Review

Cerebroprotection in the endovascular era: an update

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Received 11 September 2022
Accepted 19 November 2022
Published Online First 6 December 2022

To cite: Schneider AM, Regenhardt RW, Dmytriw AA, *et al*. *J Neurol Neurosurg Psychiatry* 2023;**94**:267–271.

ABSTRACT

Despite advances in clinical diagnosis and increasing numbers of patients eligible for revascularisation, ischaemic stroke remains a significant public health concern accounting for 3.3 million deaths annually. In addition to recanalisation therapy, patient outcomes could be improved through cerebroprotection, but all translational attempts have remained unsuccessful. In this narrative review, we discuss potential reasons for those failures. We then outline the diverse, multicellular effects of ischaemic stroke and the complex temporal sequences of the pathophysiological cascade during and following ischaemia, reperfusion, and recovery. This evidence is linked with findings from prior cerebroprotective trials and interpreted for the modern endovascular era. Future cerebroprotective agents that are multimodal and multicellular, promoting cellular and metabolic health to different targets at time points that are most responsive to treatment, might prove more successful.

INTRODUCTION

In the last several decades, ischaemic stroke treatment has been improved thanks to better patient selection with imaging modalities and the introduction and expansion of eligible patients for recanalisation therapies.[1] Yet, despite these advances, stroke and its clinical consequences remain foremost among leading health issues worldwide. There are over 7.6 million new ischemic strokes each year, with 3.3 million deaths and 63 million years of healthy life lost each year attributable to this disease.[2] Among the most pressing problems are quantifying the disparity between reperfusion success and clinical outcomes, the lack of access to thrombectomy in many locations both within the USA and globally, and the complexity of translating promising neuroprotective agents into human studies.

While recanalisation of the occluded artery remains central for ischaemic stroke treatment, improved patient outcomes could be achieved through additional therapeutic options to preserve and enhance brain structure and function through cerebroprotection.[3–6] However, translation of cerebroprotective trials has so far remained unsuccessful. This may be explained by several factors that encompass practical considerations such as study design, implementation, and evaluation, focusing on a singular putative target in the ischaemic cascade or failing to consider potentially influencing factors such as the patient's reperfusion status.[7 8] Indeed, many drugs that were unable to show a treatment effect in the pre-endovascular thrombectomy (EVT) era, in which most patients were not reperfused, may be more potent when administered as a bridge to save tissue before EVT reperfusion or when administered to rescue tissue after EVT, directly into the reperfused brain.[9–11]

Potential cerebroprotective targets, corresponding pharmacological strategies to address them, and unsuccessful trials have been well enumerated by others.[12 13] This narrative review considers the evidence and suggests future research directions. While the goal of recanalisation therapy is very apparent and has good indicators for translation, cerebroprotection must ideally fulfil a multitude of purposes, including the improvement of cerebral microcirculation, the reduction of infarct progression, the tight regulation of metabolic processes, and the prevention of reperfusion injury, inflammation and haemorrhagic transformation.[6] The optimal approach to achieve clinically significant cerebroprotection is likely multimodal and multicellular, promoting metabolic and cellular health to different targets at different times when most responsive to treatment.[14]

Central to cerebroprotection is the 'brain-time continuum' or the 'time-tissue-target window', as defined by the Stroke Treatment Academic Industry Roundtable (STAIR) XI Consortium.[15] This new, timely paradigm centres on recent advances in the reperfusion era of ischaemic stroke management. The concept of the 'time-tissue-target window' can be expanded to include three primary principles for future ischaemic stroke treatment research: First, cerebroprotective stroke therapy needs to be considered in relation to the timing of reperfusion therapy (ie, before, during or following). There are different cell-specific pathophysiological events in the acute, subacute and chronic phases of ischaemic stroke.[16] Second, cerebroprotective treatment is optimal when linked to a specific tissue or target cell line. There are distinct effects of cerebroprotective therapies on white versus grey matter and different cell types within the brain.[17 18] Third, cerebroprotective treatment can be improved by targeting multiple pathways in concert with polytherapy. Cellular-based cerebroprotective therapy may most likely succeed if pleiotropic effects with multiple pathophysiological targets are considered.[14]

Principle 1: time

The first principle highlights the importance of time sensitivity of the ischaemic lesion and differentiates putative therapeutic options depending on whether they are given before, during or after recanalisation

Table 1 Overview of the compounds mentioned in the review representing the different principles and timings of cerebroprotective therapy in relation to endovascular approaches to improve patient outcomes after ischaemic stroke

