Assessment of Brain Insulin Resistance in Alzheimers Disease with Insulin Clamp

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Research Abstract

? DESCRIPTION (provided by applicant): There is growing interest in the relationship of type II diabetes and its pathophysiological mechanisms with Alzheimer’s disease. We previously demonstrated profound insulin resistance in postmortem brain tissues from people with AD

using a novel ex vivo insulin stimulation paradigm and further characterized abnormalities in the activation states of many insulin signaling pathway proteins in MCI, AD and mouse models. Remarkably, neuronal insulin resistance was found in AD even in the absence of known diabetes, suggesting that insulin resistance may be an intrinsic pathophysiological feature of AD. The presence of brain-specific insulin resistance in humans with or without AD has not been directly demonstrated in vivo. Here, we propose to use the hyperinsulinemic-euglycemic clamp approach with advanced MRI neuroimaging and electrophysiological methods to establish whether brain insulin response is disrupted in living humans with AD. This would validate epidemiological, postmortem and animal model findings linking insulin resistance to AD and will also advance our understanding of the role of insulin in normal brain physiology in general. If we can successfully measure brain insulin responses in patients, we then may be able to use this dynamic biomarker approach to determine the effects of insulin sensitizing medications on brain function in AD, diabetes and other disorders. We hypothesize that people with MCI or mild dementia due to AD show attenuated neurophysiological responses to hyperinsulinemia compared to cognitively normal controls. In Aim 1, we will determine the effects of hyperinsulinemia on brain physiology and function in patients with AD and matched normal controls using functional MRI. This will include resting state and cognitive task activated arterial spin label (ASL) MRI measures of regional cerebral perfusion, and resting state blood oxygen level dependent (BOLD) MRI to measure default mode network connectivity. In Aim 2, we will determine the effects of hyperinsulinemia on brain physiology and cognitive function in patients with AD and matched normal controls using P300 auditory event related potential EEG. In Aim 3, we will investigate the effects of hyperinsulinemia on cognitive function using computerized cognitive tests with a focus on spatial learning. In Aim 4, we will determine the relationship of brain insulin responses as measured in Aims 1-3 with steady-state peripheral glucose utilization in the clamp procedure and with metabolic parameters including fasting serum lipids, leptin, and adiponectin. These analyses will help determine if brain insulin resistance in AD is related to systemic insulin resistance.

Further information available at:

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