

Neuroprotection in Stroke

Aspirin and thrombolysis are the main strategies for therapeutic intervention in acute ischaemic stroke.^{1,2} Alteplase (rt-PA) has been approved as a thrombolytic agent in many countries, but its uptake has been slow because of the risk of symptomatic intracerebral haemorrhage and the short 3 hour therapeutic time window. An alternative additional intervention is neuroprotection because of its relative safety, evidence of efficacy in animal models and potential to administer in the pre-hospital setting. However none of the neuroprotective agents has proven effective in clinical trials for the last two decades. The exception is the recently presented preliminary results from the SAINT I (Stroke - Acute Ischaemic - NXY-059 - Treatment) trial in which NXY-059, a free radical scavenger, was shown to improve clinical outcomes when given within 6 hours of ischaemic stroke onset.³ In this review we will summarise the rationale for the use of neuroprotectants and discuss their potential problems.

Basic concepts of neuroprotection

Ischaemic cascade

The ischaemic cascade is a time dependent series of neurochemical events initiated by intracerebral vessel occlusion and energy failure. Early events include the activation of glutamate receptors and influx of extracellular Ca^{2+} , while later recruitment of inflammatory cells, production of free radicals and initiation of apoptosis are seen (Figure). The basis of neuroprotection is that interruption of the propagation of these cascades allows brain tissue to be salvaged, or at least protected until reperfusion occurs. The majority of the ischaemic cascade occurs within the ischaemic penumbra.

Ischaemic penumbra

The ischaemic penumbra is functionally impaired but potentially viable tissue surrounding the infarct core⁴ and may persist for up to 48 hours after ischaemic stroke onset. However this penumbral tissue is destined to be necrotic

unless intervention occurs. Hence, the penumbra is the major target for intervention, either by attenuating the ischaemic cascade with neuroprotective compounds or promoting reperfusion with thrombolysis.

The main categories of neuroprotective agents and clinical trials to date

There are numerous categories of neuroprotective agents which have been shown to be effective in animal models and many have been subjected to clinical trial. While not an exhaustive list, the main categories and trials are described here and listed in the Table.

Glutamate receptor antagonists and calcium channel blockers

As mentioned earlier, focal cerebral ischaemia causes release of excitatory amino acids, principally glutamate which activates various postsynaptic receptors including NMDA (N-methyl-D-aspartate), AMPA (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) and metabotropic receptors. Activation of most of these receptors is associated with calcium influx leading to cell damage. Hence, both glutamate receptor antagonists and calcium channel blockers might have a neuroprotective role.

Although animal studies of glutamate receptor antagonists showed excellent neuroprotective effects, clinical trials in acute ischaemic stroke have been disappointing.⁵ The IMAGES trial of intravenous magnesium (NMDA antagonists) within 12 hours of stroke onset was the largest yet conducted, but was negative except for the lacunar subset.⁶ Trials of calcium channel blockers mainly involved nimodipine,⁷ but no real benefit was found on meta-analysis.⁸ Phase III trials with YM872 (AMPA antagonists) and magnesium are ongoing.

Free radical scavengers

Oxygen free radicals are produced during reperfusion as well



Shuji Arakawa is a Strokologist and trained in Strokology at the National Cardiovascular Center, Japan. He is currently a clinical research fellow in the National Stroke Research Institute, Australia. His research concerns imaging of the ischaemic penumbra.



Nilupul Perera is a Neurologist from Sri Lanka. He currently works as a Clinical Research Fellow in the National Stroke Research Institute, Australia. His main research interest is inflammation after stroke.

