SAHA reduced cAMP levels and inhibited renal cyst growth through HDAC6

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BACKGROUND

Targeting cyclic adenosine monophosphate (cAMP) has been proven clinically by using Tolvaptan to treat patients with autosomal dominant polycystic kidney diseases (ADPKD). However, it has not been approved by USA FDA because of its side effects. Recent study shows that inhibition of Histone deacetylases 6 (HDAC6) reduced cyclic adenosine monophosphate (cAMP) levels and inhibited kidney growth in ADPKD animal models. We therefore hypothesized that treatment with suberoylanilide hydroxamic acid (SAHA), a FDA approved HDAC inhibitor, could retard PKD progression and lower cAMP levels in cystic kidneys.

METHODS

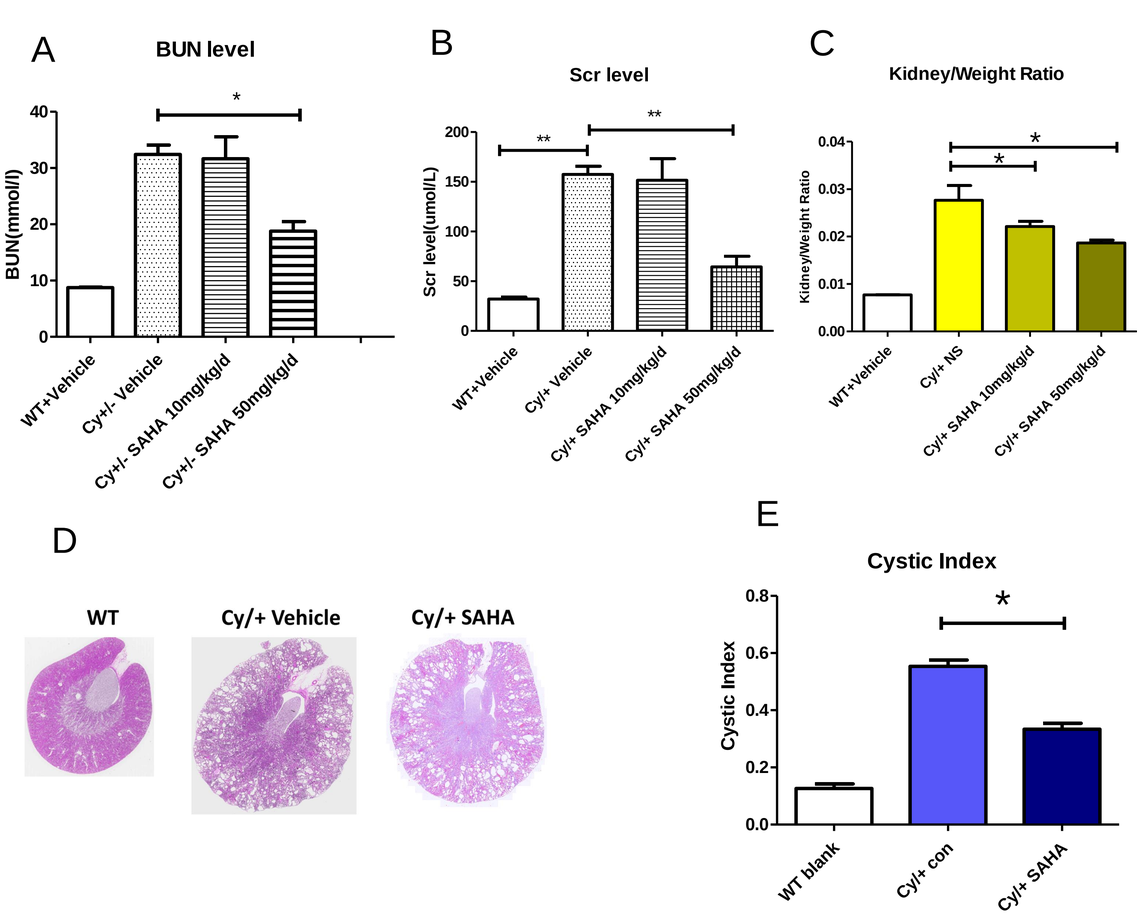
In vitro

- **Molecular mechanism: HDAC6 and cAMP pathway.**
- **ADPKD cells(WT9-12) were treated with various concentration of SAHA**
- **Functional study: cell proliferation in ADPKD cells with SAHA and HDAC6 inhibitor tubacin.**

In vivo

- **Male Cy/+ and +/+ rats were weaned and then treated with 50 mg/kg/day SAHA or vehicle at 4 weeks of age by gavage for 12 weeks**
- **Disease progression: BUN, creatinine levels, two-kidney/total body weight ratio (2K/TBW) and cyst volume density (CVD)**
- **Molecular mechanism: HDAC6/cAMP pathway.**

