Commentary

Ischemia-reperfusion injury: evidences for translational research

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First used in the early nineteenth century, the term ischemia refers to impaired blood supply to tissues caused by reduced or obstructed arterial inflow. Restoration of blood flow at the earliest remains the cornerstone of all current treatment options to ischemia, nevertheless reperfusion may paradoxically induce and worsen ischemic tissue damage, leading to ischemia-reperfusion injury (IRI). IRI contributes to pathology in a wide range of conditions, such as single organ infarction and revascularization (stroke; myocardial, renal, intestinal infarction), multiple organ ischemia-reperfusion (trauma, circulatory arrest, sickle cell disease, sleep apnea), organ transplantation or surgery (1). The mechanisms underlying IRI development have not been completely defined yet, and include: (I) reduced ATP levels and intracellular pH as a result of anaerobic metabolism and lactate accumulation, followed by dysfunctional ATPase-dependent ion transport mechanisms, intracellular and mitochondrial calcium overload, cell swelling and rupture, and cell death by necrotic, apoptotic and autophagic mechanisms during prolonged ischemia; (II) generation of reactive oxygen and nitrogen species (ROS, RNS) and tissue infiltration by proinflammatory neutrophils upon reperfusion; (III) opening of the mitochondrial permeability transition pore as a common end-effector of the pathologic events triggered by ischemia-reperfusion (2). In spite of the progress achieved into the pathophysiology of ischemia and reperfusion, the complete knowledge of IRI mechanisms and the introduction of new treatments represent main challenges. In fact, research in this field continues to be afflicted by the failure to translate the results to clinically effective therapies. Dissecting the complex pathways involved in clinically relevant animal models of IRI is needed to provide the rationale for novel therapeutic agents. However, a great deal of work is needed to translate our current know-how from bench to bedside in the continuing effort to enhance the overall success of clinical IRI management.

In the past years, experimental models have provided considerable advances in understanding IRI mechanisms, as well as in testing new strategies to reduce tissue damage, such as prolylhydroxylase inhibitors or adenosine receptor agonists (3-5). To date however, due to complexity of IRI, few pharmacological treatments have been investigated in clinical Phase III trials to prove whether a pharmacological or technical approach could be suitable to provide a beneficial effect in humans. For instance, most clinical trials consider the administration of caspase inhibitors, P-selectin antagonists or antioxidant compounds in order to limit IRI during organ transplantation (6).

The study by Karadimas and co-workers investigates the neuroprotective role of riluzole on IRI induced by surgical decompression in cervical spondylotic myelopathy (CSM). The first interesting finding of this work is related to the demonstration of a IRI mechanism underlying neurological complications occurring after surgical decompression in CSM. To this, the Authors analyzed data from human CSM trials to record short- and long-term neurological outcomes; afterwards, they performed surgical decompression in a rat model of CSM finding a transient post-operative neurological decline sustained by mitochondrial dysfunction and oxidative damage in neurons.

Animal models are widely used to define molecular mechanisms underlying spinal cord IRI and to conceive novel therapeutic strategies. *In vivo* studies are carried out both in large and in small animals (7). Insights gleaned in preclinical models are not reliably translated to the human

context, nevertheless the model applied in this study shows a transient postoperative neurological decline similar to that seen in humans. Moreover, they find that surgical decompression of the spinal cord is associated with nuclear oxidative damage in rat cervical spinal cord sections, and this finding is also reported in post-mortem cervical spinal cord sections from CSM patients who underwent surgical decompression. The neural tissue is very susceptible to oxidative damage, due to its high oxygen requirement (up to 20% of the total oxygen intake, even though it is 2% of the total body weight) and its low antioxidant activity with respect to other tissues (8). Nevertheless, IRI in the spinal cord is also caused by microglial activation as well as blood spinal cord barrier disruption (9,10). Thus, a promising therapeutic approach to CSM has to target multiple mechanisms of injury.

The second outcome of this investigation is related to the beneficial effect of riluzole in the recovery of forelimb function, motor neuron and axonal preservation as well as attenuation of neuropathic pain in CSM rats after decompression surgery, which is associated with the reduction of neuronal oxidative damage and mitochondrial dysfunction. Riluzole (2-amino-6-trifluoromethoxy benzothiazole) shows protective effects for the spinal cord since it acts both as sodium channel blocker and as anti-glutamatergic agent (11). This compound is effective in the protection against experimental IRI not only in the spinal cord, but also in the heart and retina (12-14). The study by Karadimas *et al*. confirms *in vitro* that the neuroprotective effect of riluzole is related to its antioxidative properties. In the last years, many promising compounds showing antioxidant properties have been under investigation for the prevention and treatment of neural IRI. However, some evidences on other tissues, albeit proving oxidative stress, suggest that the contribution of oxidative damage to human IRI may be less than commonly thought and propose a re-evaluation of the mechanism of IRI (15). It is conceivable that the beneficial properties of riluzole in neural IRI may be the result of a combination of different mechanisms.

The research field of neuroprotection is characterized by a huge number of failed attempts to translate successful therapeutic strategies for preventing neural IRI in the basic science laboratory into the clinical setting. Many previous translational approaches have been unsuccessful because of the use of inappropriate experimental models, the clinical testing of inconclusive therapies, and poor clinical trial design. Above all, validation of the animal model in the study of Karadimas *et al*. allows the researchers to test the hypothesis that surgical decompression induces an IRI in the spinal cord parenchyma. Moreover, since flow-sensitive alternating inversion recovery magnetic resonance in CSM rats shows an increase in the blood flow to the decompressed spinal cord within 24 h of decompression surgery, this suggests that diagnostic tools able to identify CSM patients with high-risk of decompression-mediated IRI may help in the selection of appropriate patients for well-designed clinical trials. Finally, the results by Karadimas *et al*. seem promising for the ongoing CSM-Protect multicenter clinical trial, funded by AOSpine North America, which aims at testing the efficacy of perioperative riluzole to improve postsurgical recovery in CSM patients (16). As riluzole may also reduce the blood-brain barrier and inhibit microglial activation, this compound is a potential candidate to make the translational leap to clinical trials from preclinical research in spinal cord injury (11,17).

To conclude, this recent discovery promotes multicenter, randomized clinical trials to investigate emerging therapeutic strategies for reducing IRI and improving clinical outcomes in CSM patients undergoing surgical decompression.

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Footnote

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