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Acute Brain Injury after Subarachnoid Hemorrhage

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BACKGROUND

Spontaneous subarachnoid hemorrhage (SAH) caused by the rupture of cerebral aneurysms is a subtype of stroke that carries particularly high mortality and morbidity⁷. Immediately after aneurysmal rupture, many physiological derangements, such as elevated intracranial pressure, decreased cerebral blood flow, and global cerebral ischemia, may occur⁴. These immediate responses trigger various cascades of events resulting in pathological changes in the affected brain within the acute phase of SAH. Moreover, excessive amount of extravasated blood and its degradation products are known as the major contributors to brain injury after hemorrhagic stroke.¹ As yet, the few clinically available treatments for SAH mainly focus on prevention of aneurysmal rebleeding and prophylaxis of delayed cerebral ischemia caused by vasospasm; however, no effective treatments against SAH-induced acute brain injury are available. We briefly describe the recent advances and future direction in the research for SAH-induced acute brain injury.

NEURONAL DEATH

The leading cause of neuronal death after SAH is transient global ischemia induced by elevation of intracranial pressure. Global ischemia seems to initiate disruption of the BBB as well initiating inflammation which contributes to additional neuronal death.⁴ In addition, excessive iron, the major degradation products of hemoglobin, has been determined as a key factor that causes neuronal death post SAH⁶. In a rat arterial perforation model, there was excessive accumulation of nonheme iron and iron-handling proteins in tissue adjacent to

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SAH. High iron content in neurons leads to oxidative DNA injury and results in neuronal death. Iron chelator, deferoxamine, effectively reduced elevations of iron and iron-handling proteins in the brain and has been shown to acute neuronal injury after SAH⁶. These results suggest that iron and iron-handling proteins are potential therapeutic targets to limit acute brain injury post SAH.

WHITE MATTER INJURY

It is well known that the components of white matter, axons and myelin-producing oligodendrocytes, are extremely vulnerable to damage in a various neurological diseases². Surprisingly, only few previous reports have focused on white matter injury post SAH. We recently demonstrated the evidence of SAH-induced acute white matter injury in mice. In that report, MRI clearly showed the abnormality along the corpus callosum at 24 hours after SAH induction, and this abnormality correlated with the axonal damage, myelin degradation, and blood-brain barrier (BBB) disruption³. It was also demonstrated that iron-handling protein lipocalin 2 depletion attenuated white matter injury after SAH (Figure 1). Lipocalin 2 is known as a mediator of iron uptake, and is implicated in various brain diseases including stroke. These results suggested that lipocalin 2 plays an important role in SAH-induced acute white matter injury. However, the involved mechanisms in this injury, including the detailed role of lipocalin 2, still remain to be elucidated. The mechanistic understanding of white matter injury post SAH could provide therapeutic targets.

ACUTE HYDROCEPHALUS

Acute hydrocephalus is a common and life-threatening complication after SAH, and has seldom been studied in animal models. Okubo et al.⁸ recently confirmed by MRI that 44% of animals developed acute hydrocephalus at 24 hours after SAH was induced. The rate of acute hydrocephalus in rats seems to be comparable to that in humans⁵. In humans, poor grade SAH and the presence of intraventricular hematoma were determined as associated factors for symptomatic hydrocephalus in our large clinical study⁹. Similarly, there was significant correlation between SAH severity and ventricular size in the rat model of SAH. The volume of intraventricular hematoma, ventricular wall damage, and periventricular iron deposition correlated with the development of acute hydrocephalus after SAH (Figure 2). Our EM analyses of rats undergoing SAH show loss of cilia on ependymal surface. Further elucidation of the mechanism of HCP post SAH has the potential of improving clinical outcome as well as preventing shunt dependence and associated complications.

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Abbreviations used in this paper

BBB	blood-brain barrier
MRI	magnetic resonance imaging

SAH subarachnoid hemorrhage

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Figure 1.

Representative coronal T2-weighted images (T2WI; A) and NG2 (marker for oligodendrocyte precursors), β-amyloid precursor protein (β-APP; marker for damaged axon) and degraded myelin basic protein (DMBP; marker for degraded myelin) immunohistochemistry in white matter of sham and WT and LCN2^{-/-} animals 24 hours after SAH (B). Quantification of each result. (C). ***P*<0.01, **P*<0.05 vs. WT, and ##*P*<0.01, #*P*<0.05 vs. LCN2^{-/-} animals. Scale bar = 100μm. (Reproduced with permission from: Egashira Y, Hua Y, Keep RF, Xi G: Acute white matter injury after experimental subarachnoid hemorrhage: potential role of lipocalin 2. *Stroke* 45:2141–2143, 2014.)

Figure 2.

(A) Ventricular volume 24 hours after endovascular perforation or sham procedure (A). Correlation of ventricular volume and subarachnoid hemorrhage (SAH) grade at 24 hours (B). Coronal T2* images of sham and SAH animals with or without hydrocephalus at 24 hours. Rats with hydrocephalus have a larger hypointensity volume than the sham animals or rats without hydrocephalus (C). Hematoxylin and eosin staining of sham and SAH animals with or without hydrocephalus. Note the presence of intraventricular hemorrhage in the hydrocephalic rat. Boxes show intact ependyma (sham, SAH without hydrocephalus) and disrupted ependyma with intraventricular hemorrhage (SAH with hydrocephalus). SAH animals with hydrocephalus have more ventricular wall damage compared with sham or SAH animals without hydrocephalus (D). * $P < 0.05$ and # $P < 0.01$. Scale bar = 100 μ m. (Reproduced with permission from: Okubo S, Strahle J, Hua Y, Keep RF, Xi G: Subarachnoid hemorrhage-induced hydrocephalus in rats. *Stroke* 44: 547–550, 2013.)