Compound	Mechanism of action	Study reference	Treatment time in relation to recanalisation
Intra-arterial hypothermia	Multifaceted; Suppression of apoptotic pathways and excitotoxicity; Regulation of inflammatory pathways, metabolism and CBF; Upregulation of cell survival pathways.	*Chamorro et al* 2021[7], *Sahin et al 2010*[29]	Before
Remote ischaemic conditioning	Poorly understood; Repeated, temporary cessation of blood flow to a limb to create ischaemia may trigger self-protective pathways with cerebroprotective effects.	Chamorro *et al* 2021[7], Hougaard *et al* 2014[20]	
Nerinetide	Disruption of postsynaptic density protein 95 protein-protein interactions that would normally lead to cell death caused by excitotoxicity.	Hill *et al* 2020[21]	
Verapamil	A calcium-channel blocker that perturbs the developing complication of post-ischaemic vasospasm and cell death.	Chamorro *et al* 2021[7], Fraser *et al* 2017[23]	During
Uric acid	Antioxidative properties by scavenging reactive oxygen species, reactive nitrogen species, and non-radicals.	Chamorro *et al* 2021[7]	
Peritoneal haemodialysis	Reduction of blood glutamate levels to accelerate brain-to-blood glutamate clearance.	Chamorro *et al* 2021[7]	After
Activated protein C	Acts on the protease-activated receptor 1 (found on neurons, endothelial cells, pericytes, and astrocytes), promoting anticoagulant and cell-signalling properties.	Chamorro *et al* 2021[7], Lyden *et al* 2021[15]	
Intra-arterial alteplase	Local injection of the thrombolytic agent alteplase following recanalisation using thrombectomy.	Renú *et al* 2022[27]	

CBF, cerebral blood flow.

therapy (table 1). Initially, a critical factor in the decision-making process on whether or not to treat a patient with recanalisation therapy was the time interval since a patient was last known to be well. These time thresholds have been defined by trials studying the efficacy of EVT and intravenous thrombolysis (IVT) to optimise the likelihood of clinical improvement without dramatically increasing the risk of side effects that positively correlate with time, such as haemorrhagic transformation (ie, time window).[15] However, because of the high variability of this time window among patients, imaging can help evaluate the potential treatment benefit of revascularisation for the individual by defining the volume of infarcted tissue versus salvageable penumbra (ie, tissue window).[19] Further, recanalisation therapy also changes the pathophysiological processes initiated by the ischaemic event.[1 3] For example, hyperaemia following reperfusion leads to biochemical imbalances, such as calcium overload and increased production of reactive oxygen species that initiate a cascade of biochemical changes that result in mitochondrial damage, ultimately increasing cell death.[16] Therefore, the effects of additional putative cerebroprotective therapy options need to be interrogated in relation to the timing of recanalisation therapy.

Before recanalisation therapy

The central aims of cerebroprotection given before recanalisation therapy are to slow down the rate of infarct core growth and preserve penumbral tissue for salvage, thereby augmenting the treatment success of IVT or EVT. Furthermore, putative protective agents might extend the ischaemic time window for thrombolysis and EVT and increase the overall number of patients treated. For patients ineligible for recanalisation therapy, the initiation of cerebroprotective therapy ideally also mitigates acute molecular and cellular damaging effects due to the initiated ischaemic injury. For example, selective intra-arterial hypothermia, given immediately before and following EVT, was safe and feasible in a small study of 26 patients.[7] Future studies will increase the sample size and include control groups to investigate the efficacy of this anatomically targeted intervention.[7] Remote ischaemic conditioning (RIC) is another generalised cerebroprotective approach that can be initiated in the prehospital setting before recanalisation therapy. For example, Hougaard *et al* tested RIC, administered as four cycles of inflation and deflation of a standard upper limb blood pressure cuff as an adjunct treatment for patients that would later receive IVT.[20] It was found that, while overall, the results were neutral when adjusting for baseline perfusion and diffusion lesion severity, RIC showed neuroprotective properties by reducing tissue risk of infarction (p=0.0003) in a patient population in which the majority (48 of 81 patients) did not complete all four cycles in order to not delay recanalisation therapy. Since only a blood pressure cuff is required, this approach could theoretically be initiated by first responders in field and during transport to the hospital. Further clinical trials investigating the effect of RIC on ischaemic stroke outcomes and potential underlying neuroprotective strategies are underway.[7] The most promising result for cerebroprotective treatment stems from the ESCAPE-NA1 trial. In patients undergoing thrombectomy, administration of nerinetide, which interferes with neuronal excitotoxicity, has shown to be beneficial in a subset of patients that did also receive thrombolysis.[21]

