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"Insulin in the Hippocampus: Memory Enhancement and Impact of Type 2 Diabetes"

DESCRIPTION (provided by applicant): The long-term goals of this proposal are, first, to develop understanding of how insulin acts on the brain - specifically, the hippocampus - to modulate cognitive processes; second, to determine how systemic insulin resistance, as seen in type 2 diabetes (T2DM), affects insulin's actions on the brain. We aim to build on our preliminary data to establish the physiological role of insulin within the hippocampus. Research in our laboratory has shown that insulin enhances cognitive performance in rats when given directly to the hippocampus, a brain region densely populated with insulin receptors and GluT4 (insulin-sensitive) glucose transporters. Our preliminary data suggest that this enhancement is accompanied by modulation of local brain metabolism. However, the mechanism(s) by which insulin acts within the hippocampus remain to be determined. The fact that insulin acts to enhance cognitive processes is of particular interest when taken together with reports of cognitive impairment accompanying diabetes, and in particular deficits in memory. Moreover, T2DM has recently been shown to markedly increase the risk of dementia, and to be associated with alterations of central beta-amyloid processing, a key marker for Alzheimer's disease. We hypothesize that the systemic insulin resistance seen in T2DM is accompanied by reduced central sensitivity within the hippocampus, which contributes to the cognitive impairment found in diabetic patients. Our initial data suggest that, indeed, a rodent model of T2DM shows impaired cognitive function accompanied by impaired responsiveness to hippocampal insulin administration and impaired hippocampal amyloid processing. LAY LANGUAGE: Insulin has recently been identified as having actions within the brain, as well as on skeletal muscle and fat. We seek to understand how insulin acts to modulate cognitive processes, particularly within the hippocampus - a key brain region for learning and memory - and, critically, how dysregulation of insulin contributes to (i) the cognitive dysfunction seen in Type 2 diabetes, and (ii) the increased risk of developing Alzheimer's disease found in such patients.