# Activation of the TWEAK/Fn14 Pathway Drives Neuroinflammation after Subarachnoid Hemorrhage

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Background and Significance:
The term “early brain injury” describes the acute pathological events that cause neurological dysfunction after subarachnoid hemorrhage (SAH). There is a growing consensus that neuroinflammation is the driving force behind early brain injury and vasospasm after SAH. Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) is a cytokine that binds to the receptor fibroblast growth factor 14 (Fn14). The TWEAK/Fn14 pathway is activated after ischemic stroke and in other neurological diseases, and clinical trials utilizing TWEAK inhibition are underway. This study was undertaken to determine if the TWEAK/Fn14 pathway could be a therapeutic target for reducing neuroinflammation and early brain injury after SAH.

Methods:
SAH was induced in mice via endovascular puncture technique modified so that only the external carotid artery was manipulated and cerebral blood follow was not interrupted. Real-time PCR was used to quantify mRNA production and Western blot was used to measure protein levels.

Results:
Inflammation, as measured by pro-inflammatory cytokine induction, was widespread throughout the brain after SAH, even distant from the site of SAH. Fn14, but not TWEAK, in the brain was increased acutely after SAH. The transcription factor NF-kB, which is activated downstream of Fn14, is activated after SAH. TWEAK and Fn14 knockout mice experienced reduced neuroinflammation after SAH while increased TWEAK in the blood worsened neuroinflammation after SAH.

Conclusions:
Neuroinflammation is present acutely after SAH, and spreads throughout the brain. The TWEAK/Fn14 pathway is activated after SAH, and contributes to early brain injury. Reduction of TWEAK-Fn14 signaling reduces neuroinflammation, while an increase in blood-borne TWEAK worsens neuroinflammation. This indicates that the TWEAK-Fn14 interaction is due to the interaction between Fn14 in the CNS and TWEAK in the peripheral blood. Therapies targeting the TWEAK/Fn14 pathway could reduce neuroinflammation and reduce early brain injury and vasospasm after subarachnoid hemorrhage.