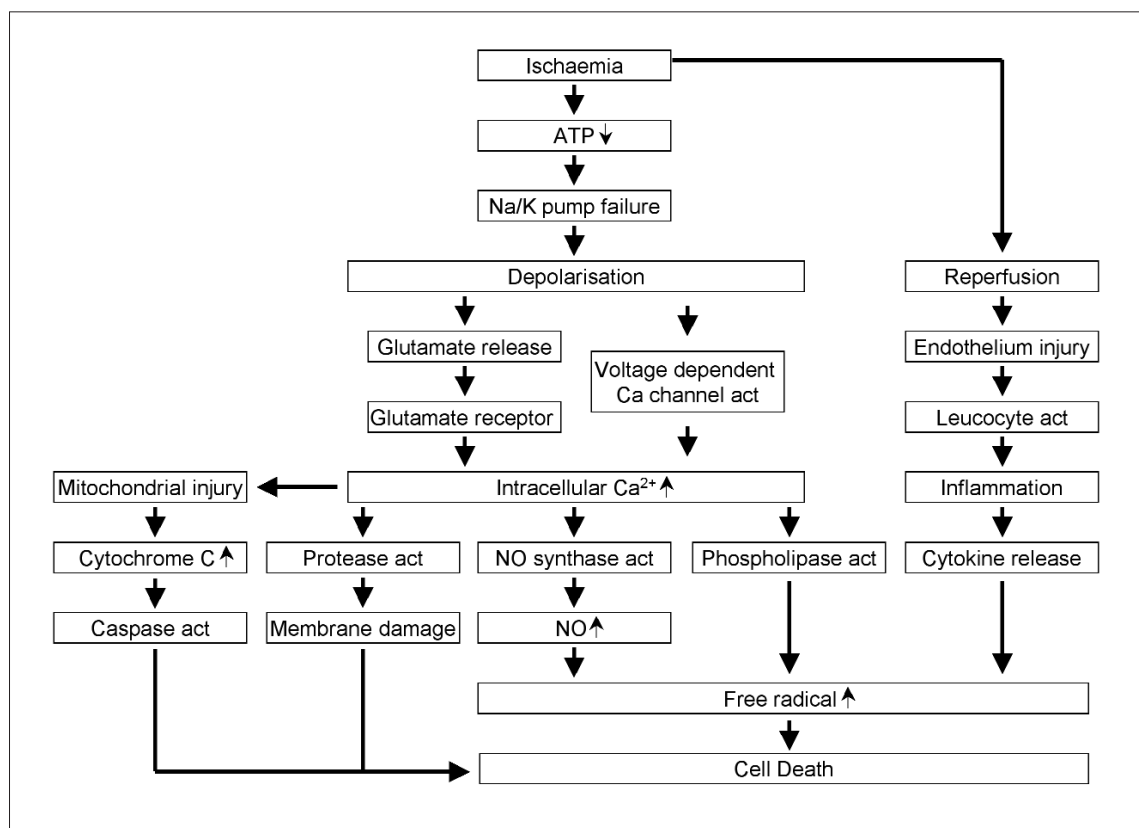


Geoffrey A Donnan, MD is Professor of Neurology, University of Melbourne and Director of the National Stroke Research Institute in Australia. He was co-founder of the Australian Stroke Trials Network (ASTN). Research interests include neuroimaging and clinical stroke trials including acute studies and secondary prevention. He has been involved in the conduct of numerous international stroke trials as either Chair of Steering Committee, Steering Committee Member or Chair of DSMB.

Correspondence to:

Geoffrey A Donnan, MD, FRACP,
National Stroke Research Institute,
300 Waterdale Rd,
Heidelberg Heights,
VICTORIA 3081.
Tel: (613) 9496 2699,
Fax: (613) 9496 2650,
Email: gdonnan@unimelb.edu.au

The ischaemic cascade leading to cell death.
Act; activation



as ischaemia and can cause widespread damage to cellular components such as lipids, proteins and DNA, leading to necrosis or apoptosis.

In May 2005, preliminary results from SAINT I study were released.³ In this trial NXY-059, a free radical trapping agent, was tested in patients with acute ischaemic stroke within 6 hours of onset. A significant reduction in post-stroke disability (modified Rankin Scale) was observed in NXY-059 group. Although the results need to be confirmed in other studies (SAINT II is in progress), NXY-059 might be the first neuroprotectant for the treatment of acute ischaemic stroke.