During recanalisation therapy

One significant advantage of cerebroprotective treatment during recanalisation therapy is that it can be given intra-arterial, which might increase the speed and likelihood of reaching the target area of the brain to exert its effects in an anatomically efficient way. The intra-arterial application of a cerebroprotective agent in addition to EVT uses the newly reopened brain vessel as a route of administration. This has been previously proven to be an effective adjunct treatment in a preclinical model of focal ischaemia in mice.[22] The Superselective Administration of Verapamil During Recanalisation in Acute Ischaemic Stroke-I phase 1 trial, in which the calcium channel blocker verapamil was given immediately following EVT, found no increased risk of intracerebral haemorrhage or other side effects.[23] However, the study lacked a control group, and a larger trial investigating whether verapamil adds clinical benefit to EVT has not yet been conducted. The treatment effect of cerebroprotective agents might be conditional on successful recanalisation, as shown by the URICO-ICTUS trial describing a positive impact of uric acid administration only in patients with successful EVT.[7] That some cerebroprotective agents require reconstitution of blood

flow suggests the doubly negative circumstances of patients not receiving recanalisation therapy or for which the treatment effect remains absent. Further, recanalisation does not necessarily mean reperfusion due to the 'no-reflow phenomenon', which is suggested to be related to pericyte constriction in hypoxic conditions.[24] Therefore, cerebroprotective therapies may also serve to target these related cerebrovascular deficiencies.

After recanalisation therapy

Another approach is cerebroprotection after recanalisation therapy.[7] The paradoxical exacerbation of cellular dysfunction and death following reperfusion, termed ischaemia-reperfusion injury (IRI), is one of the main targets of cerebroprotective therapies given during this time.[14] Efforts to understand the underlying mechanism of IRI and identify the therapeutic options that target them are ongoing. Glutamate excitotoxicity, one of the mechanisms described to account for IRI, triggers large quantities of reactive oxygen species production that overwhelms the endogenous antioxidant capacity of cells, thereby damaging the cell's structural components and inducing death pathways.[7 10] There is a renewed focus on reducing postischaemic excitotoxicity. The ongoing DIAGLUICTUS2 study investigates the effects of peritoneal haemodialysis to reduce blood glutamate levels that have shown promising results in preclinical studies.[7 25] Another component of IRI is the infiltration of circulating leukocytes into the ischaemic tissue, which can lead to damage by disrupting the extracellular matrix and increasing the risk of haemorrhagic transformation.[10] To address this, the RHAPSODY trial investigated postrecanalisation treatment with activated protein C, a serine protease with anti-inflammatory effects and the ability to enhance vascular integrity and angiogenesis. However, while haemorrhagic transformation was reduced, the overall clinical outcome was nevertheless less favourable.[26] Another example of adjunct post-EVT treatment feasibility is intra-arterial alteplase, which was recently shown to improve outcomes after EVT in the CHOICE trial.[27]

Principle 2: tissue and target

The second principle provides an overview of the pathophysiological responses of the individual cells of the neurovascular unit (NVU), distinct responses of white and grey matter tissue to ischaemic stroke, and its potential impact on cerebroprotective therapy. Individual elements that constitute the NVU have selective time-sensitive vulnerabilities and respond to the ischaemic damage in different ways over different times in various brain regions.[18] For example, neurons, endothelial cells, astrocytes, microglia and pericytes react differently to ischaemia, as outlined in figure 1. Therefore, treatment approaches addressing these responses vary depending on the cell type targeted and the cell-specific time window in question.[18]

