Neuroprotection in ischemic stroke: what does the future hold?

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Neurodegenerative and vascular disease processes are commonly found concurrently in the brains of elderly patients, highlighting the difficulty in determining which processes may be responsible for cognitive impairment. Therapeutically, it may be more sensible to assume that most patients have mixed dementia. Therefore, therapies with multimodal modes of action would be expected to confer neuronal protection. Ischemic stroke is also associated with a complex pathophysiology and a high incidence of post-stroke cognitive impairment, but evidence for the efficacy of neuroprotective treatments in humans is contradictory (mainly due to a failed translation from bench to bedside). Nevertheless, emerging drug therapies continue to undergo testing in prospective, randomized, controlled studies. Natural biologicals, such as Actovegin, or smaller biological molecules with multifaceted effects in the restorative phase of ischemia are likely candidates for efficacy testing. In addition, a number of non-pharmacological interventions, especially lifestyle interventions, are also the subject of current research and would eventually be expected to supplement the treatment and prevention of ischemic stroke.

Recent data have indicated that the direct and indirect costs of brain disorders in Europe are far greater than previously estimated, and that of these, the total annual cost of dementia is among the highest, amounting to €105 billion [1]. In Europe in 2010, the costs for stroke alone were estimated at around €64 billion, while adding approximately 20% of the cost of dementia due to vascular causes is equivalent to another €20 billion. This figure does not include the costs of milder forms of vascular cognitive impairment (VCI) that are not yet equivalent to dementia, even though a substantial proportion of these cases develop into clear-cut dementia later. However, VCI in itself is one of the most burdensome and prevalent types of cognitive impairment to afflict the global ageing population. In many instances, people afflicted with VCI suffer subjectively from memory impairment and notice a reduction in their capacity to use other cognitive and mental abilities.

Diagnostic criteria for VCI remain imprecise due to differing definitions used, such as in neuropsychological testing, even though the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published in May 2013, recognizes VCI as a disease category. The criteria listed in the DSM-5 continue to feature memory impairment as one of the most reliable features for diagnosis, but difficulties arise when deciding if cognitive impairment is due to the vascular lesions observed. The criteria also make it difficult to reliably distinguish other symptoms such as slowness, lack of motivation, poor initiative and depression from cognitive impairment, and establish whether cognitive impairment would affect a stroke patient's activities of daily living independently of their physical incapacity. Finally, the criteria might not sufficiently differentiate between the additive or interactive nature of disease processes triggered by vascular brain lesions, such as those that can be seen by autopsy [2,3].

Delineating the separate contribution of neurodegenerative and vascular pathologies has also so far proven to be

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of little help when treating dementia pharmacologically. This is reflected in the fact that there is a lack of drugs available specifically for vascular dementia and the growing appreciation that many cases of dementia can be attributed to mixed dementia [4]. The most sensible pharmacotherapeutic strategy for mixed dementia would seem to be one which targets multiple pathogenic mechanisms rather than a single one, given the cascade of events following a vascular lesion in the brain.

Another factor is importance of neuroinflammation. Inflammatory responses are a normal reaction to tissue injury and thus may be expected to occur after stroke. Although some of the inflammatory mediators are likely to have restorative effects, other may add to the damage already done by several mechanisms, including opening of the blood–brain barrier as well as direct damage to neurons or cell processes [5,6].

Stroke itself elicits a systemic inflammatory response, which may have detrimental consequences, including further tissue damage. Serum cytokine levels correlate with brain infarct volume, stroke severity and clinical outcome, as well as certain pathological changes such as amyloid deposition, white matter lesions and angiogenesis. Individuals with elevated inflammatory responses to the ischemic insult may thus be more vulnerable to further tissue damage.

Therapeutically targeting multiple pathogenic processes is also relevant to the treatment of the consequences of cerebral ischemia. The transition of tissue from injury to repair in the sub-acute phase of stroke depends on multiple processes of the post-ischemic cascade and thus provides an opportunity for intervention with neuroregenerative therapies.

Other therapeutic approaches have been discussed by Teuschl *et al.* and by Ihara *et al.* [7].

