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Niemann-Pick C disease and Cyclodextrin therapy

Norman B. Javitt
New York University, USA

On the basis of prior knowledge that 2-hydroxypropyl beta cyclodextrin (HPBCD) is safe for intrathecal and intravenous administration and that it solubilizes sterols as well as many pharmaceuticals, a therapeutic trial of a commercially available HPBCD in a mouse model of NPC disease indicated slowing of the neurologic disease. This dramatic effect has hastened its application to children suffering from progressive NPC disease, although the mechanisms for the apparent initial beneficial effect are not defined. The focus is on transporting cholesterol in the torus of the cyclodextrin molecule, which thus may function as an artificial vehicle that replaces the functions of the mutated NPC1 and NPC2 proteins. Currently available HPBCD is very inefficient, with a molar ratio (cholesterol/HPBCD) of only approximately 0.05 at saturation but other degrees of hydroxypropyl substitution can provide greater efficiency. Also, other derivatives of beta cyclodextrin may prove to be of greater use. The preponderance of cholesterol in tissues probably accounts for its entry into the torus even though oxysterols have a greater solubility. The recently reported oxysterol biomarkers of NPC, cholestane-3β, 5α, 6β-triol and 7-ketocholesterol may be directly modified by HPBCD treatment. Referring to the interaction of sterols with cyclodexrin as "complex" formation , masks our evidence favoring hydrogen bonding which may provide a clue for tailoring more efficient cyclodextrins that directly address the cause of the neurodegeneraton.

Biography

Norman B. Javitt is Professor of Medicine and Pediatrics and directs studies that relate to changes occurring in the lanosterol to cholesterol metabolic pathway in physiologic states and acquired and genetically determined diseases such as Alzheimer's disease and Smith-Lemli-Opitz syndrome. He is the author of more than 170 publications and served on the editorial board of the Journal of Lipid Research. Before his current focus, he established conjugation with glutathione as a major metabolic pathway for detoxifying pharmaceuticals and defined the oxysterol pathway of bile acid synthesis that is relevant to neonatal cholestatic diseases including Niemann-Pick C.

Norman.Javitt@nyumc.org