Report

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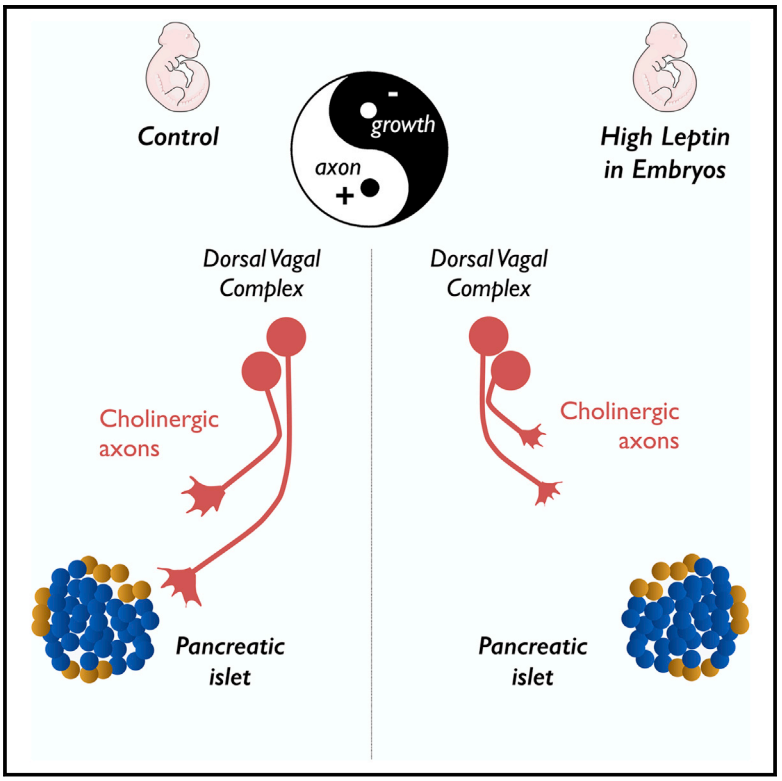
Leptin Controls Parasympathetic Wiring of the Pancreas during Embryonic Life

Graphical Abstract



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In Brief

The autonomic nervous system is essential for the regulation of blood glucose levels. Croizier et al. report that prenatal leptin inhibits parasympathetic innervation of the pancreatic islets, with long-term consequences on glucose homeostasis. These findings improve of our understanding of the neural mechanisms involved in the early-life origins of diabetes.

Highlights

- Autonomic innervation of pancreatic islets develops during mid-gestation in mice
- Leptin is required for normal parasympathetic innervation of pancreatic β cells
- Acute leptin injections in embryos cause lifelong disturbances in glucose homeostasis
- Leptin acts directly on the hindbrain to modulate cholinergic axon growth

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Leptin Controls Parasympathetic Wiring of the Pancreas during Embryonic Life

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SUMMARY

The autonomic nervous system plays a critical role in glucose metabolism through both its sympathetic and parasympathetic branches, but the mechanisms that underlie the development of the autonomic innervation of the pancreas remain poorly understood. Here, we report that cholinergic innervation of pancreatic islets develops during mid-gestation under the influence of leptin. Leptin-deficient mice display a greater cholinergic innervation of pancreatic islets beginning in embryonic life, and this increase persists into adulthood. Remarkably, a single intracerebroventricular injection of leptin in embryos caused a permanent reduction in parasympathetic innervation of pancreatic β cells and long-term impairments in glucose homeostasis. These developmental effects of leptin involve a direct inhibitory effect on the outgrowth of preganglionic axons from the hindbrain. These studies reveal an unanticipated regulatory role of leptin on the parasympathetic nervous system during embryonic development and may have important implications for our understanding of the early mechanisms that contribute to diabetes.

INTRODUCTION

The autonomic nervous system is essential for the regulation of critical physiological functions including cardiac output, body temperature and blood glucose levels (Schmidt and Thews, 1989). Classically, the autonomic nervous system is divided into two anatomically and functionally distinct branches: the sympathetic nervous system and the parasympathetic nervous system. Consistent with a role of the autonomic nervous system in the maintenance of glucose homeostasis, sympathetic and parasympathetic neurons densely innervate the endocrine pancreas and, in particular, the islets of Langerhans (Ahrén, 2000; Thorens, 2014; Woods and Porte, 1974). Notably, the sympathetic and parasympathetic systems exert distinct actions on pancreatic islets: whereas sympathetic nerve stimulation inhibits insulin secretion from pancreatic β cells and promotes glucagon secretion from pancreatic α cells, parasympathetic input stimulates the secretion of both glucagon and insulin (Bloom and Edwards, 1975). Despite the critical role of the autonomic nervous system in the regulation of islet hormone secretion, relatively little is known about the mechanisms involved in the development of the autonomic innervation of the pancreas.

The parasympathetic fibers that innervate the endocrine pancreas originate primarily from neurons in the intrapancreatic ganglia, which receive preganglionic inputs from the hindbrain via the vagus nerve (Fox and Powley, 1986). In contrast, sympathetic fibers within in the pancreas originate from preganglionic cell bodies that are located in the thoracic and upper lumbar segments of the spinal cord (Furuzawa et al., 1996). Both the parasympathetic and sympathetic systems develop before birth, and autonomic nerve fibers can be observed in various peripheral organs as early as mid-gestation (Black, 1978; Burris and Hebrok, 2007; Rinaman and Levitt, 1993). Notably, the onset of autonomic innervation coincides with stages of rapid growth, differentiation, and maturation in the embryonic pancreas (Jørgensen et al., 2007).

In addition to being controlled by the autonomic nervous system, pancreatic function is also regulated by hormonal factors, including the adipocyte-derived hormone leptin. Although leptin was initially described as a regulator of energy balance and neuroendocrine function, it has subsequently been shown to influence sympathetic tone and glucose homeostasis (Enriori et al., 2011; Marino et al., 2011; Morton and Schwartz, 2011; Simonds et al., 2014). The effects of leptin are now recognized to be mediated by a distributed neural network that includes neurons located in both the hypothalamus and hindbrain (Gautron et al., 2015; Grill and Hayes, 2012; Leinninger and Myers, 2008). In addition to the physiological effects it exerts during adult life, leptin provides trophic support to hypothalamic neural projections during development (Bouret et al., 2004). However, whether leptin influences the development of non-hypothalamic circuits remains unknown.

In this report, we investigated the development of the parasympathetic innervation of the endocrine pancreas. We demonstrated that exposure of the embryonic brain to leptin during a discrete developmental period results in permanent alterations in the cholinergic innervation of pancreatic β cells as well as long-term perturbations in glucose homeostasis. Furthermore, we showed that leptin directly inhibits cholinergic neurite