Preface

Protecting the Ischemic Brain

Despite many years of research, treatment and prevention of ischemic stroke continue to be one of the major challenges in current medicine.

Progressive understanding of the complex mechanisms of cerebral ischemia has influenced the development of a large number of molecules to block the ischemic cascade at different levels. Many of these drugs have demonstrated considerable efficacy in a range of animal models of cerebral ischemia. The transfer of these results to human clinical practice has not, however, proved to be sufficiently satisfactory. More than 140 clinical trials have been conducted in stroke and some 250 drugs, either alone or in combination, have been studied both in ischemic stroke and in cerebral hemorrhages. From this research, only revascularization of the occluded cerebral arteries has proven to be effective, but only when it has been utilized at a very early stage, and in selected patients.

Much recent neurovascular research has been designed to identify molecular changes deriving from cerebral ischemia that are capable of becoming therapeutic targets: mechanisms associated with energy failure, excitotoxicity, lesions associated with free radicals, inflammation and apoptosis. The hope of having a drug available for universal application that by itself cures ischemic stroke is, without a doubt, an unattainable utopia. However, analyses and reviews of successes as well as of various failures that have occurred in clinical trials developed for studying neuroprotection in ischemic stroke, permit us to be reasonably certain that in the near future we will have available neuroprotectors that are effective in particular situations and for particular patients with stroke.

The therapeutic margin for neuroprotectors, which at present is very narrow, may be even more challenged by the progressively more common use of thrombolytic treatment in regular clinical practice. However, the knowledge that recanalization may permit the arrival of a neuroprotector to the ischemic zone with greater ease and effectiveness does not allow us to be despondent.

Faced with this situation, it seems to be appropriate to ask what the therapeutic margin for pharmacological neuroprotection will be. Considering that the therapeutic objective in acute cerebral infarction is to boost reperfusion and to reduce damage by ischemia-reperfusion, the most reasonable expectations for neuroprotection suggest that this will have its place in a variety of clinical situations: maintaining viability of the ischemic tissue longer and lengthening the therapeutic window for thrombolysis, inhibiting or controlling adverse reactions arising from reperfusion and reducing the risk of brain hemorrhage in those patients who receive thrombolytic treatment. This gives us the opportunity for a combined therapy for thrombolysis with neuroprotection, for which there already are satisfactory experiences in animal models.

Pressure from industry to develop a neuroprotective drug for universal application that is highly effective and has maximum tolerance, has probably led to two major methodological errors: (1) simplifying the complexity of ischemic damage that affects the brain as a functional unit by blocking one single molecular mechanism, and (2) overlooking the value of neuroprotection in enhancing neurorecovery and plasticity, which is essential for the recovery of a stroke patient.

Consequently, in order to achieve better results in acute stroke trials in the future, many changes are needed

in study designs. Future therapeutic options will probably include, in the following order and in accordance with the various time windows, neuroprotection, reperfusion, neuroprotection once again and treatments to enhance neurorepair.

We think that only optimism is acceptable, because never before have so many positive factors existed simultaneously: extensive understanding of the mechanisms involved in cerebral ischemia, overwhelming biotechnological development, investment by the pharmaceutical industry that would have been unimaginable in the past times of therapeutic nihilism, and a growing awareness

among health authorities and the public that stroke is a treatable neurological emergency.

In this context, the present supplement of *Cerebrovascular Diseases* is well justified. The supplement addresses widely neuroprotection in cerebral ischemia. It covers not only molecular, cellular, cerebral and vascular aspects, with particular mention of neurorepair, but also clinical entities that are most susceptible. We hope that the timely information offered here will be of use to the readers.

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