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THE ROLE OF NF- κ B p65 IN SUBARACHNOID HEMORRHAGE INDUCED SECONDARY BRAIN INJURY

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Subarachnoid hemorrhage (SAH), primarily caused by rupture of a cerebral aneurysm, refers to the extravasation of blood into subarachnoid space between the pial and arachnoid membranes. With high mortality and morbidity rates, the initial hemorrhage itself is often fatal, but the primary cause of poor outcomes is through the secondary brain injuries that develop in the days following SAH. There are two separate categories of these damages, distinguished as early brain injury (EBI) and delayed cerebral ischemia (DCI). Occurring 1-3 days following SAH, EBI presents as neuroinflammation, cerebral edema, and blood-brain barrier (BBB) disruption. DCI, the more common and devastating category, describes the slower onset damages, 4-12 days post-SAH, including microcirculatory deficits and large artery vasospasm. There is strong evidence that vascular deficits are the main cause of these secondary brain injuries, with blood-brain barrier (BBB) disruption leading to EBI and large artery vasospasm leading to DCI. Several previous studies have shown that a strong genetic risk factor for these poor outcomes after SAH is the presence of apolipoprotein E4 allele. The APOE4 linked pathway involves cyclophilin A (CypA), a cell signaling molecule that causes inflammation through activation of transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) p65 and resulting induction of matrix metalloproteinase-9 (MMP9) and BBB disruption. However, the role of CypA in secondary brain injury has not yet been clearly established. Early findings showing high levels of CypA in rodents after SAH, we hypothesize that the CypA- NF- κ B p65 -MMP9 pathway plays a critical role in SAH-induced EBI and DCI.

With CypA inhibition and MMP9 knockouts displaying reduced post-SAH BBB leakage and vascular deficits, our objective for this study was to confirm the role of NF- κ B p65 in this pathway. To assess this, wild-type C57BL6 mice were administered a pharmacological inhibitor of NF- κ B p65, ammonium pyrrolidinedithiocarbamate (PDTC), via intraperitoneal injection the day of SAH surgery and daily for three days following (Day 0 - Day 3). Cognitive and motor skills of the mice were assessed Day 0 - Day 3 via neuroscoring and rotarod along with their littermate controls (also administered SAH). On Day 3, the mice were sacrificed by India ink-gelatin perfusion, which fixes and stains the brain vessels to allow imaging and measurement of the middle cerebral artery to assess vasospasm. The mice with p65 inhibition showed significantly less cognitive impairment and vasospasm than their littermate controls, corroborating our hypothesis of the role of the transcription factor in the induction of post-SAH deficits and suggesting p65 to be a promising potential therapeutic target for SAH.