LEPTIN REGULATES AMYLOID-B PRODUCTION VIA THE Ψ-SECRETASE COMPLEX

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Introduction: Type 2 Diabetes Mellitus confers an increased risk for Alzheimer’s Disease (AD) that has yet to be fully explained. The adipose-derived hormone leptin has been shown to be neuroprotective and low serum leptin has recently been shown to confer an increased risk of AD.

Aims: To determine if leptin plays a role in the regulation of Aβ generation and accumulation.

Methods: We measured plasma leptin, brain Aβ, and the secretase components in a mouse model of AD. We also treated H4 neuroglioma cells with leptin and measured Aβ, APP cleavage, and β- and Ψ-secretase mRNA.

Results: We determined that plasma leptin is strongly, inversely correlated (p< 0.0001) with brain Aβ in the APP/PS1 knock-in mouse. We also found that treatment of H4 neuroglioma cells with leptin reduced Aβ secretion and increased accumulation of APP C-terminal fragments, indicative of Ψ-secretase inhibition. We subsequently determined that mRNA expression of many of the Ψ-secretase components was reduced upon leptin treatment. Finally, presenilin protein expression was inversely correlated (p< 0.0001) with plasma leptin and positively correlated (p< 0.004) with Aβ in the mouse brain.

Conclusions: We conclude that leptin functions as a physiological brake to Aβ generation by inhibiting the expression of presenilin in the brain. We are currently investigating the pathways by which leptin facilitates these changes. Additionally, we are interested in the role of leptin resistance, a phenomenon commonly observed in obese and diabetic patients, in the increased risk of AD seen in diabetics.