The failure of neuroprotective therapies in ischemic stroke is a reflection of unsuccessful translation from bench to bedside. Reasons for this unsuccessful translation include the choice of drug, dose and administration mode; difficulties with penetration into the brain and the timing of application, which may not have been accounted for in proof-of-concept studies in animals. However, even neuroprotective agents that have fulfilled all Stroke Treatment Academic Industry Roundtable recommendations for experimental stroke research have shown no clinical efficacy [8,9], perhaps as a result of overestimated efficacy in animal studies or poor adherence to protocols. The failure of these clinical studies has led some to believe that the entire concept of neuroprotection should be abandoned.

Nevertheless, based on the understanding that the pathophysiology of ischemic stroke is complex, a number of promising biological agents continue to undergo investigation for their neuroprotective properties. Our understanding of the mode of action of many of these agents continues to evolve. For example, Actovegin (a deproteinized ultrafiltrate of calf blood) has been shown to exert pleiotropic metabolic and neuroprotective activity [10,11]: it reduces oxidative stress and ameliorates $A\beta_{25-35}$-induced apoptosis, thereby maintaining neurons in culture [11]. It has recently been demonstrated that another biological agent, Cerebrolysin, may also modulate the balance of neurotrophic factors in the central nervous system, in so doing conferring neuroprotection [12]. Although the most recent clinical study of Cerebrolysin in ischemic stroke has failed to demonstrate efficacy versus placebo based on the primary endpoint, *post-hoc* analyses identified effects on secondary endpoints that could yet be explored in future, prospective, randomized controlled studies [13]. Actovegin is also currently under investigation for its possible symptomatic and disease-modifying effects in post-stroke cognitive impairment [14] with results expected in late 2014.

Small biological molecules are also the subject of current investigation. Dimethyloxalylglycine, an ester of *N*-oxalylglycine that inhibits prolyl-4-hydroxylase domain enzymes that stabilize hypoxia-inducible factor, has been shown to confer neuroprotection in adult male Wistar rats following middle cerebral artery occlusion [15]. Hypoxia-inducible factor is an attractive target for neuroprotection, because of its link with pathways activating VEGF, endothelial nitric oxide synthase and erythropoietin, which may be associated with neuroprotection. Another attractive target for small biological molecules is IL-1 which, via inflammatory pathways, has been shown to be implicated in neuronal injury [16]. Recently, the effects of endogenous IL-1 receptor antagonist (IL-1ra) have been documented in experimental ischemia in animals with clinically relevant comorbid conditions [17]. The effect of IL-1ra on clinical outcomes in patients suffering from an acute stroke has also been investigated in a small-scale clinical study [18]. The study found recombinant IL-1ra to be well-tolerated, whereas an exploratory analysis revealed that it led to better clinical outcomes than placebo, in patients with cortical infarcts. However, for both of these therapeutic targets (hypoxia-inducible factor and IL-1), it is important to remember that only further multicenter, prospective, randomized, controlled studies will either confirm or discredit their potential in ischemic stroke.

To improve both sensorimotor and cognitive function over a longer term following ischemic stroke, non-pharmacological interventions may also need to be considered in the clinical management of patients. A number of approaches, such as hypothermia [19] and transcranial laser therapy [20] have been suggested after testing in single cases. Cognitive stimulation therapy [21] and transcranial magnetic stimulation [22] have also been proposed, but further, large-scale prospective studies are needed to determine the effectiveness of these interventions. Other emerging approaches include the use of enriched environments, which are designed to facilitate cognitive, motor, sensory and social activity. Experimental studies, primarily in rodents, have shown that the use of enriched environments may enhance neuroplasticity and neurogenesis [23]. Data from a pilot study have also indicated that enriched environments increase patient activity levels [24], but further studies are warranted before making a clinical recommendation on their use.

Conclusions

The translation of proposed neuroprotective agents from bench to bedside has so far failed to deliver proven neuroprotective therapies. However, our understanding of the post-ischemic

cascade is evolving. This may be due to the heterogeneity of the underlying process. For example, anti-inflammatory drugs may be helpful in some cases while of little value in others. An increased knowledge of the pathophysiology of ischemic stroke and natural recovery mechanisms may subsequently lead to the emergence of effective neuroprotective therapeutics. Further studies of non-pharmacological interventions may also help to deliver more robust strategies capable of improving sensorimotor and cognitive function over a longer term and thus supplementing the holistic management of the stroke patient.

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