RESULTS



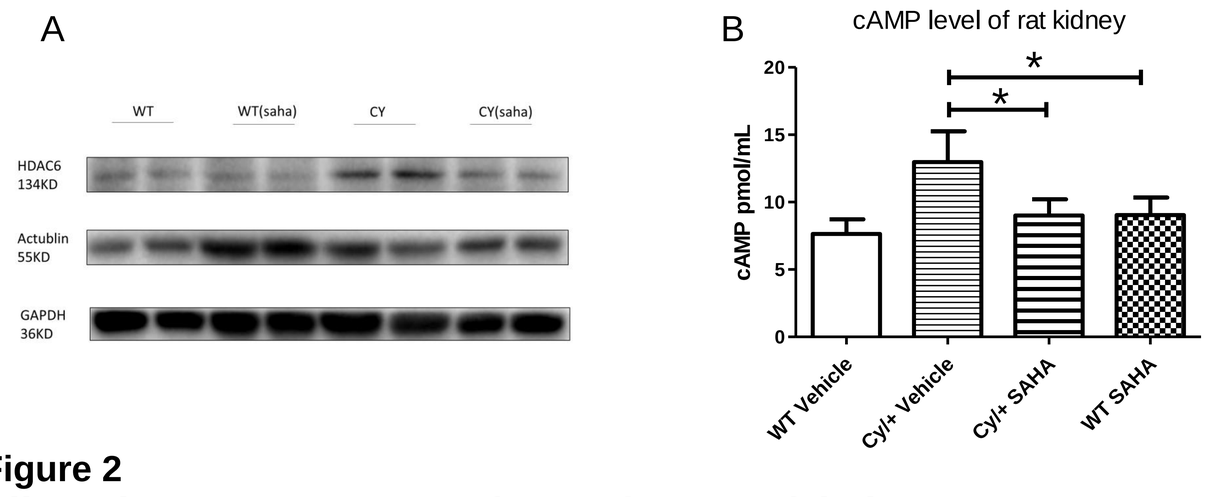


Figure 2
Effect of SAHA on HDACs and cAMP in rat model of PKD.
A. The expression of HDAC6 and Ac-tublin were measured by Western blot in SAHA- or vehicle-treated wild type (+/+) and cystic (Cy/+) Han:SPRD rats at week 16. C. cAMP was measured by ELISA in SAHA- or vehicle-treated wild type (+/+) and cystic (Cy/+) Han:SPRD rats at week 16. ***P < 0.05**

Figure1
Effect of SAHA on disease progression in a rat model of PKD. A-B BUN and creatinine levels in SAHA- or vehicle-treated wild type (+/+) and cystic (Cy/+) Han:SPRD rats from week 4 to week 16. C.Two-kidney/total body weight (2K/TBW) ratio of 16-week old +/+ and Cy/+ rats. D. Hematoxylin and eosin (HE) staining on kidney of 16-week old +/+ and Cy/+ rats. E. Quantification of cyst volume density (CVD). D. *P < 0.05, **P < 0.01

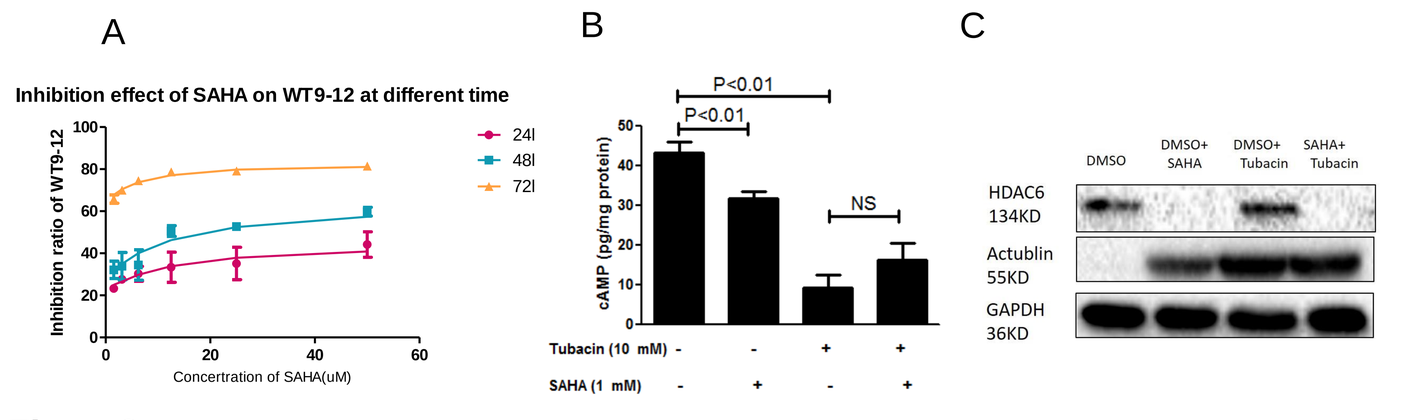


Figure3
SAHA inhibited ADPKD cell proliferation and reduced the cAMP level through HDAC6 in ADPKD cells. A. The inhibitory effect of SAHA on WT9-12 cell proliferation was assessed by MTT assay; B. the expression of HDAC6 and ac-tubulin was measured by Western blot in SAHA and HDAC6 inhibitor tubacin treated ADPKD cells; C. cAMP was measured by ELISA in SAHA and HDAC6 inhibitor tubacin treated ADPKD cells.

Conclusions

- **SAHA delayed disease progression in rat model of PKD, which was correlated with down regulation of HDAC6 and cAMP levels**
- **SAHA inhibited cell proliferation and HDAC6 expression in ADPKD cells**
- **Our study suggests that SAHA reduced cAMP concentration in ADPKD probably through HDAC6**

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