Lack of activation of the unfolded protein response in mouse and cellular models of Niemann-Pick type C disease

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Background: Niemann-Pick type C (NPC) disease is a fatal lysosomal storage disease related to progressive neurodegeneration secondary to abnormal intracellular accumulation of cholesterol. Signs of endoplasmic reticulum (ER) stress have been reported in other lipidoses. Adaptation to ER stress is mediated by the unfolded protein response (UPR), an integrated signal transduction pathway that attenuates stress or triggers apoptosis of irreversibly damaged cells. Objective: To investigate the possible engagement of ER stress responses in NPC models. Methods: We used NPC1 deficient mice and an NPC cell-based model by knocking down the expression of NPC1 to measure several UPR markers through different approaches. Results: Despite expectations that the UPR will be activated in NPC, our results indicate a lack of ER stress reactions in the cerebellum of symptomatic mice. Similarly, knocking down NPC1 in Neuro2a cells leads to clear cholesterol accumulation without evidence of UPR activation.