Review Article

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The Future of Stroke Neuroprotection

Abstract

There are hundreds of putative Neuroprotectants that have been evaluated in preclinical models, but none have entered the clinical realm, despite the fact that researchers acknowledge the limitations of rodent or non human primate stroke models. In the beginning, research primarily focused on the neuron; however, in more recent years, research has expanded to include astrocytes, pericytes, endothelial cells, and other neural cells that make up the neurovascular unit. There are some new developments that give neuroprotection new hope, new compounds with multiple mechanisms of action or the establishment of new guidelines for stringent preclinical testing In the past five years, only uric acid and nerinetide have been tested for clinical efficacy at the bedside in RCTs, where all patients had to receive reperfusion therapies, such as intravenous thrombolysis or mechanical thrombectomy. Reperfusion therapy was also tested with otaplimastat, 3K3A-Activated Protein C (APC), intra arterial verapamil, and intra arterial hypothermia, but only in RCTs with only feasibility or safety outcomes. In this review, some of these compounds are discussed for their promising outcomes. The testing of putative neuroprotectants in enriched clinical studies of patients receiving reperfusion therapies, a better preselection and evaluation of drugs at the preclinical stage, and a deeper understanding of the mechanisms that are involved in the ischaemic death process at the neurovascular unit may prove to be more effective than in the past in reversing a dire situation that has already lasted for an excessive amount of time.

Keywords: Neuroprrotection • Stroke Model • Astrocytes • Pericytes • Endothelial Cells • Thrombactomy • Preselectin

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Introduction

The recognition of the value of thrombectomy in appropriately selected patients or the utility of brain imaging techniques to individualize the use of thrombectomy up to 24 hours after stroke onset, including wake up strokes, has led to an evolution in the treatment of Acute Ischaemic Stroke (AIS). Despite this, stroke continues to be a significant problem for patients, their families, and the global health care system. This is due to the fact that even the benefits of reperfusion therapies are only partially realized in about half of the patients who are given them. Treatment with compounds made to protect brain cells from ischaemia seems like a reasonable alternative to recanalization. Hundreds of putative neuroprotectants have been tested in preclinical models over the past quarter century, but none have made it into the clinic. Other authors have provided a comprehensive list of the specific issues that may be responsible for previous translational failures. By, interest in brain safety has returned. Three major occurrences in stroke community was initially energized by the introduction of Endo Vascular Thrombectomy (EVT) as a viable treatment option. EVT offers the opportunity to examine or in some cases, re examine brain protective therapies in conjunction with recanalization, which is not just a new and effective treatment for patients. One observes a profound lack of attention to patients' recanalization status in previous clinical trial failures. Brain protective therapies are much more likely to be successful when used in reversible occlusion models, which are the animal version of EVT. This is one lesson from animal studies that probably applies to stroke patients in humans. Second, newer agents with multiple mechanisms of action have been developed. Uric Acid (UA), NA 1, and 3K3A APC, for instance, have multiple cytoprotective effects by targeting various nervous system targets. Drugs that only acted on one putatively important pathway or receptor in the ischaemic cascade were the cause of previous

failures. Thirdly, new guidelines like RIGOR, CAMAREDES, and ARRIVE have emerged as a result of a deeper comprehension of rigor in the laboratory. We sought to describe the likelihood of future clinical trial success for all three of these reasons. According to the opinions of the authors, who have been fully involved in these advancements over the past decades, this review updates the main advancements made in the field non systematically [1-3].

Discussion

Neuroprotection

An evolving concept, neuro protection in ischemic stroke aims to preserve brain tissue that has been damaged by ischemia and will die if not treated. It is closely related to the penumbra, a tissue that is not directly affected by the stroke but is subjected to metabolic and hypoperfusional changes that increase the likelihood of delayed cell death. While cells in the infarct center are viewed as anoxic and hopelessly lost, the encompassing hypo perfused obscuration locale highlights tissue that at first is feasible however in danger of deferred cell passing. The goal of neuroprotection is to protect this area [4].

