Cholesterol Trafficking in the Brain and in Niemann-Pick C Disease

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Impaired cholesterol metabolism in the brain has been linked to several neurodegenerative disorders. In the neurodegenerative disorder Niemann-Pick C (NPC) disease the intracellular trafficking of cholesterol is impaired resulting in cholesterol sequestration in late endosomes/lysosomes (LE/L). Recent studies have shown that cyclodextrin (CYCLO), a cholesterol sequestering agent, increases survival and improves neurodegeneration of Npc1-/- mice. We have investigated (i) the cell types in the brain that respond to CYCLO, (ii) the CYCLO concentration that is beneficial, and (iii) mechanisms underlying the effects of CYCLO in neurons and glial cells from Npc1-/- and Npc1+/+ mice. Cells were incubated for 24 h with 0.1-10 mM CYCLO. 10 mM CYCLO killed all the neurons whereas neuron survival was not impaired by 0.1 mM or 1 mM CYCLO. Cholesterol sequestration in LE/L of Npc1-/- cells was eliminated by 0.1 and 1 mM CYCLO. Moreover, 0.1 mM CYCLO reduced cholesterol synthesis and expression of genes involved in cholesterol synthesis and uptake, and markedly increased cholesterol esterification in Npc1-/- astrocytes. In contrast, 1.0 mM CYCLO exerted the opposite effects on cholesterol homeostasis. Thus, cholesterol stored in LE/L of Npc1-/- neurons, astrocytes and microglia is mobilized by low doses of CYCLO. The data support the hypothesis that 0.1 mM CYCLO mobilizes cholesterol from LE/L of Npc1-/- cells thereby normalizing cholesterol homeostasis at the ER whereas 1 mM CYCLO removes cholesterol from the plasma membrane in addition to releasing sequestered cholesterol from LE/L. These studies are important because peripheral and CNS administration of CYCLO is currently being considered/used as a therapeutic agent in NPC patients