Effect of Maltosyl-Beta-cyclodextrin on in vitro and in vivo models of Niemann-Pick disease type C

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Niemann-Pick disease type C (NPC) is an autosomal recessive disorder that causes severe hepatosplenomegaly and progressive neurodegeneration. 2-Hydroxypropyl-Beta-cyclodextrin (HPBCD) is compassionately used for the treatment of NPC. HPBCD improves cholesterol sequestration in organs and prolongs the lifespan in Npc1 deficient mice. However, HPBCD shows adverse effects such as ototoxicity and pulmonary toxicity. So there is still need of new therapeutics for the treatment of NPC. Maltosyl-Beta-cyclodextrin (MABCD), in which one of the primary hydroxyl groups of Beta-cyclodextrin is substituted by maltose through the alpha-1,6 glycosidic linkage, has been receiving increasing attention, because it forms soluble inclusion complexes with cholesterol. MABCD and cholesterol/MABCD inclusion complexes can alter cellular cholesterol content. The purpose of this study was to investigate the effects of MABCD on in vitro and in vivo models of NPC.

Wild-type and Npc1 deficient (Npc1 KO) Chinese hamster ovary (CHO) cells were used for in vitro experiment. The attenuating effects of both cyclodextrins against NPC manifestation were evaluated by reduction in lysosomal volume and intracellular cholesterol content. We also compared cytotoxicity of cyclodextrins in wild-type CHO cells. The modes of interaction of cholesterol with cyclodextrins were determined by the solubility method and proton 1H-NMR spectroscopy. The effects of subcutaneous administrations of MABCD (2.9 mmol/kg, once a week) were evaluated in Npc1 deficient (Npc1-/-) mice. The effects of cyclodextrins were analyzed by serum transaminase levels, hepatic cholesterol content and histological examinations.

MABCD and HPBCD comparatively decreased the abnormal lysosomal volume and intracellular cholesterol content in Npc1 KO CHO cells. No significant difference was observed between MABCD and HPBCD in cytotoxicity. MABCD showed slightly higher cholesterol solubilizing ability than HPBCD, although no significant changes in 1H-NMR chemical shifts of cholesterol with MABCD were detected, due to the limited aqueous solubility of cholesterol. The in vitro evidences suggest that MABCD has comparable therapeutic potentials against NPC manifestation to HPBCD. We also confirmed the significant attenuating effects of MABCD on the abnormalities in Npc1-/- mice. These results suggest that MABCD is a potential drug candidate for treatment of NPC.