Evaluation of CNS Blockade of AMYR on Pramlintide function in Alzheimer's Disease

Corrigan et al.

Rachel Corrigan, John Grizzanti and Gemma Casadesus

School of Biomedical Sciences, Kent State University, Kent, OH

The cause of late-onset AD pathogenesis remains largely unknown, however poor lifestyle choices that lead to metabolic dysfunction such as obesity and Type II Diabetes Mellitus in normal aging increase the risk for developing dementia two-fold. Amylin, a pancreatic hormone, known to regulate glucose homeostasis through its ability to increase insulin sensitivity. We have previously shown that an analogue of amylin, Pramlintide (PRAM), reduces amyloid beta plaque burden and recuses hippocampal-dependent cognitive decline in AD mouse models. However, while beneficial in therapy, amylin/PRAM mechanisms of action remain largely unknown. Here we begin to address whether the beneficial effects of PRAM on APP/PS1 mice are mediated through the activation of CNS amylin receptors (AMYR) in cognition-related areas or alternatively by improving general metabolic tone. To address this question, male and female APP/PS1 mice were treated chronically with PRAM or saline peripherally in the presence or absence of AC187 (an AMYR antagonist) delivered centrally. Our data thus far suggests differential effects of peripheral amylin on cognitive behavior, APP processing, and soluble amyloid-beta levels when in the presence or absence of AC187.