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"Long-lasting neuroprotection and neurological improvement by PAF-receptor antagonist plus a lipid mediator in transient focal cerebral ischemia in rats"

Neuroprotective efficacy observed during short survival periods may not necessarily apply to more extended survival periods, and some stroke-impaired behaviors recover naturally in rodent models 1-2 weeks after stroke. The objective of the present study was driven by the hypothesis that acute LAU-0901 plus NPD1-induced neuroprotection endures in animals allowed to survive for several weeks after focal ischemic insult. Two small bioactive molecules were investigated: LAU-0901 (LAU), a PAF-R antagonist that blocks pro-inflammatory signaling, and neuroprotection D1 (NPD1), which activates cell-survival pathways, and their combination exerts potent anti-inflammatory activity in the brain. Male Sprague-Dawley rats were subjected to 2h of middle cerebral artery occlusion (MCAo) by an intraluminal filament and treated with vehicle, LAU (IP), NPD1 (IV) or LAU+NPD1 at three hours after onset of MCAo. Rats received neurobehavioral examinations during MCAo (60 min) and then on days 1,2,3, and 7, as well as weekly during an eight-week survival period. This is followed by *ex vivo* MRI using 11.7 T on weeks 4 and 8. Physiological variables showed no significant differences among groups. No adverse behavioral side effects were observed after the administration of LAU, NPD1, or LAU+NPD1. LAU and NPD1 treatments alone significantly improved the behavior compared to the vehicle on day 1 (33 and 31%), day 7 (38 and 32%), and week 4 (39% and 36%). Combinatory treatment with LAU+NPD1 dramatically improved total neurological score on days 1 (by 36%), 2 (38%), 3 (36%), 7 (42%), and on weeks 4 (44%), 5 (by 43%), 6 (45%), 7 (44%), and 8 (47%) when compared to the vehicle group. MRI analysis is ongoing. In conclusion, these data suggest that LAU and NPD1 alone provide high-grade neuroprotection in the MCAo model. The combinatory treatment also offers dramatic neuroprotection in the MCAo model; however, improvement does not significantly differ from LAU-0901 and NPD1 alone at this stage in the research.