Type 2 Diabetes Mouse Model: Insights into the Contribution of Metabolic Defects to Neurocognitive Decline

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Background and Hypothesis: Metabolic diseases, including type 2 diabetes (T2D), have become increasingly prevalent and their associated medical costs have skyrocketed. Furthermore, recent epidemiological evidence suggests links between metabolic defects and neurodegenerative diseases, such as Alzheimer's Disease (AD). The increasing coincidence of AD and T2D, and unmet treatment needs, necessitates research investigating potential shared mechanisms. To study glucose and lipid metabolism defects and neurocognitive deficits, we have generated non-obese insulin resistant mouse models, named GLUT4-mediated Insulin Receptor KnockOut (GIRKO). Insulin-responsive glucose transporter, Glut4, is expressed in muscle, fat, and a subset of neurons in the brain. Our previous publications show that GIRKO mice are highly insulin resistant and insulin sensitive GLUT4 neurons are critical mediators for glucose metabolism. We hypothesize that central insulin resistance in GIRKO mice instigates neurocognitive defects.

Experimental Design: We will measure the neurocognitive function of 3- to 4-month old GIRKO mice using Morris water maze (MWM) test.

Results: GIRKO mice exhibited increased escape latency. Additionally, they spent less time in the target quadrant in the probe trial, in which the platform is removed. GIRKO performed equally compared to control mice in raised platform tests, which demonstrates that motor competencies do not confound our findings.

Conclusion and Potential Impact: GIRKO mice have learning and memory deficits, which illustrates a possible link between neurocognition and metabolism. Our results support the notion that insulin resistance precedes cognitive decline and necessitates early intervention therapy to treat insulin resistance and protect cognitive function.