NAMPT mediates hypoxic conditioning-induced neurovascular protection in subarachnoid hemorrhage

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Abstract

Hypoxic postconditioning (HPostC) induces powerful protection against sustained SAH-induced vasospasm and paralysis. However, the mechanisms underlying HPostC-mediated neurovascular protection remain incompletely understood. Here, we sought to determine whether hypoxic postconditioning initiated 1 hour after SAH (HPostC) protects microvascular structures in vivo and if HPostC-mediated neurovascular protection occurs via a mitochondrial-dependent mechanism. Using a mouse model of SAH, we observed that HPostC-induced neurovascular protection was mediated by a mitochondrial-dependent mechanism. HPostC was associated with increased expression of NAMPT, a mitochondrial enzyme that mediates hypoxic preconditioning. These findings suggest that mitochondrial NAMPT may play a key role in mediating HPostC-induced neurovascular protection.

Experimental Design

1. Hypoxic postconditioning (HPostC) induces powerful protection against SAH-induced DCI.

2. SIRT1 contributes to the DCI protection afforded by HPostC.

3. HPostC-induced DCI protection is lost following pharmacological inhibition of SIRT1.

4. Genetic overexpression of SIRT1 mimics the DCI protection afforded by HPostC.

Research Endpoints

Figure 4. HPostC-induced DCI protection is lost following pharmacological inhibition of SIRT1. HPostC-induced protection against vasospasm (A), neurobehavioral deficits (B), and microvascular thrombosis (C) induced by SAH is abrogated by the SIRT1 inhibitor EX527. Wild-type mice were subjected to SAH or sham surgery followed by treatment with EX527 (mM 30; 300; 3, 12, 1 hour) and sham surgery or sham surgery and sham surgery with vehicle. Microvascular thrombosis was assessed on Day 2, and neurobehavioral deficits were assessed on Day 3.

Figure 5. Genetic overexpression of SIRT1 provides strong protection against DCI. Extent of SAH-induced vasospasm (A), neurological deficits (B), and microvascular thrombosis (C) are all significantly reduced in SIRT1 transgenic mice (SIRT1/+) compared to wild-type mice (WT). WT and SIRT1 (+/−) mice underwent sham or SAH surgery. Vasospasm was assessed on Day 2, while neurological deficits were assessed on Day 3. Neurobehavioral deficits were assessed on Day 3.

Figure 6. Resveratrol provides robust SIRT1-mediated protection against DCI. WT mice or sham-operated mice were subjected to SAH or sham surgery followed by treatment with resveratrol (30 mg/kg) or vehicle. Vasospasm was assessed on Day 2, and neurological deficits were assessed on Day 3.

Conclusions

Our findings suggest that mitochondrial NAMPT may play a key role in mediating HPostC-induced neurovascular protection. These findings provide a potential therapeutic target for the treatment of SAH-induced DCI.

Significance

This work indicates that mitochondrial NAMPT is a novel therapeutic target for the treatment of SAH-induced DCI. The findings suggest that NAMPT may play a role in mediating HPostC-induced neurovascular protection, and this may provide a potential therapeutic target for the treatment of SAH-induced DCI.