Neurovascular unit

The possibility of the neurovascular unit has given a productive theoretical structure for researching instruments of stroke pathophysiology. We look at three recent developments and improvements to this overall concept first, during stroke recovery, help me signaling facilitates the transition from injury to recovery within the neurovascular unit; second, the neurovascular unit communicates with systemic physiology, and third, Systemic variables like age, comorbidities, and circadian rhythm have an impact on the neurovascular unit [5].

Because cells in the penumbra do not die immediately after ischemic onset, the penumbra offers stroke patients hope and an opportunity. Instead, depending on how much intermediate perfusion is maintained by collaterals, the penumbra will eventually collapse. It has become increasingly clear over the past few years that the penumbra is not just actively dying. Many mediators play biphasic roles are deleterious in the acute stage but potentially beneficial during recovery. For instance, the alarming HMGB1 may be released by reactive astrocytes in the delayed phase as a homing signal for endothelial progenitors in order to amplify angiogenesis. As a framework for understanding these endogenous recovery pathways in the injured central nervous system, the overall concept of help me signaling has been proposed. Damaged but not yet dead cells can recruit the exchange of help me signals within the remodeling neurovascular unit, such as lipocalin 2, 17 vascular endothelial growth factor 18, and even extracellular mitochondria [6].

Enhancing the effectiveness of stroke translational research

In order to evaluate potential beneficial treatments, preclinical stroke models attempt to recapitulate a few aspects of human stroke. Although researchers acknowledge the limitations of rodent or nonhuman primate stroke models, they believe it is essential to demonstrate improved outcome in an animal stroke model prior to initiating large, costly clinical trials. There hasn't always been blinding for outcomes like behavioral ratings and histological measurements, which could lead to bias from researchers who favor one outcome over another. Underpowered examinations can lead specialists to distribute as before long as they accomplish a genuinely critical outcome, this can be defeat with a prespecified treatment impact size and test size. The observation that some results cannot be replicated outside of the laboratory that produced the initial positive result is referred to as reproducibility and generalizability. As a result, numerous authorities recommend requiring positive results from multiple labs employing multiple models. The common practice in basic science labs of ignoring "dropout" animals and replacing them with additional subjects is known as "attrition bias" [7].

The inclusion of all enrolled subjects in the experiment, even if they "drop out" prior to the final outcome, eliminates the possibility that the "dropouts" represent biological realities that could influence the stroke model's outcome. Before a clinical trial begins, sample sizes, power analysis, and treatment effects are frequently specified. Heterogeneity among subjects is a confounded point with huge issues on the two sides. On the one hand, avoiding the

enrollment of non-informative patients may make it easier to demonstrate a treatment effect with a population that is more uniform. On the other hand, stroke is a diverse condition, and if clinical trials reflect this, the findings ought to be more applicable to other conditions [8].

In the past five years, two significant advancements have given neuro protection new hope: the publication of new standards for rigorous preclinical development that go beyond the venerable Stroke Treatment Academic Industry Roundtable (STAIR) guidelines and include compounds with multiple mechanisms of action. Putative neuro protectants must have a single, well established mechanism of action, typically involving a single target, according to established dogma. Therapeutic hypothermia, for example, was a multifunctional treatment that lacked a clear mechanism of action, which is why it drew little interest. Our field gradually came to accept the ischaemic cascade's complexity, that multiple harmful pathways were preceding simultaneously, and that neuro protectants should target multiple pathways to be effective. To reiterate, however, ideas regarding the most effective method for selecting the appropriate neuroprotectants remain speculative in the absence of any clinical success. After that the development of testing guidelines is the second significant development that provides new hope for neuro protection. In depth examination of stroke and neuro degeneration preclinical development programs has revealed significant issues that must be resolved, beginning with a variety of biases that have plagued animal research in general and stroke modeling in particular selection bias, attrition bias, detection bias, and performance bias. Working groups in Europe and the United States recognized the necessity of working together to address these issues [9].

The need for multisite preclinical trials is acknowledged by the majority. These multicentre trials need to have important design components that can overcome previous failures.

