DREADD[ed] evidence for modulation of blood [glucose] by the dorsal hindbrain

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The brainstem dorsal motor nucleus of the vagus (DMV) contains the preganglionic parasympathetic motor neurons that provide motor output to most subdiaphragmatic viscera important in regulating metabolism. The DMV serves as the final central modulatory point for descending parasympathetic activity and its activity is tightly controlled by GABAergic inhibitory synaptic input arising from the nucleus tractus solitarius (NTS). Thus inhibitory, GABAergic neurotransmission from the NTS contributes significantly to parasympathetic visceral control. Together with area postrema, the DMV and NTS make up the dorsal vagal complex (DVC), a brainstem site critical in mediating the gut-brain-liver circuit controlling systemic [glucose]. Specifically, GABA neurons in the NTS are glucose sensing, and elevated glucose increases GABA neurotransmission in the DMV. Chronic hyperglycemia also induces a variety of neuroplastic events within the DVC. Therefore, we hypothesized that modulating GABA neuron activity in the DVC causes changes in peripheral blood [glucose] through an efferent vagal pathway. This hypothesis was tested by integrating in vitro electrophysiology with chemogenetics using genetically targeted designer receptors exclusively activated by designer drugs (DREADDs) in the whole animal. Electrophysiological results confirm previous reports that GABA neurons in the NTS respond to changes in [glucose] through specific intracellular mechanisms, including glucokinase (GCK) activation. Activation of dorsal hindbrain GABA neurons through chemogenetic manipulation resulted in elevated blood [glucose]. This elevation in blood [glucose] was abolished when animals were pretreated with methscopolamine, a muscarinic antagonist, to block parasympathetic nervous system signaling. Electrophysiological measurements found that chemogenetic activation excites GABAergic neurons in the NTS, increases inhibitory postsynaptic events in the DMV, and decreases DMV firing. These studies are the first to demonstrate that GABAergic signaling in the DVC regulates systemic glucose homeostasis. Defining the glucoregulatory functions of the DVC provides a fresh perspective on our understanding of autonomic control of energy homeostasis and will likely translate to novel therapeutic targets for diabetes.