A Central Nervous System Link to the Endocrine Pancreas

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Abstract

Beta cells in the pancreas are the site of the body's insulin secretion. Insulin plays a critical role in the take up of glucose from the blood and in its storage as glycogen in the liver, muscle cells, and fat cells. As over 200 years of historical data has shown, certain hypothalamic and brainstem injuries in humans have led to development of obesity and diabetes in affected individuals. While such observations have been made, the precise neuronal pathway involved in regulating insulin secretion from pancreatic beta cells remains largely unknown. In this study, we are beginning to unveil a three dimensional map of the brain that traces this pathway and indicates which anatomical parts of the brain connect to pancreatic endocrine cells and are likely involved in regulating their function. By infecting the pancreas of mice with a retrograde neuronal tracer, attenuated pseudorabies virus expressing the LacZ gene reporter (PRV-BaBlu) and immunostaining brain sections cut from these mice for beta-galactosidase detection, we were able to detect the specific areas of the brain reached by the virus. Our experiment reveals strong PRV-BaBlu tracing to the brainstem and to certain hypothalamic nuclei, especially the dorsal medial nucleus, the ventral medial nucleus, the lateral hypothalamus, and the arcuate nucleus, clearly indicating their central role in endocrine metabolic homeostasis areas of the brain. While PRV-BaBlu tracing mostly ends in the hypothalamus, that indicates the major link of the CNS to the endocrine pancreas, to a lesser extent the virus was also detected in limited extrahypothalamic sites that include the habenula in the thalamus and the hippocampus, suggesting the "fight or flight" process may utilize the hypothalamic nuclei to relay its regulatory effects on endocrine pancreas. While the precise central nervous system (CNS)-endocrine pancreas map is currently being refined, these extrahypothalamic sites could regulate insulin secretion via the hypothalamus or eventually join the autonomic pathways that exit the CNS at the brainstem. Also, some restricted PRV-BaBlu staining was found in parts of the

cerebellum, indicating the possibility of a motor neuron-regulated process in control of metabolic homeostasis. In summary, the data obtained to this point have generated the first map of the CNS link to the endocrine pancreas that is mostly directed at the hypothalamus, a central regulator of metabolic homeostasis and, now, likely also of endocrine pancreas physiology.