Suberoylanilide Hydroxamic Acid (SAHA) Attenuates Neurodegeneration and Glial Activation after Intracerebral Hemorrhage

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Introduction

Spontaneous intracerebral hemorrhage (ICH) is a stroke subtype that induces severe neurological injury. Notably, there is no effective treatment for ICH and the molecular mechanisms of neurological injury after ICH remain largely uncharacterized. Herein we demonstrate that ICH results in a significant reduction in histone acetylation status, a tightly controlled epigenetic mechanism that plays a cardinal role in the regulation of gene expression. Based on this, the present study addresses whether Suberoylanilide hydroxamic acid (SAHA), a clinically well tolerated pan-histone deacetylase inhibitor (HDACi), could modulate neurological injury after ICH.

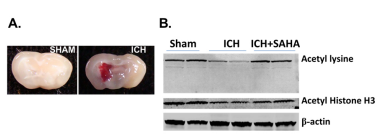
Methods

Adult male CD-1 mice were subjected to experimental ICH and treated with SAHA (1h post-ICH; 70 mg/Kg, i.p.).

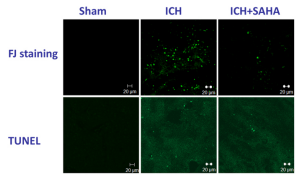
Results

Brain sections from SAHA-treated mice exhibited less neurodegeneration as evidenced by reduction in both Fluoro-Jade B and TUNEL staining after ICH in comparison to placebo treated mice. In addition, SAHA treatment attenuated microglial activation, a characteristic feature of neuroinflammation and downregulated the expression of Heme oxygenase 1, a stress-inducible enzyme that plays critical roles in neurological damage. More importantly, SAHA treatment significantly reduced severe astroglial activation, characterized by glial proliferation, and improved neurological outcome after ICH.

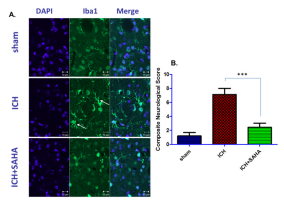
ICH induced histone hypoacetylation



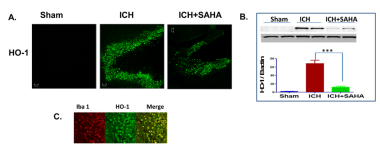
SAHA attenuated neurodegeneration after ICH



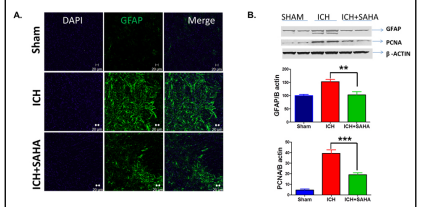
SAHA attenuated microglial activation after ICH



SAHA attenuated heme oxygenase-1 expression after ICH



SAHA attenuated severe astrogliosis after ICH



Conclusions

The data strongly suggest the role of epigenetic mechanisms in inducing neurological injury after ICH and raise the possible clinical utility of SAHA for therapeutic intervention after ICH.

Learning Objectives

By the conclusion of this session, participants should be able to identify the effects of the compound SAHA on neurodegeneration and microglial activation and describe the potential therapeutic role of SAHA following ICH.

Acknowlegements

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References

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