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Role of Sphingomyelin on spine phisiology and pathology: implication in the mental retardation sindrome Niemann Pick disease type A

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ABSTRACT OF THE TALK

Recent evidence has pointed to the involvement of cholesterol and sphingomyelin (SM) in the formation and maintenance of neuronal synapses. Thus, depletion of both lipids leads to dendritic spine loss in cultured primary hippocampal neurons (Hering et al. 2003). A hallmark of many mental retardation syndromes is the alteration of dendritic spines. The mental retardation syndrome Niemann Pick disease type A (NPA), is caused by loss of function mutations in the acid sphingomyelinase (ASM), an enzyme that converts SM into ceramide.
Using mice lacking ASM (ASMKO) we have analyzed dendritic spines in vivo and in vitro. We show that ASMKO synaptosomal membranes contain a drastic SM increase compared to wt. This is accompanied by altered dendritic spine morphology as determined by in vivo and in vitro experiments. We also show, trough gain and loss of funcion experiments, that the molecular mechanism underlying such defects is the deficient binding of the RhoA GTPase to the SM loaded membrane.
These results reveal a crucial and unexpected role of the ASM in synaptic membrane organization suggesting that defects in such event could play a key pathological role in NPA.