

Heat shock protein-based therapy for sphingolipidoses

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Lysosomal diseases often manifest with severe systemic and central nervous system (CNS) symptoms. The existing treatment options are limited and have no or only modest efficacy against neurological manifestations of disease. We recently demonstrated that recombinant HSP70 improves the binding of several sphingolipid-degrading enzymes to their essential co-factor, bis(monoacylglycero)phosphate, *in vitro*. HSP70 treatment reversed lysosomal pathology in primary fibroblasts from 14 patients with eight different lysosomal diseases. HSP70 penetrated effectively into murine tissues including the CNS and inhibited glycosphingolipid accumulation in murine models of Fabry disease (Gla^{-/-}), Sandhoff disease (Hexb^{-/-}) and Niemann-Pick disease type C (Npc1^{-/-}), and attenuated a wide spectrum of disease-associated neurological symptoms in Hexb^{-/-} and Npc1^{-/-} mice. Oral administration of arimoclomol, a small molecule co-inducer of heat shock proteins, currently in clinical trials for Niemann-Pick disease type C, recapitulated the effects of recombinant HSP70, suggesting that heat shock-based therapies merit clinical evaluation for treating lysosomal diseases.