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**Diabetes, Insulin, Amyloid and AD: Cognitive and Metabolic Mechanism**

Defining characteristics of Alzheimer's disease (AD) include (1) lowered brain metabolism and cognitive impairments, especially on hippocampally based tasks; and (2) elevation of oligomerised beta-amyloid (Abeta) within several regions including specifically the hippocampus. Abnormal brain Abeta accumulation has long been suggested to be a causative agent of cognitive and brain metabolic deficiencies seen in AD. We will directly test, for the first time, whether Abeta may act via impairment of hippocampal insulin signalling to produce BOTH (i) reduction in hippocampal metabolism and (ii) cognitive impairment.

Type 2 diabetes mellitus (T2DM, defined by systemic hyperinsulinemia) and AD show comorbidity. T2DM causes cognitive impairment, impaired brain Abeta processing, and high risk for development of dementia. Recent work suggests that insulin competes with Abeta for protease degradation (hence, chronic hyperinsulinemia may cause Abeta accumulation) and also that (i) insulin modulates removal of Abeta from the brain, and (ii) Abeta oligomers may act, at least in part, by blockade of neuronal insulin binding.

We have recently shown that insulin plays a critical role in hippocampal memory processes and metabolism. Critically, ENDOGENOUS insulin signalling is required for optimal hippocampal function. Moreover, we developed a physiologically relevant model of T2DM (rats placed on a high-fat diet (HFD) as juveniles) which develops (i) impaired central insulin signalling and (ii) impaired brain processing of Abeta. These rats show cognitive and metabolic impairments akin to those seen in AD.

Abeta delivery to the whole brain (i.c.v.) and/or over extended periods is known to impair cognition. However, if amyloid acts rapidly to impair insulin signalling, cognitive impairment and hypometabolism should also be rapid following intrahippocampal Abeta administration. The mechanistic link, if any, between Abeta elevation and local hypometabolism has not been determined, but would be consistent with amyloid impairing insulin signalling. Finally, an insulin sensitizing drug (pioglitazone) is in clinical trials for AD as an anti-inflammatory; whether, and how, such drugs can reverse cognitive and metabolic deficits requires testing.

Key data obtained since the original submission provide support to these hypotheses. We have shown that acute microinjection administration of Abeta (but NOT monomeric beta-amyloid) markedly impairs spatial memory within 10 min after administration, accompanied by reduced translocation of the insulin-sensitive glucose transporter GluT4.

Specific Aims (in brief):

1. Determine (using spatial memory testing with simultaneous hippocampal microdialysis) the impact of intrahippocampal Abeta administration on hippocampal cognitive processes, metabolism, and insulin signalling and mechanism(s) for this impact.
2. Determine whether pioglitazone can reverse impairments seen with HFD and/or Abeta administration.