VORINOSTAT, A HISTONE DEACETYLASE INHIBITOR, AMELIORATES THE SOCIABILITY AND COGNITIVE MEMORY IN AN ASH1L-DELETION-INDUCED ASD/ID MOUSE MODEL

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HIGHLIGHTS

- Postnatal administration of vorinostat (SAHA) **ameliorates** the **core ASD-like behaviors** in the Ash1L-deletion-induced ASD/ID mouse model.
- Postnatal administration of vorinostat (SAHA) **ameliorates** the **cognitive memory** in the Ash1L-deletion-induced ASD/ID mouse model.
- Different behavioral deficits have **distinct responses** to vorinostat (SAHA) treatment.
- **No obvious drug toxicity** was observed during low-dose vorinostat (SAHA) treatment.

INTRODUCTION

ASH1L (Absent, Small, or Homeotic discs 1-Like) is identified by multiple studies as a high ASD risk gene. Some children diagnosed with ASD and/or intellectual disability (ID) acquire de novo disruptive or missense mutations of ASH1L. In addition to ASD and ID, patients also display various developmental abnormalities including delayed myelination, microcephaly, craniofacial deformity, and skeletal abnormality, suggesting critical roles of ASH1L in normal embryonic and postnatal development. Using a conditional Ash1L knockout mouse model, researchers have shown that deletion of Ash1L in the developing mouse brain (Ash1L-Nes-cKO) was sufficient to cause multiple developmental defects, core autistic-like behaviors, and ID-like memory deficits, suggesting that the disruptive ASH1L mutations are likely to be the causative drivers leading to the human ASD/ID development.

Functionally, ASH1L is a member of Trithorax-group (TrxG) proteins that facilitate gene expression during normal development. Studies showed that deletion of ASH1L in the differentiating neural progenitor cells (NPCs) reduced the expression of genes involved in brain development, suggesting that the impaired neurodevelopment-related gene expression is likely to be a key molecular mechanism linking ASH1L disruptive mutations to abnormal brain development and pathogenesis of ASD/ID.

Biochemically, ASH1L is a histone methyltransferase that mediates dimethylation of histone H3 lysine 36 (H3K36me2). Histone H3K36me2 facilitates transcriptional activation by antagonizing Polycomb repressive complex 2 (PRC2)-catalyzed histone H3K27me3 modification and its-mediated gene silencing. The histone acetylation and deacetylation are catalyzed by histone acetylases (HATs) and deacetylases (HDACs), respectively. HDAC inhibitors (HDACi) repress HDACs' enzymatic activity and shift the equilibrium of histone acetylation/deacetylation to hyperacetylation, which increases the accessibility to transcription factors and facilitates gene expression. Therefore, researchers propose to use HDACs inhibitors to rescue the Ash1L-deletioninduced impaired gene expression during brain development, and consequently ameliorate the ASD/ID-like behavioral deficits in the Ash1L-deletion-induced ASD/ID mouse model.

In this study, researchers investigate the effects of vorinostat (suberoylanilide hydroxamic acid, SAHA), a pan-HDAC inhibitor that inhibits the enzymatic activity of all HDAC classes, in ameliorating the ASD/ID-like behaviors in the Ash1L-deletion-induced ASD/ID mouse model. ***The results showed that postnatal administration of low-dose SAHA significantly ameliorated the sociability, repetitive behaviors, and cognitive memory of the Ash1L-deficient mice, suggesting SAHA is a potential promising reagent for the treatment of ASD/ID behavioral and memory deficits caused by disruptive ASH1L mutations.***

RESULTS

SAHA ADMINISTRATION DOES NOT AMELIORATE THE POSTNATAL GROWTH RETARDATION OF ASH1L-NES-CKO MICE

Postnatal SAHA administration did not ameliorate the postnatal growth retardation of Ash1L-Nes-cKO mice. No other significant gross developmental defects were observed in the SAHA-treated mice. No obvious abnormalities in peripheral blood cell counts as well as liver and renal functions in the SAHA treated Ash1L-Nes-cKO mice.

SAHA ADMINISTRATION AMELIORATES THE CORE ASD-LIKE BEHAVIORS OF ASH1L-NES-CKO MICE

SAHA treated Ash1L-Nes-cKO mice spent more time with the social stimulus. Both grooming episodes and time were largely reduced in SAHA-treated Ash1L-Nes-cKO mice. It is suggested that the postnatal SAHA treatment ameliorated the core ASD-like symptoms including impaired sociability and repetitive behaviors in the Ash1L-deletion-induced ASD mouse model.

SAHA ADMINISTRATION AMELIORATES THE COGNITIVE MEMORY OF ASH1L-NES-CKO MICE

Both male and female SAHA-treated Ash1L-Nes-cKO mice had a significant increased discrimination index towards to the novel object, suggesting that the postnatal SAHA treatment significantly ameliorated the cognitive memory of Ash1L-Nes-cKO mice.

SAHA ADMINISTRATION DOES NOT ALLEVIATE ANXIETY-LIKE OR ATAXIA-LIKE BEHAVIORS

The SAHA-treated Ash1L-NescKO mice did not show significant changes in time spent in exploring the central arena, indicating that SAHA treatment did not ameliorate the anxiety-like behavior of Ash1L-Nes-cKO mice. SAHA-treated Ash1L-Nes-cKO mice had higher incidences of paw clasping compared to the wild-type controls, indicating the SAHA treatment could not ameliorate the ataxia-like behavior.

DISCUSSION

In this study, results demonstrated that the early postnatal treatment of SAHA for around two months ameliorated the core ASD-like deficit in sociability, repetitive behaviors, and the ID-like deficit in cognitive memory. Compared to its effect in ameliorating the sociability, the effect of SAHA in improving cognitive memory appeared to be more prominent since all conditional Ash1L-KO animals received SAHA treatment showed enhanced object recognition memory, suggesting that SAHA might improve the cognitive memory through a general mechanism in enhancing hippocampal function. In contrast to the SAHA treatment ameliorating the social behavior and cognitive memory in the conditional Ash1L-KO mice, the same treatment did not show obvious effects in ameliorating the postnatal growth retardation, the anxiety-like behavior, or the ataxia-like bodily movement.

SAHA is a pan-HDACs inhibitor approved by the U.S. Food and Drug Administration (FDA) to treat human cutaneous T-cell lymphoma (CTCL). To reduce the possible drug toxicity caused by SAHA treatment, researchers used a low dose of SAHA (5 mg/kg/day) in this study, which was 12 ~ 20 times less than the recommended dose for the human CTCL treatment. The low dose of SAHA used in this study is well tolerated and has low toxicity to mice. However, its safety and efficacy in treating human patients merit further investigation.

In summary, this current study provides experimental evidence to show that the postnatal administration of low-dose SAHA significantly ameliorates the sociability, repetitive behaviors, and cognitive memory in the Ash1L-deletion-induced ASD/ID mouse model, indicating that SAHA is a promising reagent for the pharmacological treatment of core ASD/ID behavioral and memory deficits caused by disruptive ASH1L mutations.