Insulin resistance and inflammation as risk factors for Alzheimer's Disease

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Epidemiological and neuroimaging evidence indicates a shared pathophysiology between Alzheimer's Disease (AD) and Type 2 Diabetes (T2DM). AD brains show glucose hypo-metabolism and insulin resistance that correlates with increased number of neuritic plaques leading to the hypothesis that AD might be Type 3 Diabetes. One of the pathological hallmarks of AD brain is neurofibrillary tangles composed of hyper-phosphorylated tau protein. Utilizing our *Drosophila* model of tauopathy we have elucidated the mechanistic linkage between the exacerbation of tau pathology and insulin resistance thereby suggesting a link between AD and T2DM. The biochemical changes observed *in vivo* have been complemented *in vitro* using SHSY5Y cell lines.

The longest isoform of human tau (2N4R) was driven in the *Drosophila* eye using an eye-specific *GMR*-Gal4 driver to generate *GMR*-Gal4-*gl*Tau transgenics or pan-neuronally by *Elav*-Gal4. These transgenics were combined to mutant flies from the insulin signalling pathway obtained from Bloomington stock centre Indiana.

Utilizing genetic interactions and biochemical analysis, we observed that in an "insulin-resistant" condition, the *Drosophila* tauopathy models demonstrated a worsening of tau-induced neurotoxicity, hyperphosphorylation and formation of aggregates. In addition, under insulin-resistant state we observed significant alterations in the mammalian target of rapamycin (mTOR) kinase and autophagy pathway components suggesting that the tau toxicity under these conditions was mediated partly by impaired tau clearance. Interestingly, these pathological features were ameliorated in an "insulin sensitive" state. These results were further replicated in SHSY5Y cell lines. We also found an enhancement of antimicrobial peptides in the tauopathy models suggesting the involvement of inflammation in exacerbating Alzheimer's Disease.

Insulin resistance plays an important role in mediating tau-induced pathology via interlinked pathways conserved *in vitro* and *in vivo*. Our findings elucidate shared pathophysiological connections between AD and T2DM that may be important for early AD diagnostics and future therapeutic studies.