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TITLE: Analysis of Dendritic Spine Alterations in Niemann-Pick Disease Type A Neurons

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PROJECT DESCRIPTION

Neurodegeneration and mental retardation are hallmarks of the Niemann Pick disease type A. This disease is caused by mutations in the acid sphingomyelinase (ASM), which is responsible for the conversion of Sphingomyelin (SM) into ceramide in the lysosomes. In previous projects financed by the NNPDF we have analyzed the consequences that ASM deficiency has in neurons. For this we have examined brains and primary neurons in culture from wild type mice and mice lacking the ASM. Our research has revealed that the aberrant accumulation of SM is not restricted to the lysosomes but also occurs at the cell surface membrane. This leads to alterations in the distribution and trafficking of certain membrane molecules. The synapses, highly specialized membrane sites of cell-to-cell contact, responsible for the propagation of information between neurons, show increased SM content as well. This is accompanied by alterations in synaptic composition, morphology, number and functionality. In particular, we have found altered levels of proteins that control the actin cytoskeleton. These proteins are responsible for the maintenance of dendritic spines, specific protrusions on the neuronal surface receiving most of the excitatory input. Indeed, synaptic transmission efficacy largely depends on these structures. In the present project we aim to understand the mechanism by which SM accumulation leads to such alteration and whether it is possible to revert it by modulating the levels of SM and/or actin related proteins at least in vitro.

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The final goal of our research is to understand the molecular mechanisms underlying neuronal functional impairment and degeneration in Niemann Pick disease type A (NPA). We believe this knowledge will allow us to provide not only with targets for therapeutical strategies but with read out systems to test them in vitro and in vivo. Thanks to the support of the NNPDF we have been able to detect alterations in the number and morphology of dendritic spines of mice that lack the acid sphingomyelinase (ASMKO) and mimic the human disease. Dendritic spines are protrusions in the surface of the neurons that sustain the synapses. Changes in their number and shape upon stimuli are essential to learning and memory capacities. The results we have obtained reveal that dendritic spine alterations in NPA are due to the drastic increase of the lipid sphingomyelin at the synaptic membrane, which is caused by the lack of activity of the acid sphingomyelinase. Importantly, the addition of exogenous sphingomyelinase rescues the aberrant phenotype restoring the amount of SM and the number of dendritic spines in ASMKO mice-derived neurons to levels similar to those in normal mice-

derived neurons. We believe our work identifies dendritic spine alterations as a pathological feature in NPA disease and suggests that the use of sphingomyelinase, to reduce the high levels of sphingomyelin at the synapses, could be a strategy to ameliorate the cognitive deficits in NPA patients.

PUBLICATIONS:

http://www.molbiolcell.org/cgi/content/abstract/19/2/509