Abstract

Optimizing Nicorandil for Spinal Cord Protection in a Murine Model of Complex Aortic Intervention

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Background: There are currently no clinically utilized pharmacological agents for the induction of metabolic tolerance to spinal cord ischemia-reperfusion injury in the setting of complex aortic intervention. Nicorandil, a nitric oxide donor and ATP-sensitive potassium (KATP) channel opener, has shown promise in neuroprotection. However, the optimized clinical application of the drug and its mechanism of neuroprotection remains unclear. We hypothesized that 3-days pretreatment would confer the most effective neuroprotection, mediated by mitochondrial KATP channel activation.
Methods: Spinal cord injury was induced by 7 minutes of thoracic aortic cross-clamping in adult male C57BL/6 mice. Time course: mice received 0.1 mg/kg nicorandil for 10 min, 4 hours, and 3 consecutive days prior to ischemia compared with control. Dose challenge: mice received 3-days nicorandil pretreatment comparing 0.1 mg/kg, 1.0 mg/kg, 5.0 mg/kg, and saline administration. Mitochondrial KATP channel blocker 5-hydroxy-decanoate (5HD) was co-administered to elucidate mechanism. Limb motor function was evaluated, and viable anterior horn neurons quantified.
Results: Nicorandil pretreatment at 4 hours and 3 days before ischemia demonstrated significant motor function preservation; administration 10 min before ischemia showed no neuroprotection. All nicorandil doses showed significant motor function preservation. Three days administration of Nicorandil 1.0 mg/kg was most potent. Neuroprotection was completely abolished by 5HD co-administration. Histological analysis showed significant neuron preservation with nicorandil pretreatment, which was attenuated by 5HD co-administration.
Conclusion: Three days administration of Nicorandil 1.0 mg/kg showed near-total motor function preservation in a murine spinal cord ischemia-reperfusion model, mediated by the mitochondrial KATP channel.

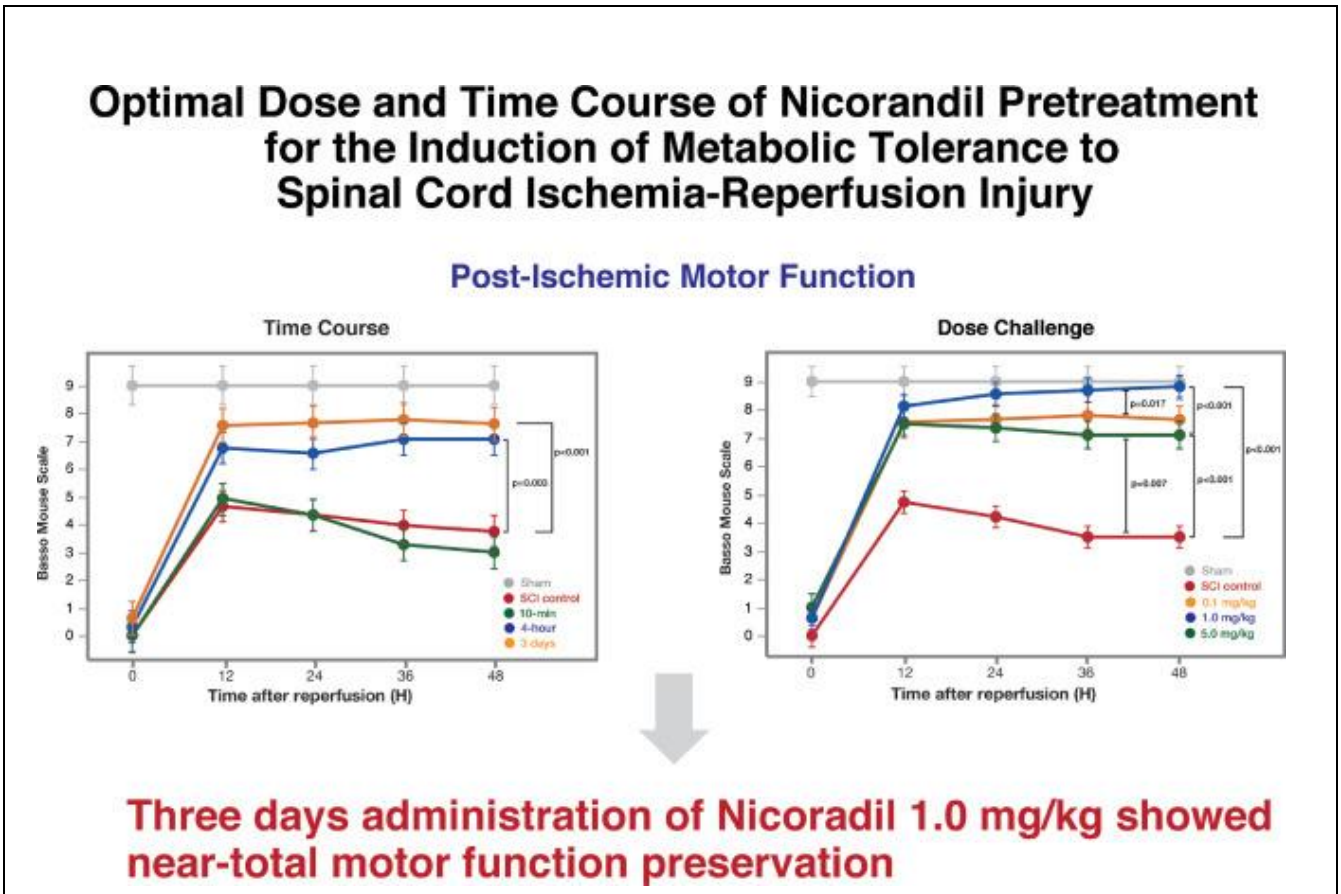

Figure 1: Summary of the results. Three days administration of Nicorandil 1.0 mg/kg showed the most potent motor function preservation in a murine spinal cord ischemia-reperfusion model.