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Mini-review

Autonomic nervous system and pancreatic islet blood flow

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ABSTRACT

Vascularization and innervation of the islet of Langerhans are highly interconnected and are critical for intercellular and intertissular communication. They are both involved in the control of islet blood flow which has been shown to have an important role in the control of endocine secretion. Both parameters are disturbed during the course of metabolic pathologies and particularly diabetes. A better understanding of these mechanisms has and will greatly benefit from the rapidly-emerging technologies particularly *in vivo* imaging enabling to study both anatomy and functions of the islet.

1. Introduction

Since the original observation of Langerhans, numerous studies have confirmed a rich and dense innervation of endocrine pancreas. Sympathetic (splanchnic nerve) and parasympathetic (vagus nerve) fibres are directly connected to the islets of Langerhans an in such they modulate hormonal secretion and particularly insulin secretion [1–3].

The autonomic nervous system can also participate to the control of insulin secretion indirectly via the regulation of pancreatic and islet blood flow [4]. This is achieved via 1) the delivery of nutrients and/or other circulating factors involved in the regulation of insulin secretion and 2) the dispersion of insulin itself in the blood stream.

The aim of the present paper is to briefly review data obtained during the last years focusing on both innervation and vascularization of the islet and the role of islet blood flow in insulin secretion in normal and pathological conditions, thanks to new techniques especially imaging one.

2. Islet innervation and vascularization

Vascularization and innervation of the endocrine pancreas are highly entangled and interconnected and are critical for intercellular and intertissular communication. Although the main effect of the nervous system is the regulation of pancreatic hormones secretion, an important role of parasympathetic activity is the stimulation of endocrine cell proliferation whereas recent data demonstrate the involvement of sympathetic innervation in the islet architecture [5–7].

Till recently due to the particular neuroanatomy, absence of classical synapses to the endocrine cells, small size of the axons and their terminal, the description of the innervation and vascularization pattern of the islet was not totally sure. By using and combining various techniques different groups have brought new information on the fine architecture of innervation and vascularization of the islets of Langerhans both in rodents and human beings. These techniques included fluorescent imaging to label pancreatic blood vessels, staining to reveal islet innervation and microstructures, optical clearing to allow 3D confocal microscopy to visualize the sympathetic neuro-vasculature complex [7–11].

2.1. Microvasculature

The blood supply of the endocrine pancreas is provided by one to five arterioles by islet. Endocrine cells are closely associated to the vasculature. In situ imaging reveals a highly dense and tortuous vascularization inside the islets of Langerhans [12] (Fig. 1). The density of vasculature is around 17%, i.e. four times more than the exocrine part. The endocrine pancreas, although representing only 1% of pancreatic mass, receives 5–15% of the organ's blood supply [12,13]. The fenestrated capillaries form a dense network that looks

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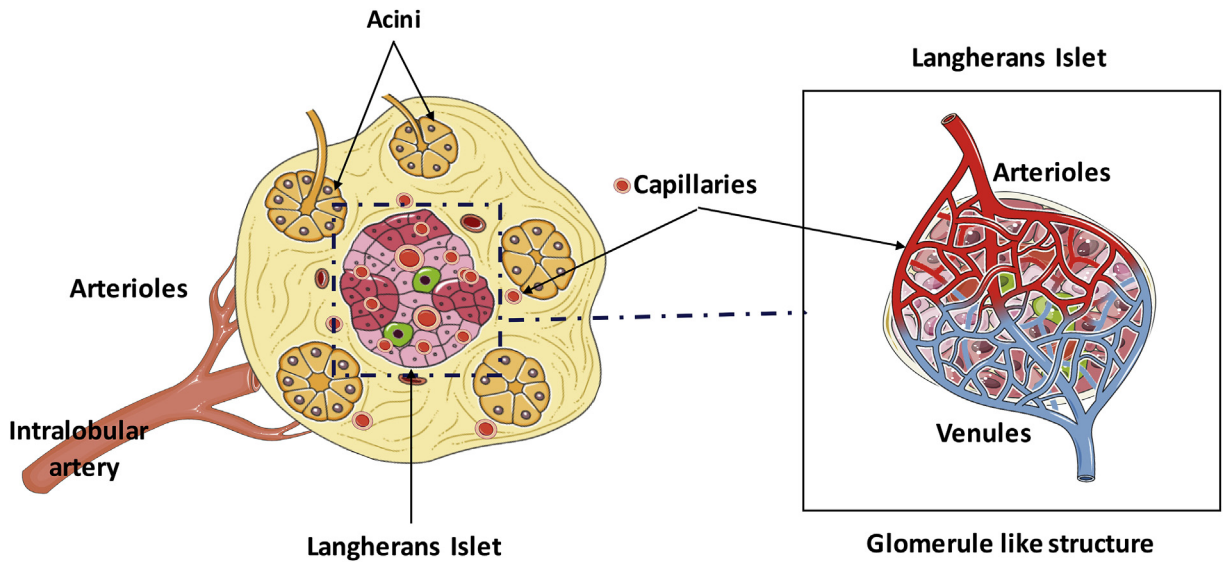

