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Neural control of the endocrine pancreas

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The autonomic nervous system affects glucose metabolism partly through its connection to the pancreatic islet. Since its discovery by Paul Langerhans, the precise innervation patterns of the islet has remained elusive, mainly because of technical limitations. Using 3-dimensional reconstructions of axonal terminal fields, recent studies have determined the innervation patterns of mouse and human islets. In contrast to the mouse islet, endocrine cells within the human islet are sparsely contacted by autonomic axons. Instead, the invading sympathetic axons preferentially innervate smooth muscle cells of blood vessels. This innervation pattern suggests that, rather than acting directly on endocrine cells, sympathetic nerves may control hormone secretion by modulating blood flow in human islets. In addition to autonomic efferent axons, islets also receive sensory innervation. These axons transmit sensory information to the brain but also have the ability to locally release neuroactive substances that have been suggested to promote diabetes pathogenesis. We discuss recent findings on islet innervation, the connections of the islet with the brain, and the role islet innervation plays during the progression of diabetes.

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Introduction

Glucose homeostasis is a process that stabilizes blood glucose levels in response to changes in internal and external conditions. Central to glucose homeostasis is the secretion of the hormones insulin and glucagon from the endocrine pancreas, the islets of Langerhans. These hormones prevent raises and drops in blood glucose levels (hyperglycemia and hypoglycemia, respectively) even under extreme conditions such as prolonged fasting or exercise. A disturbance of glucose homeostasis is life threatening, and deficient insulin secretion causes diabetes.

The islet of Langerhans, however, does not achieve glucose homeostasis alone. It is part of a complex set of interacting organs that must operate in a coordinated fashion. Islet hormones are delivered directly to the liver where they regulate glucose production. Influenced by islet signals, it is the liver that buffers the entry of glucose from the portal vein into the systemic circulation and minimizes plasma glucose fluctuations. On the other hand, islets are exposed to humoral factors, such as circulating autonomic hormones (e.g. adrenaline) or incretins derived from the gastrointestinal tract that modulate glucose-induced insulin and glucagon secretion. Given its central role as a control system, it is not surprising that the brain also helps regulate islet hormone secretion by recruiting the autonomic nervous system.

The autonomic nervous system works subconsciously and controls many functions of visceral organs. It operates throughout the body to adapt organ function to changes in the internal and external environment. The autonomic nervous system integrates visceral, somatic and special sensory input in neural centers located mainly in the brainstem and the hypothalamus. It operates in part through visceral reflexes in which sensory signals from visceral organs activate central autonomic regions that in turn send back subconscious reflex responses to visceral organs to change their activities. The efferent autonomic signals are transmitted to the organs through the parasympathetic and sympathetic nervous systems.

Although the basic principles are clear, we know relatively little about autonomic control of particular organs such as the pancreatic islet. This is likely because of the diffuse nature of the autonomic nervous system. For instance, most parasympathetic axons travel in the vagus nerves that pass and innervate the entire thoracic and abdominal regions of the body. This makes experimental manipulation of particular pathways extremely difficult. Moreover, recording specific physiological activity in axons going to or leaving the pancreatic islet is almost impossible. In addition, the physiological processes involved are subconscious. As a result, it is difficult to estimate how much information flows through the neural circuits regulating islet function. We barely have a notion about the magnitude and quality of the information the autonomic nervous system exchanges with the pancreatic islet.

In this chapter, we discuss recent progress made on neural control of pancreatic islet function keeping in mind these major limitations. We address three questions [1]: What are the central neural circuits projecting to and from the pancreatic islet? [2] How is the pancreatic islet innervated? and [3] What is the role of innervation during the progression of diabetes? We describe hurdles investigators commonly encounter, and propose solutions to elucidate the neural circuits associated with islet function.

Central neural connections to the pancreatic islet

Before discussing the neural circuits associated with the pancreatic islet, it is important to mention that the pancreatic islet is not controlled entirely by the autonomic nervous system. Indeed, in patients that undergo vagotomy and thus have denervated islets, glucose homeostasis is barely affected [1–4]. The pancreatic islet is self-sufficient as it has the necessary machinery to detect changes in blood glucose levels and to produce an adequate hormone response. Unlike other organs, which have total neural control, regulation of pancreatic islets by autonomic nervous input is better described as adaptive control. Here, the brain uses a principle called feed-forward control in which the brain sends signals to the pancreatic islet before changes in blood glucose levels occur. The autonomic input to the islet thus helps adjust glucose homeostasis to food intake or stress [5,6]. For instance, the mere presence of food in the mouth results in an increase in insulin secretion during the so-called cephalic