EDITORIAL

Perspective in current neuroprotection strategies

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THE publication of 5 randomized clinical trials in 2015 supporting mechanical thrombectomy for the treatment of acute stroke has refueled the search for more ways to minimize or prevent disability caused by this disease.^{3,4,9,11,14} Some of the areas being explored include prehospital stroke severity assessment, imaging modalities, new thrombectomy strategies, and rehabilitation programs. Neuroprotection is another area that is gaining significant traction these days after many disappointing results on the past.

In this issue, Babadjouni et al. provided an in-depth review of all major randomized clinical trials involving neuroprotection.² They summarized the current and past clinical trials of clinical relevance, focusing on when and how to intervene in the timeline of acute stroke therapy. The authors mention not only neuroprotective drugs but also other brain protective strategies, including remote ischemic preconditioning, induced hypothermia, intraarterial stem cell delivery, and intravenous cooling during acute ischemic stroke. This review covers in detail the pathophysiological mechanisms of ischemic injury and the neuroprotective effects of each drug. Here, we contribute more information regarding action mechanisms of brain protection drugs and include citations to other recent literature.^{7,8} We also discuss other neuroprotectants not mentioned in the authors' literature review.

The first molecular mechanism of ischemic brain tissue damage is excitotoxicity, in which the excitatory glutamate plays the leading role to activate a plethora of downstream signaling pathways, resulting in an increase in intracellular calcium concentrate.⁶ Magnesium sulfate works in this stage, by acting as the *N*-methyl-D-aspartic (NMDA) ion channel inhibitor and calcium antagonist. Thus, the concept of the FAST-MAG trial, i.e., to deliver neuroprotectant agents during the hyperacute stage with the help of prehospital cooperation, seems theoretically reasonable.¹⁵ The relatively slow permeability rate of magnesium sul-

fate in crossing the blood-brain barrier (BBB), taking 4 hours to peak, is considered to be one of the causes of failure in this study as well as the long study period of over 8 years, given that the delivery of conventional therapy evolved during the time of the study.¹⁶ NA-1 is another promising NMDA antagonist that has shown the effect of stopping glutamate excitotoxicity in experimental studies to reduce the volume of infarction.¹⁰ Thus, it is rational to want to examine earlier administration, i.e., in the in-hospital setting; however, the authors' method of comparing the iatrogenic infarction volume after endovascular aneurysm coiling is thought to have low statistical power because of its rare occurrence.^{2,10} Neu2000KWL is another promising neuroprotective drug that targets both NMDA receptor-mediated excitotoxicity and free-radical toxicity and, coupled with endovascular treatment, is now being tested in a Phase 1 trial.²

Oxidative and nitrosative stress is the next target of the neuroprotective potential, resulting from an increase in secondary messenger systems coupled with the generation of free radicals.⁶ Uric acid is one of the most anticipated neuroprotective agents in this stage, which is the final oxidation product of purine catabolism in humans and has been shown to prevent glutamate-induced cell death by blocking the generation of free radicals at the vessel wall.^{5,6} Uric acid has also shown synergistic neuroprotection with alteplase in a rodent model. Furthermore, some encouraging results have been derived from the clinical trial by Chamorro et al., including a lower incidence of early clinical worsening and more functional independence among patients treated with uric acid, although it did not show significant improvement in functional outcome as the primary end point (modified Rankin Scale score at the 90-day follow-up).⁵ The tendency of reducing the infarct volume in each subgroup of women and hyperglycemia proved in the subanalysis of this trial is another reassuring potential of this compound, suggest-

ing the potential for further investigation.^{1,12} Edaravone is also an antioxidant drug that inhibits peroxidation of the phosphatidylcholine liposomal membrane through several pathogenic mechanisms.^{6,7} It is also the only available neuroprotective drug in clinical use in Japan and China, because of its early success in a randomized trial in Japan in which significant improvement in independence at 90 days was demonstrated.⁷ Edaravone is distinguished by its low molecular weight, which enables better BBB permeability; reduction of endothelial injury, brain edema, tissue injury, and delayed neural death have been reported.⁷ Despite the inconclusive evidence in a systematic review,¹⁷ some encouraging evidence has been reported in recent articles that show the improvement in functional recovery⁸ or the preventive effect for hyperperfusion syndrome after carotid revascularization.¹³ It may be meaningful to reexamine the efficacy of this drug coupled with endovascular treatment.

The immune-mediated inflammatory response is potentially the third therapeutic target after ischemic brain injury and is currently under investigation.⁶ It is triggered by the damage associated with molecular pattern molecules, such as heat shock protein, and is characterized by orchestrated infiltration of the brain parenchyma by immune cells: brain-intrinsic microglia, neutrophils, monocytes, and lymphocytes. Fingolimod, natalizumab, and interleukin-1 receptor antagonist and minocycline are the representative drugs targeting the stage of the immune-mediated inflammatory response after acute stroke.⁶ The role of the immune system in the pathophysiology of stroke remains uncertain and controversial.⁶ Having insights into the pathophysiological mechanisms of each strategy is meaningful in conducting clinical trials. Numerous neuroprotective drugs have failed to prove their potential efficacy at the time of translation from preclinical or experimental animal studies into the clinical arena. Several reasons have been attributed to these failures, including differences between rodent and human response (animal model issues), difference in age and sex (in general, young male rodents have been used in the animal experiments), drug kinetics, and disposition in the human body. Moreover, the study design of the clinical trial might have led to the unsuccessful clinical results. To advance to the next step in this potentially promising field, it is crucial to address these new strategies in an appropriate “delivery platform” in the context of the current clinical settings in accordance with its pathophysiological relevance, as well as to scrutinize the other pathogenic mechanisms, such as no-reflow phenomenon or reperfusion injury. Mechanical thrombectomy has played a leading part in the “seismic” paradigm shift of acute stroke treatment over the past 2 years. It is our hope that these strategies will contribute to the long-expected positive clinical impact in decreasing the disabilities due to stroke even as an adjunct to the very efficacious mechanical thrombectomy.

<https://thejns.org/doi/abs/10.3171/2017.1.FOCUS1728>

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Disclosures

The authors report no conflict of interest.