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FOCUS ON: BASIC SCIENCE—HOT TOPICS IN PHARMACOLOGY

Current and future pharmacological interventions for the acute treatment of ischaemic stroke

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Summary Currently there are few effective therapeutic interventions for the acute treatment of ischaemic stroke. The few that do exist are primarily thrombolytics such as recombinant tissue plasminogen activator, which reperfuse the ischaemic brain region but do not otherwise aid in neuroprotection. One of the principal explanations as to why the vast majority of neuroprotective drug trials have failed is that the drugs' therapeutic windows were too narrow to be clinically effective. The inflammatory reaction post-stroke makes a significant contribution to the neurological deterioration witnessed in patients. Since inflammatory mediators have been shown to be upregulated from 1 h to 3 months post-stroke, they represent an ideal target to exploit for therapeutic interventions as their 'actions' can potentially be halted within a clinically relevant therapeutic window. There is also mounting evidence that ischaemic stroke can be exacerbated by a predisposition to chronic inflammation and autoimmunity. This review details the role of inflammation and autoimmunity in stroke and how mediators of these pathways can be developed for therapeutic interventions. Recommendations are also made for an ideal therapy regime for acute ischaemic stroke, utilizing currently available, clinically proven treatments. Lastly, novel strategies for future experimental and clinical stroke research are discussed.

Introduction

Stroke is the second greatest cause of death and the leading cause of major disability worldwide.[1] Besides the physical and emotional burden on patients and their families, this represents an enormous economic burden, estimated between 30 and 50 billion dollars per year by the American

Abbreviations: AA, Amino acid; AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazole proprinonic acid; COX2, Cyclooxygenase-2; CT, Computerized tomography; GM_1, Monosialoganglioside; GP, General Practitioner; ICH, Intracerebral haemorrhage; IL-6, Interleukin-6; NINDS, The National Institute of Neurological Disorders and Stroke; NSAID, Nonsteroidal anti-inflammatory drugs; PGI_2, Prostacyclin; rt-PA, Recombinant tissue plasminogen activator; STAIR, Stroke Therapy Academic Industry Roundtable; TACS, Total anterior circulation syndrome; TNF-α, Tumour necrosis factor-α; TXA_2, Thromboxane A_2

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Health system alone.[2] As over 80% of these strokes are ischaemic,[3] all references to stroke in this review will pertain to this subclass. An ischaemic stroke is characterized by an abrupt blockage of arteries leading to the brain. The decrease in oxygen and essential nutrients results in a metabolically unstable area of neural tissue. The core of this area has little or no blood flow and dies rapidly, mainly through necrosis (ischaemic core). The region surrounding the core (ischaemic penumbra), despite being compromised, is still capable of being saved by therapeutic intervention if there is reasonable restoration of blood flow, or if the apoptotic process is arrested. Currently, only a handful of therapeutic interventions for the acute treatment of cerebral ischaemia have exhibited clinical and statistical significance. These are primarily thrombolytic agents, which reperfuse the ischaemic tissue but do not otherwise aid in neuroprotection (for a comprehensive list of positive phase III clinical stroke trials see Table 1). This review will briefly describe problems with past clinical trials, and then focus on the future direction of neuroprotective drugs in experimental and clinical stroke research. There will be an emphasis on the therapeutic window and the roles of anti-inflammatory mediators and autoimmunity in stroke. This will be followed by recommendations for a progressive therapy regime for the acute treatment of ischaemic stroke.

The Stroke Therapy Academic Industry Roundtable (STAIR) committee

Despite the millions of dollars spent on stroke research (acute therapy) almost all phase III clinical trials of neuroprotective drugs, and many of the thrombolytic/recanalization studies conducted thus far, have been negative despite evidence of experimental success.[4] This fact alludes to fundamental flaws in one or more of three underlying processes: (1) the experimental evidence given to support a drug's ability to neuroprotect; (2) how drugs are selected to proceed to clinical trial; and (3) clinical trail design. In an attempt to improve upon all three processes, academic and industry leaders in stroke research formed a review panel called the Stroke Therapy Academic Industry Roundtable (STAIR) committee and published guidelines for experimental and clinical drug development with the main goal of expanding the number of effective and safe acute stroke therapies.[4–6]

The first STAIR meeting focused on the discrepancy between preclinical/experimental evaluations and clinical outcomes.[5,7,8] Their concern was that the information clinical trials were founded on was inaccurate and based on imperfect experimental results. The main experimental parameters tackled included: stroke severity,[8] full dose–response evaluation, drug efficacy, therapeutic window, use of appropriate models (transient and permanent focal ischaemia),[9,10] functional behavioural testing in addition to measurement of infarct volume, measurement of physiological parameters, and reproducibility of data by external laboratories. The second meeting was on phases I and II clinical trial designs and how to ensure that the parameters and endpoints were maximized so that trials would require the fewest number of patients to detect significant differences.[4] The most recent meeting deliberated on how to increase the percentage of patients who might be included in acute stroke therapy trials.[6] To progress in clinical stroke research one must first acknowledge all historical deficiencies as highlighted by past trials. However, this review is limited to a discussion on the therapeutic window, which is arguably the most important preclinical and clinical parameter and relevant to any recommendations for future therapies.

Therapeutic window

The therapeutic window is defined as the longest period of time between vessel occlusion (ischaemia) and drug treatment in which the treatment will still confer a significant amount of neuroprotection. The earlier patients present for diagnosis, the more likely they will be eligible for treatment and that the treatment will be effective. Clinically, this is a particularly problematic parameter as one of the common symptoms of stroke is mild confusion and disorientation, which entails the presence of an observer who can recognize the symptoms and expedite the process of hospital admission. The therapeutic window is a key factor in choosing treatments as many patients (approximately 58%), may not be candidates for some therapies because they do not present within 24 h.[11] For reasons such as these, preclinical criteria for putative neuroprotective drugs includes, not only exhibiting significant efficacy at a non-toxic dose, but doing so with a large therapeutic window, one that is achievable in humans (e.g. 4–6 h). Numerous drugs have met this criteria. However, almost all have failed to show clinical efficacy due, in part, to the narrow therapeutic window of the drugs and clinicians repeated failure to follow experimentally defined parameters (reviewed in Ref.[7]). For example,