Interestingly, ebselen and edaravone, both free radical scavenging drugs, also showed favourable outcome in the clinical trials for acute ischaemic stroke,^{9,10} although the time window was 16 hours and sample sizes were small.

Anti-inflammatory agents

Cerebral ischaemia triggers an inflammatory reaction, which may commence within hours and last up to several months.¹¹ Suppression of inflammation using a variety of drugs has been shown to reduce infarct volume in animal studies. Two leukocyte adhesion inhibitors, Enlimomab and LeukArrest, were studied in patients with acute ischaemic stroke, but did not show clinical benefit.^{3,12}

Why have trials of neuroprotective agents failed?

The difficulties in translating benefits of neuroprotection in animal models to the human paradigm has probably been greater than any other area of medicine; hence, the reasons for this apparent failure are worth discussing.¹³ Obviously, the two key issues are that the wrong drugs have been selected for clinical trial because of inadequate pre-clinical testing, or the right drugs have been selected but have been poorly studied in clinical trials.

Pre-morbid conditions. In pre-clinical experiments, researchers usually choose young,

healthy animals. However, stroke patients are usually old and suffer from multiple chronic diseases (e.g. hypertension, diabetes). Co-morbidities in patients can affect their outcome.

White matter. In humans, the proportion of white matter is significant (about 50%), but it is smaller in rodents (about 10%).¹⁴ Because most neuroprotectants have been developed to protect grey matter, they may be beneficial to rodents, but not humans.

Recanalisation. In many animal studies, the temporary occlusion model has been used, while in human stroke, permanent occlusion is more common (about 30% recanalisation rate at 6 hours). The temporary occlusion model may be easier for neuroprotectants to enter the ischaemic penumbra and exert beneficial effects.

Drug dose. Adequate dose escalation studies are frequently not performed in animal models and rarely in phase II clinical trials in humans.

Therapeutic windows. In many animal studies, neuroprotectants were given before or for short time windows after the onset of ischaemia. Therapeutic windows used in most clinical trials have been up to 24 hours, but more recently restricted to a more realistic figure of around 6 hours after the onset and seems late for effective neuroprotection.

Randomisation. While the majority of clinical trials have been performed in randomised, double-blinded manner this has not been the case in most animal studies.

Outcome measures. In most animal studies, efficacy of neuroprotectants has been measured by infarct volume and less frequently by functional outcomes. Although, in clinical trials the gold standard is functional outcome (e.g. Rankin Scale), magnetic resonance imaging outcomes are sometimes used in phase II trials.

Clearly there needs to be a greater rigour applied to both pre-clinical and clinical testing of neuroprotective agents. Of interest, it has been shown that when this is applied in animal models, the observed protection rates are lower. Fortunately,

criteria have now been established such as described in the STAIR documents¹⁵ and it is of interest that the NKY-059 compound investigators were one of the few groups to adhere to them.

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Table: Neuroprotective trials in acute ischaemic stroke

| Proposed mechanism | Drugs | Results |
|---|--|---|
| Glutamate receptor antagonist NMDA antagonist | Selfotel (CGS19755) Eliprodil "Aptiganel (Cerestat, CNS1102)" MgSO4 (IMAGES) MgSO4 (FAST-MAG) YM872 | Complete / No benefit Halted / No benefit Complete / No benefit Complete / No benefit Ongoing Ongoing |
| AMPA antagonist | | |
| Ion channel modulator Calcium channel blocker | Nimodipine Flunarizine | Complete / No benefit Complete / No benefit |
| Sodium channel blocker Potassium channel activator | Fosphenytoin Maxipost (BMS-204352) | Complete / No benefit Complete / No benefit |
| Free radical scavenger | NXY-059 Tirilazad (U70046F) Ebselen Edaravone | Complete / Benefit on preliminary analysis Complete / No benefit Complete / Benefit on ITT analysis Complete / Benefit |
| Anti inflammatory agents Anti-leukocyte antibody | Enlimomab LeukArrest (9Hu23F2G) Neutrophil Inhibiting Factor (ASTIN) | Complete / Worsening Halted / No benefit Complete / Worsening |