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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