Mechanisms of Metabolic Hormone Amylin Action on Alzheimers Disease Pathogenesis

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Research Abstract

? DESCRIPTION (provided by applicant): Preventative and disease modifying therapies for Alzheimer’s disease represent a large unmet medical need and therapies addressing aspects beyond targeting pathology are urgently needed. To this end, epidemiologic studies have linked metabolic changes and diseases including obesity, insulin resistance, and diabetes with

Alzheimer’s disease, and increasing therapeutic emphasis is being placed on metabolic hormones to combat the pathogenic aspects of this disease. To this end we have and others found that a novel hormone, amylin, which critical in the regulation of insulin sensitivity and glucose homeostasis in the periphery affords cognitive benefits and regulates AD-related pathogenic aspects. However, the mechanisms underlying the benefits of amylin on the AD behavioral and cellular phenotype remain unknown. Similarly whether these benefits are mediated directly through the activation of the amylin receptor or indirectly through improving overall metabolic tone is also unknown. To address these questions, we propose to address the specificity of amylin effects on cognition and AD-related aspects such as amyloid-beta and tau pathology, AD-related signaling and oxidative stress by determining: 1) whether CNS blockade of amylin receptor signaling exacerbates the AD behavioral and cellular phenotype 2) whether amylin administration normalizes or slows down accelerated cognitive decline and AD-related parameters observed in diet-induced insulin resistant APP/PS1 mice and whether these are associated with changes in central and peripheral insulin related parameters and 3) based on the fact that amylin signaling occurs via two different calcitonin-ramp receptor complexes (CLT-RAMP1 and CLT-RAMP3), we seek to also determine which receptor complex is more important in regulating AD pathology, AD-related signaling, and oxidative stress under normal and insulin-resistant conditions in vitro. Together these studies will allow us to better understan the underlying mechanisms of amylin on AD and potentially develop novel more targeted therapies for this disease.

Further information available at:

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