Normalization of Hepatic Homeostasis in the Npc1nmf164 Mouse Model of Niemann-Pick Type C Disease Treated with the Histone Deacetylase Inhibitor Vorinostat

Abstract

Niemann-Pick type C (NP-C) disease is a fatal genetic lipidosis for which there is no FDA-approved therapy. Vorinostat, an FDA-approved inhibitor of histone deacetylases, ameliorates lysosomal lipid accumulation in cultured NP-C patient fibroblasts. To assess the therapeutic potential of histone deacetylase inhibition, we pursued these in vitro observations in two murine models of NP-C disease. Npc1nmf164 mice, which express a missense mutation in the NPC1 gene, were treated intraperitoneally, from weaning, with the maximum tolerated dose of Vorinostat (150 mg/kg, 5 days per week). Disease progression was measured via gene expression, liver function and pathology, serum and tissue lipid levels, body weight and lifespan. Transcriptome analyses of treated livers indicated multiple changes consistent with reversal of liver dysfunction that typifies NP-C disease. Significant improvements in liver pathology and function were achieved by this treatment regimen; however, NPC1 protein maturation and levels, disease progression, weight loss, and animal morbidity were not detectably altered. Vorinostat concentrations were >200 μM in the plasma compartment of treated animals, but were almost 100-fold lower in brain tissue. Apolipoprotein B metabolism and the expression of key components of lipid homeostasis in primary hepatocytes from null (Npc1-/-) and missense (Npc1nmf164) mutant mice were altered by Vorinostat treatment, consistent with a response by these cells independent of the status of the NPC1 locus. These results suggest that HDAC inhibitors have utility to treat visceral NP-C disease. However, it is clear that improved blood-brain barrier penetration will be required to alleviate the neurological symptoms of human NP-C disease.

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AUTHOR CONTRIBUTIONS: ABM, NH and SLS conceived, coordinated and conducted the study and wrote the paper. RTS and RAM contributed to the toxicity study and the development of the drug administration protocol used for in vivo experiments. FWC and YAI provided technical assistance to the experiment in Figure 1. DSS provided technical assistance and contributed to the preparation of the Figure 2. KL and SJB provided technical assistance for the experiment shown in Figures 6a-e. DSO designed, performed and analyzed the experiments shown in Figures 7c-d. KH performed the experiment shown in Figures 8e. AH-O and HNG provided technical assistance to the experiments in Figures 9 and 10. ND and JJR provided technical assistance to the experiment in Figure 10. All authors reviewed the results and approved the final version of the manuscript.