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TITLE: Cellular and Molecular Mechanisms Underlying Neurodegeneration in Niemann- Pick Type C disease

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PROJECT DESCRIPTION

Niemann-Pick disease type C (NPC) is a neurological disorder marked by ataxia and dementia with neurofibrillary tangles (NFTs) (composed of hyperphosphorylated tau), and neurodegeneration. A great number of studies on NPC have been performed; however, the number of studies geared towards elucidating the mechanisms underlying neuronal dysfunction and neurodegeneration in NPC has been limited. Since neurological symptoms of NPC are definitely critical symptoms that determine the entire clinical courses, the research projects to elucidate the mechanisms, by which NPC1-deficiency cause neurodegeneration in NPC, are indispensable. During our studies on the role of cholesterol in the pathogenesis of Alzheimer's disease (AD), we found that amyloid beta-protein that causes AD affects cholesterol metabolism in neurons, which in turn leads to tau phosphorylation, synaptic dysfunction, and neuronal death, suggesting that cholesterol metabolic alterations promote AD pathologies. In this context, it is possible that alterations in cholesterol metabolism due to NPC1 deficiency are responsible for the induction of hyperphosphorylated tau, NFT formation, and neurodegeneration in NPC brains in the absence of senile plaques. Thus, we hypothesize that NPC and AD share a common pathway, in which altered cholesterol metabolism causes tauopathy, synaptic dysfunction, and neurodegeneration. However, the mechanism underlying the pathway remains to be elucidated.

Our research project is designed to determine the molecular mechanism, by which NPC1 deficiency causes neuronal dysfunction, leading to the deterioration of neuronal networks, and to develop a method that inhibits this cascade using established culture and in vivo systems. In particular, this research project is proposed to examine how the disruption of cholesterol metabolism caused by NPC1 deficiency in NPC neurons affects intracellular signaling pathways, which induce tau phosphorylation and membrane dysfunctions, resulting in neurodegeneration in a neuronal culture system. These findings obtained from cellular/molecular experiments will provide not only important information to get better understand the neuropathological process of NPC, but also new insight into an issue concerning a therapeutical strategy for neuronal damage in NPC.

FINAL STATUS REPORT
Dated 9/7/2004

We have established a primary neuron culture system prepared from the cerebral cortices of NPC1+/+, NPC1+/-, and NPC1-/- mouse brains. The cultured neurons and astrocytes isolated from NPC1-/- mouse

cortices showed similar phenotype to the cells in adult organs of NPC1-/- mouse and patients in terms of cholesterol accumulation demonstrated by filipin staining. When these neurons were cultured in a serum-free medium, impairment of neurite extension is found only in the cultured neurons prepared from NPC1-/- brains. We also observed that the amount of synaptic vesicle-related proteins decreased in the NPC1-/- brains and the cultured neurons from NPC1-/- mice compared with that in the brains and neurons of NPC1+/+ and NPC1+/- mice. Since neurite outgrowth is a critical step for synapse formation, these results suggest that synapse formation and subsequent neuronal network formation are affected in NPC1-/- mouse brains. In addition, we found that the neurons prepared from NPC1-/- brains showed enhanced vulnerability to reagents generating oxidative stress, which are found under physiological conditions, than the neurons of the other two genotypes. We have found results implying a mechanism underlying NPC1 deficiency-specific impairment of neurite extension and the high vulnerability of NPC1-/- neurons to neurotoxic reagents. If the mechanism would be completely clarified, they would provide a novel insight and direction into pursuing viable treatment options for NPC1 disease.

PUBLICATIONS:

http://www.jbc.org/cgi/content/full/280/12/11731
http://www.jbc.org/cgi/content/full/280/29/27296