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Subarachnoid hemorrhage (SAH), a unique form of hemorrhagic stroke, remains a serious health problem with a 32% mortality rate in the United States. Of those surviving the initial hemorrhage, more than half deteriorate in the days following SAH due to early brain injury or EBI (which occurs 1-3 days after SAH). The predominant vascular deficit leading to EBI is blood-brain barrier (BBB) disruption, along with the release of cytotoxic agents and inflammatory mediators. Recently, a causal link between metalloprotease 9 (MMP9) and EBI after SAH has been suggested in rodent studies. A correlation between serum MMP9 levels and vasospasm in human SAH has also been noted. While a major contributing role of MMP9 in SAH-induced brain injury is rapidly being established, the upstream molecular events leading to its upregulation and the downstream molecular events by which it causes EBI are poorly understood. Cyclophilin A (CypA) is a proinflammatory molecule that is known to drive MMP9 expression via the transcription factor NF-κB p65. Previously we discovered that CypA plays a causal role in AD-induced cerebrovascular deficits, including APOE4-linked BBB disruption and CBF deficits. CypA is secreted from cells in response to inflammatory stimuli, such as hypoxia and oxidative stress. Whether CypA plays a role in EBI and/or DCI following SAH, however, is not known. We found that MMP9 activity in the brain increases following SAH. We got the first hint that CypA contributes to EBI when increased CypA levels in CSF were found in SAH patients and mice after experimental SAH. We found that both pharmacological and genetic inhibition of CypA significantly attenuates BBB leakage, as assessed via Evans blue BBB permeability assay. This evidence suggests that CypA is a key mediator of blood-brain barrier dysfunction after SAH.