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COMMENTARY

Islet nerves in focus—defining their neurobiological and clinical role

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Abstract Although it is well established that the pancreatic islets are innervated by autonomic nerves, the detailed islet innervation pattern is still unclear. In this issue of *Diabetologia* (DOI: 10.1007/s00125-012-2699-6) novel details of the islet neuroanatomy and its plasticity in experimental diabetes are described. By using a 3-dimensional (3-D) imaging technique, it has been shown that, in islets from normal mice, sympathetic nerves mainly form a neurovascular complex in addition to innervating peripherally located islet alpha cells. There are also pronounced changes in islet neuroanatomy in experimental diabetes. These findings suggest novel neural–islet regulatory mechanisms as well as neural involvement in the development of diabetes, and therefore advance both basic and clinical knowledge of islet neurobiology.

Keywords Autonomic nerves · Islets · Neurobiology · NOD mice · Peripheral nerves · Streptozotocin-induced diabetes · Sympathetic nerves

Abbreviations
3-D 3-Dimensional
STZ Streptozotocin

Secretion of insulin and glucagon from the beta and alpha cells in the pancreatic islets is of key importance for glucose homeostasis, and both type 1 and type 2 diabetes develop as a result of islet dysfunction. Establishing the regulation and mechanism of insulin and glucagon secretion is therefore of paramount biological and clinical importance. Most scientific effort to understand the extracellular regulation of islet hormone secretion has been concentrated on circulating metabolites, such as glucose, fatty acids and amino acids, or on other hormones, such as the incretin hormones. However, it is also important to focus on the autonomic nerves innervating the pancreatic islets.

That the pancreatic islets are richly innervated has been known since the historical work of Paul Langerhans in the 1860s. Today we know that sympathetic, parasympathetic and sensory nerves innervate the islets (Fig. 1) and that the islet autonomic nerves affect both insulin and glucagon secretion [1]. Parasympathetic nerves stimulate insulin secretion, sympathetic nerves inhibit insulin secretion, and both parasympathetic and sympathetic nerves stimulate glucagon secretion. These effects are mediated by the classical neurotransmitters (acetylcholine in parasympathetic nerves and noradrenaline [norepinephrine] in sympathetic nerves) together with various islet neuropeptides [1, 2].

The classical view is that the neurotransmitters are released from the intra-islet nerves when the nerves are activated. They then diffuse a short distance to the islet beta and alpha cells to activate specific receptors resulting in stimulation or inhibition of islet hormone secretion. It is thought that the parasympathetic nerves mediate the early phases of insulin secretion, including the cephalic phase (i.e. the insulin secretion that occurs during anticipation of a meal) [3]. It is also thought that the sympathetic nerves mediate the islet hormone responses to hypoglycaemia, which involves both the glucagon counter-regulatory response to hypoglycaemia [4] and the inhibition of insulin secretion during hypoglycaemia; these two mechanisms may be achieved by cell-specific expression of adrenoceptors: β-adrenoceptors expressed mainly in alpha cells and α_2-adrenoceptors expressed mainly in beta cells [5].

Despite the advances in our knowledge of islet neurobiology, there are several questions that remain to be resolved

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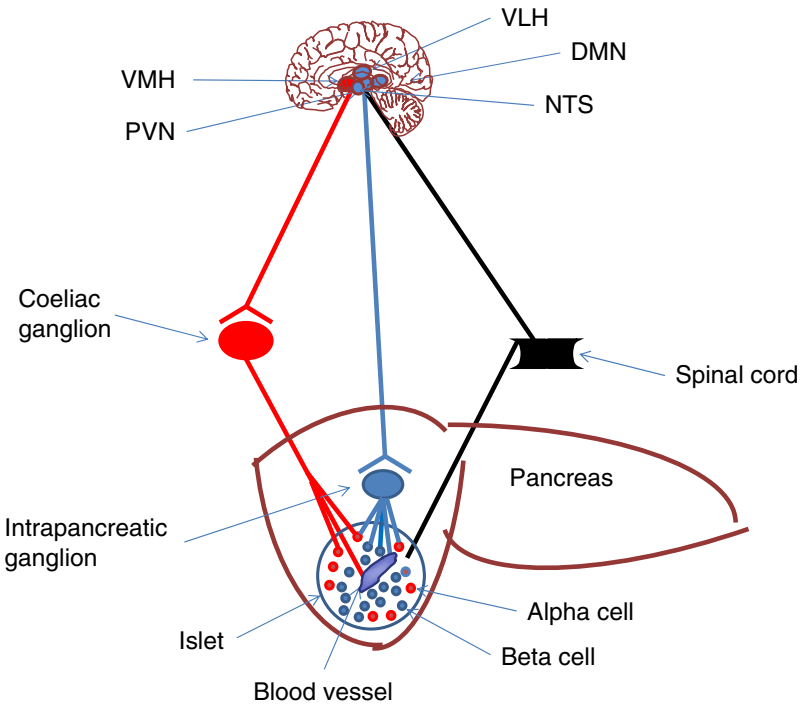

