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"Investigating Neuroprotective Efficacy of Lipid Mediators Neuroprotectin D1 (NPD1) and Resolvin D1 (RvD1) on Behavioral Outcomes and Ischemic Penumbra"

Background: In the United States, stroke is the sixth leading cause of death, and a major cause of long-term disability. Ischemic stroke elicits a cascade of immune and neuroinflammatory responses that form an ischemic core and surrounding area (penumbra) which can be salvaged upon reperfusion within a limited period of time. Reperfusion signals the release of an essential omega-3 fatty acid, Docosahexaenoic acid (DHA) from injured neuronal cell membranes. DHA is converted into its derivatives, Neuroprotectin D1 (NPD1) via 15-lypoxygenase and Resolvin D1 (RvD1) via 15- and 5-lypoxygenase. These docosanoid lipid mediators have been shown to improve neurologic outcomes after experimental stroke by promoting neuronal cell growth, activating anti-apoptotic signals, blocking pro-apoptotic signals, and restoring homeostasis. However, there is no treatment that has been proven to strengthen this innate tissue reparative pathway and hinder stroke-induced damage in humans.

Purpose: In this study, we tested the neuroprotective combinatory effects of NPD1 and RvD1 IV administration on the ischemic penumbra 7 or 14 days after experimental stroke using a well-established rat model of middle cerebral artery occlusion (MCAo).

Methods: Sprague-Dawley rats (280-300g) were anesthetized and underwent 2h MCAo. Animals were randomly assigned to four different treatment groups: NPD1 (222µg/kg) + RvD1 (222µg/kg) 7-day or 14-day survival, or vehicle (saline) 7-day or 14-day survival (n=6-8 per group). At 3h after MCAo, vehicle or NPD1 was administered followed by RvD1 15 minutes after NPD1. All treatment was administered IV. Animals were monitored for body weight, temperature (rectal and cranial), and behavioral function (postural reflex, tactile, visual, and proprioceptive placing). Behavior was graded on a scale of 0-12 and evaluated on the day of surgery and days 1, 2, 3, 7, or 14 after MCAo. Animals were perfused on day 7 or 14 with 4% paraformaldehyde, and the brains were removed and sent to the University of California Irvine for ex-vivo T2WI MRI.

Results: There was no significant difference between physiologic parameters across groups. In the 7-day NPD1+RvD1 treatment group, the neurological scores improved on days 1, 2, 3, and 7 by 26, 30, 36, and 36% compared to the vehicle-treated group. Additionally, there neurological score improvement in the 14-day NPD1 + RvD1 treatment group on days 1, 2, 3, 7 and 14 by 29, 32, 31, 32, and 34% compared to the vehicle-treated group.

Conclusion and Future directions: We conclude that the administration of NPD1+RvD1 in combination after stroke improves behavioral outcomes. High resolution *ex vivo* MRI will be performed on the brains and the penumbra will be characterized using Hierarchical Region Splitting.