Neuroprotection and reperfusion treatment at the bedside

Otaplimastat

In animal stroke models, otaplimastat reduces oedema and intracerebral hemorrhage caused by alteplase and inhibits the matrix metalloprotease pathway. In the SAFE TPA (safety and efficacy of Otaplimastat in patients with acute ischemic stroke requiring tPA) study, 37 80 patients started the rtPA treatment with either 40 or 80 mg of Otaplimastat or a placebo. Parenchymal hemorrhage occurred in 0% of the placebo group, 0% of the low-dose otaplimastat group, and 4.7% of the high-dose otaplimastat group. The highest percentage of positive outcomes was associated with low dose otaplimastat (mRS at day 90, 80% versus 76% for placebo). Despite the fact that it was linked to the lowest success rate in reperfusion [10].

Activated protein C

The blood protease APC is mediated by the Protease Activated Receptor 1 (PAR1), which also has cell signalling and anticoagulant functions. In stroke preclinical models, APC and analogues with cell-signaling cytoprotective activities had beneficial effects. In the randomized, controlled, and blinded RHAP SODY (safety evaluation of 3K3A APC in ischemic stroke) safety trial, 110 patients were given one of four doses of the pleiotropic PAR1 agonist, 3K3A APC, or a placebo following intravenous alteplase, thrombectomy, or both. Although the incidence of favorable outcome (90 day mRS 0 or 1) was 45% in the treatment group and 63% in the placebo, an exploratory analysis revealed a trend toward a lower hemorrhage rate in 3K3A APC-treated patients [10].

Conclusion

There are a lot of positive and negative outcomes during the clinical phase of AIS neuroprotection. This review does not provide a systematic analysis of all of the empirical evidence in the field of neuroprotection in stroke patients treated with resistance therapies, nor does it provide an accurate forecast of the field's future. The review, on the other hand, summarizes what the authors believe to be the most exciting findings from the previous five years, including the clinical benefits that were achieved in important patient subgroups with compounds like nerinetide (thrombectomy without alteplase) or UA (women, hyperglycemic, thrombectomy). In addition, the review

discusses RCT currently investigated drugs and strategies. Overall, a more in depth understanding of the ischemic death process at the neurovascular unit, improved drug selection and evaluation at the preclinical stage in the SPAN project, and ongoing and future testing of putative neuroprotectants in patients receiving reperfusion therapies could help turn around a bad situation that has been going on for too long.

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Conflict of Interest

None

REFERENCE

1. Thomalla G, Simonsen CZ, Boutitie F MRI Guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 379: 611- 622 (2018).
2. Nogueira RG, Jadhav AP, Haussen DC Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*.378: 11- 21(2018).
3. Chamorro Ángel, Dirnagl U, Urra X Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. *Lancet Neurol*. 15: 869- 881 (2016).
4. Linfante I, Cipolla MJ Improving reperfusion therapies in the era of mechanical thrombectomy. *Transl Stroke Res*.7: 294- 302 (2016).
5. Davis SM, Pennypacker KR Targeting antioxidant enzyme expression as a therapeutic strategy for ischemic stroke. *Neurochem Int*.107: 23- 32 (2017).
6. Kim K A, Shin D, Kim JH Role of autophagy in endothelial damage and Blood Brain barrier disruption in ischemic stroke. *Stroke*.49: 1571- 1579 (2018).
7. Xing C, Lo EH Help me signaling: non-cell autonomous mechanisms of neuroprotection and neurorecovery. *Prog Neurobiol*.152:181- 99 (2017).
8. Esposito E, Hayakawa K, Ahn BJ Effects of ischemic post conditioning onneuronal VEGF regulation and microglial polarization in a rat model of focal cerebral ischemia. *J Neurochem*.146: 160- 172 (2018).
9. Gao L, Jiang T, Guo J *et al*. Inhibition of autophagy contributes to ischemic postconditioning-induced neuroprotection against focal cerebral ischemia in rats. *PLoSOne*. 7: e46092 (2012).
10. Kim J H, Park S-H, Han J Gliome database: a comprehensive web based tool to access and analyze glia secretome data. *Database*. 2020