Fig. 1 Schematic view of the brain–islet innervation pattern with the three branches of the autonomic nervous system. Sympathetic nerves (in red) pass from the brain to the coeliac or paravertebral ganglia (shown as a red circle); the postganglionic sympathetic nerves then pass to the islets. Parasympathetic nerves (in blue) pass, mainly through the vagus nerve, to intrapancreatic ganglia (shown as a blue circle); the postganglionic parasympathetic nerves then pass to the islets. Finally, sensory nerves (in black) pass from the islets to the dorsal root of the spinal cord (shown in black) from which postganglionic nerves pass centrally. Some sensory nerves also pass through the vagus nerve (not shown). As demonstrated in the new studies by Chiu et al [6] and Rodriguez-Diaz et al [8] in mouse islets, sympathetic nerves end close to islet vessels and islet alpha cells (in red) whereas islet beta cells (in blue) do not receive such input; on the other hand, as demonstrated by Rodriguez-Diaz et al [8], islet parasympathetic nerves end close to islet vessels, beta cells and alpha cells; islet sensory nerve connections have not yet been established. The figure also schematically illustrates that several brain centres control the autonomic nerves in a complex pattern [10]. Although still unresolved in detail, the ventromedial hypothalamus (VMH) is important for sympathetic nerves whereas the ventrolateral hypothalamus (VLH), the paraventricular nucleus (PVN), the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus (DMN) are important for parasympathetic nerves. The central connection for sensory nerves important in islet function is still unclear

for a full understanding. Important unresolved issues are the detailed islet innervation pattern, the functional relevance and physiology of the nerves, the potential relevance of the islet nerves for islet dysfunction in diabetes, and the potential of the islet nerves and neurotransmitters as targets for diabetes therapy. One reason for the delay in resolving these and other important issues is the lack of proper tools for investigating islet neuroanatomy and neurophysiology, particularly in humans.

In this issue of *Diabetologia*, an elegant study by Y.-C. Chiu and collaborators describes a novel experimental tool for investigating islet neuroanatomy [6]. The authors took advantage of their recently developed penetrative imaging technique based on the preparation of transparent tissues (‘optical clearing’) for 3-D imaging of the gut with the enteric nervous system [7], and translated this technique to islet studies in mice. Their main finding is that, in the normal mouse islet, there is a sympathetic neurovascular complex with pronounced perivascular innervation and innervation of the vessel smooth muscle. There are also sympathetic nerves in close contact with the peripherally located glucagon-producing alpha cells, whereas there is no apparent direct innervation of the centrally located beta cells. Therefore, the pattern of sympathetic nerve innervation in a normal mouse islet seems to be more complex and heterogenous than inferred from previous studies.

These results suggest that sympathetic nerves primarily innervate the islet vasculature and the alpha cells in normal mouse islets. This may have implications for understanding regulatory mechanisms, and three different types of regulation are anticipated. One mechanism is the classical direct activation of islet endocrine cells, which then translates primarily into the stimulation of glucagon secretion by alpha cells. A second mechanism may be executed through the release of neurotransmitters into the afferent blood vessels; the neurotransmitters then pass downstream in the circulation to affect islet beta and alpha cells. Finally, a third mechanism could involve the reduction of blood flow

through a constriction effect; this in turn may affect islet hormone secretion.

A limitation of the study is that it was only undertaken in mouse islets. It is now, therefore, important to repeat the studies using this technique in normal human islets, not least against the background of another recent elegant study, by Rodriguez-Diaz et al, on the innervation pattern in human islets [8]. That study visualised axons in three dimensions and quantified axonal densities and contacts within pancreatic islets, demonstrating species differences in islet innervation patterns, and specifically showed that, in human islets, sympathetic nerves mainly innervate the islet blood vessels, rather than the endocrine cells.

Chiu et al [6] also examined whether islet innervation is altered in experimental diabetes in the mouse. In streptozotocin (STZ)-induced diabetes, which is caused by the toxic action of STZ on beta cells, they found that intra-islet axons are particularly prominent, with a twofold increase in nerve density compared with islets from normal mice. This sympathetic hyperinnervation may be a response to beta cell destruction, and may worsen the beta cell destruction by inhibiting beta cell function and reducing islet blood flow through vasoconstriction.

The authors also examined NOD mice, which have a condition similar to type 1 diabetes with insulitis caused by lymphocytic infiltration resulting in beta cell destruction. They found that, in the early stages of diabetes in NOD mice, the insulitis is patchy and the lymphocytic infiltration develops only in certain domains of the islets, leaving an apparently normal part intact. They demonstrated that, in the transition zone between these two islet domains, there is a prominent remodelling of the sympathetic axons with sympathetic hyperinnervation. In contrast, in areas with manifest insulitis, sympathetic innervation is reduced, which is similar to the previously demonstrated reduced sympathetic innervation in insulitis in NOD mice [9]. Altogether, there thus seem to be an important plasticity and remodelling of the islet sympathetic innervation in experimental diabetes.

For the future, it is important, in addition to examining normal human islets, to further examine the impact of neural plasticity on islet function during the development of various forms of diabetes in humans. Moreover, the impact of sympathetic hyperinnervation in diabetic islets on hypersecretion of glucagon and beta cell dysfunction, and the relation between sympathetic nerves and insulitis in type 1 diabetes need to be explored in more detail. Finally, it is also of great interest to explore the sympathetic nerve–islet complex as a potential target for the treatment of diabetes, for example by alpha adrenoceptor antagonism to protect the progressive islet dysfunction due to enhanced sympathetic innervation. Islet neurobiology has therefore again become a focus of islet research, and research on islet nerves may pay off both in basic and clinical science.

Duality of interest The author declares that there is no duality of interest associated with this manuscript.

Contribution statement The author conceived, drafted, wrote and approved this commentary.

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