Determining if Reduced Insulin Response in the Brain is Linked to Cognitive Loss

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1

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Research Abstract

Project Summary As people age, their risk for developing dementia increases. This risk is enhanced for those with type II diabetes. In fact, individuals with type II diabetes are more than

twice as likely to suffer from dementia, either through the development of Alzheimers disease (AD), Vascular cognitive impairment (CVI) or dementia in general. Examination of brains from AD patients also reveals this correlation as most brains from AD patients display insulin resistance in the hippocampus, even in patients that have not been clinically diagnoses with type II diabetes. This brain form of insulin resistance is referred to as type III diabetes. In previous studies we examined the effect of reduced presenilin activity utilizing known loss of function mutations of Drosophila presenilin (psn). We found that flies with reduced psn activity (psn-hets) displayed an age-onset loss-of-learning and memory in the classic courtship learning and memory paradigm. In more recent studies of the psn-het brains we have found that they develop brain insulin resistance with age. We find that when the psn-het flies are young (day 5 of adulthood) and display normal cognition, their brains display increased insulin signaling and increased sensitivity to insulin stimulation. Old psn-het brains (day 30 of adulthood) that display loss of learning and memory fail to respond to insulin stimulation. We hypothesize that the establishment of insulin resistance in the brains of the old psn-hets causes the cognitive deficits displayed by this model. In the first aim of this proposal we will determine if psn mutations linked to familial Alzheimers disease (FAD) also lead to altered insulin signaling in the brain, brain insulin resistance and age onset cognitive loss. We will then explore if the reduction of insulin signaling in the brain can rescue the formation of brain insulin resistance and cognitive loss. In the second aim of this proposal we will determine if psn mutations lead to alterations in peripheral insulin signaling and peripheral insulin resistance. These studies will determine if loss or alteration of psn activity preferentially induce insulin resistance in the brain. We will also test if treatments that are known to induce the development of peripheral insulin resistance in flies also cause brain insulin-resistance and cognitive deficits. These studies will be performed with control flies, psn-hets and flies heterozygous for FAD mutations, allowing for an examination of the interaction of diet and reduced psn activity. These studies will explore the role that reduction of, or alteration in psn activity has on insulin signaling and the establishment of insulin resistance in the brain and whether this can cause cognitive impairment. These studies will also provide a useful model to explore the dementia due to the development of brain insulin resistance in general.

Further information available at:

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