Background: Accumulation of misfolded proteins in the endoplasmic reticulum (ER) leads to activation of the unfolded protein response (UPR), a protein quality control mechanism that initially protects the cell against ER stress toxicity. We have previously shown that the UPR is activated in neurons in the AD brain very early in pathology. Decreased glucose metabolism is an established trigger to activate the UPR. Interestingly, multiple epidemiologic studies indicate that the metabolic syndrome is a strong risk factor for AD and that AD patients have disturbed glucose metabolism.

Aim: In this study we investigate if metabolic stress results in activation of the UPR to restore glucose homeostasis.

Methods: Differentiated SK-N-SH cells were treated with ER stressors and the levels of UPR markers and glucose transporters were analyzed using Western Blotting, qPCR and immuno-fluorescence. Uptake of glucose was analyzed using a hexokinase assay.

Results: We show that UPR activation affects the expression of the major neuronal glucose transporter GLUT3 via a post-transcriptional mechanism and consequently increase glucose uptake.

Conclusion: Our data indicate that activation of the UPR under conditions of metabolic stress actively enhances the capacity of the cell to restore the energy homeostasis. Failure to restore the homeostasis will result in prolonged activation of the UPR which can lead to tau phosphorylation. We propose that the UPR provides a mechanistic connection between metabolic disturbances and AD pathology.