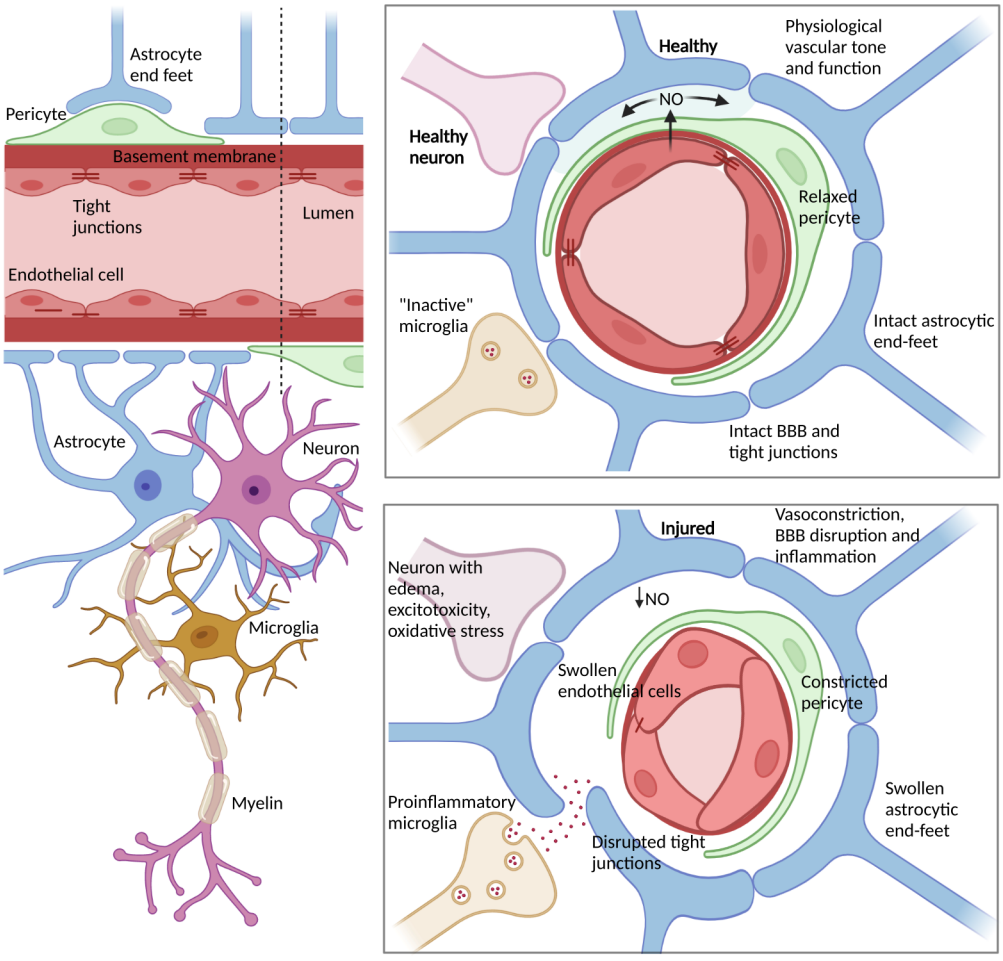

Figure 1 Brain microvascular anatomy, function and dysfunction. During a healthy state, the NVU forms a tight seal around the capillary lumen. It regulates molecular exchange between the blood and brain parenchyma while maintaining a physiological vascular tone and function. During injury, the individual components of the NVU are damaged, leading to neuronal damage, vasoconstriction, BBB disruption and inflammation. Created with BioRender.com. BBB, blood–brain barrier; NUV, neurovascular unit.

The responses of the individual cellular components of the NVU to cerebral ischaemia are comprehensively discussed elsewhere.[14 16] In neurons, the ionic imbalance caused by the ischaemic event will lead to widespread anoxic depolarisation with dramatic ion disturbance, ultimately leading to oedema, injury and aberrant neurotransmission. Endothelial cells lose their tight junction integrity and decrease nitric oxide production, leading to impairment of both blood–brain barrier (BBB) integrity and microvessel vasodilation with increased peripheral immune cell adhesion. Astrocyte structural and functional reactions to cerebral ischaemia are less well understood but include astrocytic end-feet swelling, impaired fluid regulation, glutamate-mediated excitotoxicity and disrupted astrocyte-neuron signalling. Microglia, the resident immune cells, change from a resting to an activated structure and alter their polarisation. Ischaemia-induced pericyte contraction and microthrombotic events lead to the 'no-reflow' phenomenon, while pericyte injury also leads to BBB disruption on a microcirculatory level.

Each putative cerebroprotective therapy option will exert its effects at different time points and therefore necessitates treatment administration schedules that consider these anticipated effects accordingly. The complex pathophysiological cascade on the target and temporal axes (figure 1) suggests that a significant reason for the lack of success of past cerebroprotective therapies is that they were single-action, single-target therapeutic approaches at single time points. Future ischaemic stroke treatments could include multiple-action, multiple-approach strategies tailored for specific time intervals for a higher likelihood of having a clinically relevant effect.

