Intra-arterial IL-1α is well tolerated and neuroprotective after experimental ischemic stroke

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Endovascular thrombectomy combined with t-PA is the current standard of care for emergent large vessel occlusion (ELVO) stroke. Unfortunately, despite rising recanalization rates, stroke remains the leading cause of long-term disability worldwide suggesting that additional therapies are needed. Severe stroke morbidity may be due, in part, to the acute and sustained inflammatory stroke response. Preclinical research has shown some promise with anti-inflammatory agents in limiting brain injury and improving functional outcome; however, the post-stroke inflammatory cascade appears to have both beneficial and deleterious effects making the translation of such anti- inflammatory approaches perilous. Indeed, we have recently demonstrated that delayed (3 day) post-stroke IV administration of the interleukin (IL)-1α (one of the two major isoforms of the pro- inflammatory family of cytokine IL-1), unexpectedly promoted, rather than suppressed, post-stroke angiogenesis in stroked mice (transient middle cerebral artery occlusion, MCAo). In this study, we investigated the potential for IL-1α, administered acutely IV or IA (n=5) after mouse MCAo, to also be neuroprotective. For the latter, our lab has recently developed a model of selective intra-arterial (IA) drug delivery in mice that can directly target stroke-affected brain with little to no systemic distribution. We noted that IV IL-1α (1 ng) is neuroprotective (as measured by cresyl violet stained infarct volumes) with mild, transient side effects (blunted hypertension and bradycardia) that were well tolerated, and with better functional recovery in free motion behavioral tests. IA IL-1α (0.1 ng) administration was even more neuroprotective without the systemic changes seen with IV treatment. Additionally, we noted that IL-1α is directly neuroprotective of primary mouse cortical neurons exposed to oxygen and glucose deprivation conditions in vitro. Taken together, these results suggest that IL-1α could be therapeutic after stroke when administered IV or IA, and the latter may eliminate potentially harmful hemodynamic side effects.