Department of Physiology

Dissertation Defense Seminar

Jordan Wean

METABOLIC AND ELECTROPHYSIOLOGICAL EFFECTS OF FIBROBLAST GROWTH FACTOR 19 IN THE DORSAL VAGAL COMPLEX

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Doctoral Committee Members

Dr. Bret Smith
Department of Neuroscience, Mentor

Dr. Olivier Thibault
Pharmacology & Nutritional Sciences

Dr. John McCarthy
Department of Physiology

Dr. Ken Campbell
Department of Physiology

Dr. Lisa Tannock
Department of Internal Medicine

Outside Examiner

Dr. Tadahide Izumi
Department of Toxicology and Cancer Biology

University of Kentucky

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Abstract of Dissertation

The dorsal vagal complex (DVC) is an important homeostatic regulatory center located in the hindbrain that alters vagal parasympathetic activity in response to viscerosensory and humoral cues. Within the DVC, second-order sensory neurons in the nucleus tractus solitarius (NTS) integrate ascending vagal sensory input with descending regulatory inputs from higher brain areas and respond to circulating hormones and glucose. In turn, the NTS projects to the dorsal motor nucleus of the vagus (DMV) which is comprised of cholinergic motor neurons and regulates gastric motility, hepatic glucose production, and pancreatic hormone release among others.

Fibroblast growth factor 19 (FGF19) is a protein hormone that produces antidiabetic effects when administered intracerebroventricularly in the forebrain. Lateral or third ventricle administration of FGF19 was shown to increase glucose tolerance, decrease body weight, and decrease food intake. However, no studies have been performed to understand the effects of FGF19 in the DVC. Neurons in the DVC express FGF receptors and regulate many of the processes that have been proposed to explain the antidiabetic effects of FGF19. Thus, this study was understand both the cellular effects of FGF19 in the DVC as well as effects on systemic glucose regulation.

First, the FGF19 was applied to the hindbrain to understand its effects on blood glucose. Fourth ventricle administration of FGF19 produced no effect on blood glucose concentration in control mice, but induced a significant, peripheral muscarinic receptor-dependent decrease in systemic hyperglycemia for up to 12 hours in streptozotocin (STZ)-treated mice, a model of type 1 diabetes. Patch-clamp recordings from DMV neurons in vitro revealed that FGF19 application altered synaptic and intrinsic membrane properties of DMV neurons, with the balance of FGF19 effects being significantly modified by a recent history of systemic hyperglycemia.

Since the previous data indicated that FGF19 alters firing in glutamatergic neurons upstream from the DMV, the next study was aimed at understanding the electrophysiological effects of FGF19 on local glutamatergic neurons in the DVC. Receptor expression studies indicated that two nuclei were the most likely source of glutamatergic input to the DMV: the NTS and the area postrema (AP). Glutamate photolysis studies indicated that FGF19 does indeed increase the activity of glutamatergic neurons in the AP and NTS that project to the DMV. This effect was only seen in hyperglycemic mice. Further study indicated that FGF19 produced mixed effects on the intrinsic excitability of NTS neurons but increased action-potential dependent glutamate release to the NTS in hyperglycemic mice. The source of this glutamate was confirmed to be the AP.

Overall, the in vitro effect of FGF19 on DVC neuron excitability was complex. FGF19 produced mixed effects on the intrinsic excitability of some cells while substantially increasing glutamatergic transmission at multiple synapses in the DVC of hyperglycemic mice. In vivo, FGF19 in the hindbrain decreased blood glucose in diabetic mice, an effect that is consistent with its observed in vitro effects on glutamatergic transmission. These findings identify central parasympathetic circuitry as a novel target for FGF19 and suggest that FGF19 acting in the dorsal hindbrain can alter vagal output to produce its beneficial metabolic effects.