Diabetes-induced changes in brainstem GCK expression

Katalin Smith, PhD[1] • Bret Smith, PhD[1]

[1]*Physiology, University of Kentucky*

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Recent evidence supports the emerging hypothesis that brainstem autonomic neurons are affected by and contribute to systemic glucose regulation. Provocatively, activation of vagal afferent terminals at the level of the gut results in altered blood [glucose] in a manner that involves a brain- centered glucose regulatory system. Moreover, most GABAergic neurons in the brainstem nucleus tractus solitarius (NTS), which receive primary vagal afferent synaptic information, are sensitive to changes in [glucose] in a glucokinase (GCK)-dependent fashion. Vertical sleeve gastrectomy (VSG) and other bariatric surgeries can result in resolution of type 2 diabetes in humans and animal models, but information about effects of VSG on type 1 diabetes is scarce. Here, we determined if GCK expression and glucose-sensitivity are reduced in the NTS after several days of continuous hyperglycemia in the streptozotocin (STZ)-treated mouse. We also used the STZ-treated mouse model of type 1 diabetes to determine effects of VSG on uncontrolled hyperglycemia, to begin testing the general hypothesis that an insulin-independent, brain-centered glucose regulatory system contributes to systemic glucose regulation after bariatric surgery. Uncontrolled hyperglycemia (>300 mg/dl) was maintained for 3-5 days in STZ-treated mice, at which time VSG or sham surgery was performed. After VSG, blood [glucose] was normalized in ~80% of mice, an effect that was evident within three days and persisted for >4 weeks. These outcomes were independent of reduced caloric intake after VSG and were mimicked by insulin treatment in STZ- treated mice. Correspondingly, molecular and functional expression of GCK in the vagal complex were reduced after several days of hyperglycemia, as was glucose-sensitivity of NTS neurons. Thus, chronic hyperglycemia induces changes in glucose-sensitivity of NTS neurons, consistent with previous reports of diabetes-related neuronal plasticity in this area of the brain. VSG resolves uncontrolled hyperglycemia in this model of type 1 diabetes, and experiments are underway to determine if this corresponds to a reinstatement of glucose-sensitivity in the vagal complex. These studies are aimed at identifying a role for brainstem control of systemic glucoregulation involving a vagally-mediated gut-brain-liver circuit.