its clinical benefits extend beyond immunomodulation alone and additionally include stabilization of the blood–brain barrier [34,35] as well as direct neuroprotective effects [36–39].

Based on currently available preclinical and clinical evidence, citicoline has been shown to exert multifaceted neuroprotective and neuroreparative effects following ischemic stroke. In the review article by Adibhatla RM and Hatcher JF published in the International Journal of Molecular Sciences, the authors emphasized that citicoline stabilizes cellular membranes by enhancing phosphatidylcholine synthesis, limits lipid peroxidation, reduces glutamatergic excitotoxicity, and attenuates oxidative stress and inflammatory responses. These mechanisms contribute to limitation of secondary ischemic injury and promote preservation of blond-brain barrier integrity [40].

In turn, experimental studies presented by Gutiérrez-Fernández M in Brain Research demonstrated that citicoline may support reparative processes during the subacute and chronic phases following stroke through stimulation of neurogenesis, angiogenesis, and synaptic plasticity. Animal models revealed improved neural tissue reorganization together with beneficial effects on recovery of neurological function [41].

Collectively, the available evidence suggests that citicoline may modulate both early mechanisms of reperfusion injury and later neuroreparative processes, thereby making it a potentially valuable adjunctive therapeutic agent in the management of ischemic stroke.

3.2 Citicoline

Citicoline (CDP-choline) is a compound exhibiting both neuroprotective and neuroreparative properties and has been approved for the treatment of acute ischemic stroke [42-44]. Its mechanism of action is pleiotropic and encompasses both protection of neurons damaged by ischemia and support of reparative processes. The principal basis for evaluating its efficacy derives from a meta-analysis of 10 randomized, double-blind, placebo-controlled clinical trials [45-48].

Analysis of all included studies demonstrated that administration of citicoline was associated with a statistically significant increase in the likelihood of achieving functional independence (modified Rankin Scale [mRS] score of 0-2) compared with placebo. This effect remained evident regardless of the statistical model applied, with odds ratios (OR) of 1.56 under the random-effects model and 1.20 under the fixed-effects model. However, substantial heterogeneity was observed among individual study results, which was attributed to the evolution of stroke management standards over the more than 30-year period during which the analyzed trials had been conducted [45,46,48].

Cumulative analysis demonstrated a gradual reduction in the therapeutic effect of citicoline in subsequent, more contemporary trials, supporting the hypothesis that its benefits became progressively “diluted” with improvements in standards of medical care [45]. In the subgroup analysis of patients not treated with rtPA, the effect of citicoline was more pronounced (OR 1.63), suggesting limited additional benefit in thrombolysis-treated patients. The most clinically relevant assessment of efficacy under current therapeutic conditions was provided by analysis of patients who did not receive rtPA and were treated with a dose of 2000 mg/day within 24 hours of stroke onset, in whom a homogeneous and positive treatment effect was demonstrated (OR 1.27) [45,46].

3.3 Cerestat

According to the publication by Lees, Cerestat (aptiganel) represented a promising neuroprotective strategy in acute ischemic stroke as a non-competitive antagonist of the NMDA receptor ion channel. Its mechanism of action was based on inhibition of excessive calcium influx into neurons secondary to glutamate-mediated excitotoxicity. In contrast to other NMDA antagonists, such as selfotel, Cerestat enabled the achievement of plasma concentrations considered neuroprotective (10-12 ng/mL).

Contemporary perspectives on neuroprotective strategies in acute ischemic stroke focus on modulation of glutamate excitotoxicity as one of the principal mechanisms underlying neuronal injury within the ischemic penumbra. As emphasized by Chamorro Á et al., excessive activation of NMDA receptors leads to pathological calcium influx into neurons, thereby initiating a cascade of processes involving mitochondrial dysfunction, oxidative stress, protease activation, and induction of cell death. Consequently, NMDA receptors remain among the primary targets of pharmacological neuroprotection research [47].

However, despite strong pathophysiological rationale, clinical trials investigating NMDA receptor antagonists—both competitive and non-competitive—have thus far failed to demonstrate improvement in functional outcomes in patients with acute ischemic stroke. As

reported by Ortega-Gutiérrez S et al., these limitations resulted, among others, from the narrow therapeutic window, central nervous system-related adverse effects (including disturbances of consciousness and psychotomimetic symptoms), as well as difficulties in achieving selective modulation of pathological rather than physiological glutamatergic transmission [43].

Current research approaches have shifted emphasis away from global NMDA receptor blockade toward more precise modulatory strategies, including selective targeting of receptor subtypes, modulation of calcium-dependent intracellular signaling pathways, and combination therapies simultaneously directed against excitotoxicity, inflammation, and oxidative stress. Particular emphasis is also placed on appropriate patient selection, optimization of treatment timing, and integration of neuroprotective therapy with reperfusion strategies.

In summary, although the concept of suppressing excitotoxicity through NMDA receptor antagonism remains biologically justified, existing clinical experience indicates the necessity for more selective and multimodal neuroprotective interventions in acute ischemic stroke.

4. Conclusion

Acute ischemic stroke constitutes a major global health challenge and remains the second leading cause of death worldwide. Despite the availability of effective reperfusion therapies, such as intravenous thrombolysis and mechanical thrombectomy, their application remains limited due to narrow therapeutic windows, requirements for advanced diagnostic imaging, and restricted accessibility to specialized treatment centers. Furthermore, even successful reperfusion may result in secondary reperfusion injury, underscoring the need for effective neuroprotective strategies.

The pathomechanism of ischemic brain injury involves a complex pathobiochemical cascade comprising disruption of energy homeostasis, excitotoxicity, calcium influx, oxidative stress,

apoptosis, and neuroinflammation. Understanding these processes has enabled the development of various pharmacological strategies aimed at interrupting this cascade.

The review of the three presented neuroprotective strategies illustrates diverse therapeutic approaches. Fingolimod acts primarily through immunomodulation, stabilization of the blood–brain barrier, and direct neuroprotective effects, demonstrating promising results when combined with thrombolytic therapy. Citicoline, characterized by a pleiotropic neuroprotective and neuroreparative mechanism of action, demonstrated efficacy particularly in patients not receiving thrombolytic therapy, although a gradual reduction in its therapeutic effect has been observed alongside improvements in standards of medical care. In contrast, Cerestat, as an NMDA receptor antagonist, despite achieving plasma concentrations considered neuroprotective, ultimately failed to demonstrate statistically significant clinical efficacy and was additionally associated with serious adverse effects.

Conclusions derived from the analysis of these strategies indicate that effective neuroprotection in ischemic stroke requires a multimodal approach targeting various components of the ischemic cascade. Future research should focus on optimization of patient selection, tailoring interventions to individual pathophysiological profiles, and identifying synergistic interactions among different mechanisms of action. It is also of critical importance to incorporate contemporary standards of care into clinical trial design in order to accurately assess the added value of novel neuroprotective therapies. Further advances in this field may substantially improve outcomes in patients with acute ischemic stroke, particularly in those who are not eligible for standard reperfusion therapy or who develop reperfusion-related injury.

AI.

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency,

and adherence to scientific writing standards. **AI** were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

Disclossure

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Writing –rough preparation: PB, ZM, WJ

Writing –review and editing: PB, JR

Supervision: JR, ZM

All authors have read and agreed with the published version of the manuscript.

Funding - This research received no external funding.

Institutional Review Board Statement - Not applicable.

Informed Consent Statement - Not applicable.

Data Availability Statement - Not applicable.

Acknowledgements:Not applicable.

Conflicts of Interest – The authors deny any conflict of interest.

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