Regulation of Visceral Afferent Nerves by Glucagon-like Peptide-1

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Type II Diabetes Mellitus is characterized by inadequate insulin secretion after glucose ingestion and considerable research has gone into the mechanism of this deficiency. In recent years, much attention has been given to GI hormones, particularly, Glucagon-like peptide-1 (GLP-1), a cleavage product of proglucagon, and its role in insulin release. However, the exact mechanism by which GLP-1 elicits its insulinotropic effect is still unknown. While some have suggested GLP-1 acts via a classic endocrine pathway, in which GLP-1 would bind to receptors found on the β-cells in the pancreas, the hormone's short half life and low postprandial blood concentrations have raised questions of this model. Instead, we propose that GLP-1 acts via neuroendocrine circuits. More specifically, GLP-1, in the presence of glucose, stimulates GLP-1 receptors located on axons from vagal afferents on the portal vein. These afferents carry impulses to the nodose ganglion and the Nucleus tractus solitarius (NTS) thereby altering neural activity in the hindbrain. Details of this pathway were examined in this study using immunohistochemistry. Previous research has shown GLP-1 receptors on neural fibers in the portal vein. Using antibodies to the GLP-1 receptor called AB20(2) and ABdd, we were able to show that these receptors are expressed by neurons in the nodose ganglia, where the cell bodies of vagal afferent nerves are located. Vagal afferent fibers from nodose ganglia synapse in the NTS located in the hindbrain. To determine whether portal administration of GLP-1 regulates activity of neurons in the hindbrain Sprague-Dawley rats were given infusions of saline, glucose or glucose plus GLP-1 into the portal vein (n = 3 per group). Sections of brains were immunostained using an antiserum binding to *c-fos*, a protein commonly used as a marker of neuronal activity. Compared to animals who received saline infusions, GLP-1 plus glucose administration exhibited decreased c-fos expression, while animals that received glucose alone had increased NTS neuron activation (19.3 ±3.5, 12.1 ± 3.5, and 27.8 ± 7.7 c-fos positive cells per 4 mm^2 area of NTS, respectively). These findings are consistent with the proposed neuroendocrine model of GLP-1 action and indicate that intraportal GLP-1 regulates the neuronal activity of the NTS. These results augment the current views on the regulation of post-prandial insulin secretion and would impact the understanding of the pathophysiology of Type II Diabetes mellitus.