The different cellular constituents of grey matter and white matter are associated with differing susceptibilities to ischaemia based on cerebral blood flow and metabolism.[15 17] Further, there are also well-studied discrepancies between the neurochemical responses to ischaemic damage comparing grey and white matter. Specifically, glutamate-driven excitotoxicity leading to calcium entry, cellular disruption, and ultimately cell death is widely described in the grey matter.[17] However, the proportion of grey matter is considerably lower in humans than in rodents, which might help explain the reduced efficacy of cerebroprotective agents translated from rodent stroke models to human trials.[17]

The clinical importance of the differential vulnerability and unique responses to cerebral ischaemia and therapeutic strategies of grey versus white matter and the individual cell types constituting the NVU might be significant. In line with the recommendations of the STAIR XI Consortium, future research of potential cerebroprotective agents against the adverse downstream effects of ischaemic stroke may best prioritise strategies that address multiple targets to increase the chance of treatment success. Growing evidence supports that a uniform approach across all brain areas and cellular components is not a viable strategy.[15]

Principle 3: polytherapy

The third principle discusses considerations about why future cerebroprotective agents are more likely to succeed and have a clinically relevant impact if multiple pathways are targeted simultaneously or sequentially.[14] The stark differences in structural and functional responses of the various constituents of the NVU to ischaemic injury suggest that optimal therapy addresses more than one cellular dysfunction or cell type. This might be achieved through the polytherapy of pharmacological and interventional strategies to simultaneously address multiple pathways and achieve an additive or even synergistic treatment effect while mindful of potential pharmacological interactions and side effects. Indeed, some literature describes the positive impact of a combined therapeutic strategy in cerebral ischaemia models: One of the first works investigating polypharmacotherapy used a canine model of global ischaemia to show that the administration of dexamethasone (anti-inflammatory), mannitol (antioedema), tocopherol (antioxidant) and perfluorochemicals (strong oxygen-carrying capacity) increased the regeneration of brain electrical activity more when these drugs were given together than individually.[28] In a rodent ischaemic stroke model, the coadministration of citicoline (a cell membrane stabiliser) combined with the induction of mild hypothermia suppressed apoptotic processes and ameliorated cerebral damage more effectively than the administration of either intervention alone. In addition, the polytherapy of nimodipine and citicoline reduced apoptosis and infarct size in a focal model of cerebral ischaemia.[29]

Despite the encouraging results, the literature on polytherapy for ischaemic stroke is limited. To approach this gap in the literature, future studies could aim to design polytherapy options while still choosing the individual compounds parsimoniously and deliberately to test hypotheses and to achieve the best effect with as few compounds as possible to avoid unwanted interactions and side effects. An alternative approach would be to first study the proposed impacts and mechanisms of polypharmacotherapy before examining the individual compounds separately. In either case, to embed the findings of this treatment approach into the broader literature, the treatment effects could be measured with traditional means of infarct volume by imaging or pathology and by neurological or behavioural assessment. It will be crucial for funding bodies to acknowledge the importance and leverage the financial support for researching polypharmacotherapy as an ischaemic stroke treatment.

CONCLUSION

Clinical translation of cerebroprotective therapy has so far proved elusive. There are several possible underlying reasons for past failures. However, the future of this treatment strategy in the modern endovascular era is one of optimism. There are three principles for novel cerebroprotective treatment attempts: first, cerebroprotective stroke therapy may be best seen in relation to the timing and success of reperfusion therapy; second, cerebroprotective treatment could be designed for a specific tissue or target cell line at a cell-specific time window and third, a cellular-based cerebroprotective therapy may most likely succeed if pleiotropic effects with multiple pathophysiological targets are considered. Overall, with an increased understanding of the cellular and metabolic effects of cerebral ischaemia across time intervals, the combination of multiple treatment options, and optimal timing of the therapies, we are hopeful that the future will add cerebroprotection as a new cornerstone of treatment for patients suffering from ischaemic stroke.

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Acknowledgements We are grateful to Prof. Eng Lo for his insightful comments on this manuscript.

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Funding AB is funded by grants from the Leducq Foundation and the Albert Einstein. Society. JAH is funded by grants from the Neiman Health Policy Institute.

Competing interests AB is senior medical science advisor and co-founder of Brainomix, a company that develops electronic ASPECTS (e-ASPECTS). JAH is a consultant for Medtronic, Persica, and Spine Biopharma, chair for DSMB Balt, and is deputy editor at JNIS. ABP is Consultant for Penumbra, MicroVention, and Medtronic. The other authors do not declare any conflicts of interest.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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