Fig. 1. Pancreas and islet vascularization.

like that of glomeruli. They represent around 10% of the whole volume. The number of capillaries is approximately 10 times higher than in the exocrine part of the organ [14–17].

Three theories have been proposed on blood specific islet microcirculation pattern in mice [see 14, 16]. (i) from periphery to center of the islet; (ii) from center to periphery or (iii) from one pole of the islet to the other [18,19]. Although the first hypothesis received experimental support both in mice and humans this subject is still a matter of debates [17–23]. Altogether, this specific architecture facilitates the supply of nutrient and hormonal signals across the capillary endothelium as well as the dispersion of the endocrine peptides in the general circulation.

2.2. Innervation

Autonomic nervous system axons travel to the islet mainly through the vasculature stalk particularly the pancreatic artery [16] (see Fig. 2).

Presynaptic fibres of the parasympathetic system make synapses inside the pancreas itself. In the islets, postganglionic axons reach all types of cells in the mouse [24]. Acetylcholine that is the neurotransmitter liberated by the post-synaptic fibres when the vagus nerve is activated stimulates insulin secretion after binding to muscarinic receptor. Parasympathetic activation increases the release of glucagon, somatostatin, and pancreatic polypeptide although the relative contributions of acetylcholine and neuropeptides to these effects remain to be determined. By contrast, few parasympathetic axons terminate in the human endocrine tissue but beta and delta cells respond to stimulation with acetylcholine, whereas alpha cells are poorly responsive to this neurotransmitter [24,25]. However, this does not rule out the possibility that human alpha cells might respond to other neuropeptides released from parasympathetic fibres [2].

Presynaptic fibres of the splanchnic nerve make synapses at the level of the coeliac ganglia with noradrenergic fibres. Recent observations showed peri-islet contacts of sympathetic endings with alpha but not beta cells and fibres around the adjacent arterioles. Additionally, they innervate vessel smooth muscle cells and the perivascular space, forming the so called sympathetic neurovascular complex [26,27]. This particular neuroanatomy suggests both a direct effect on endocrine cells involved in glucagon secretion and an indirect, via controlling blood flow to the islet more probably involved in the regulation of insulin secretion via that of blood flow. Indeed, the stimulation of the splanchnic nerve results in an inhibition of insulin secretion after binding of norepinephrine to adrenoceptor of the α-2 subtype. Furthermore, sympathetic nervous activity inhibits the release of somatostatin, the effects being rather contradictory for pancreatic polypeptide.

3. Islet blood flow and influence of the ANS

Islet blood flow is one of the important component of islet activity as assumed and demonstrated by the pioneer observation of Claes Hellerstrom in the sixties and its followers particularly Leif Jansson in the eighties [28,29]. The techniques used to measure islet blood flow evolved over the years. Starting with quantification by the number of erythrocytes in the islets, flow deposition coupled or not with radiological techniques and since some years various and more and more sophisticated imaging techniques allowing now quantitative assessment of blood flow in whole islets in situ [12,17,28–30].

The islets is overperfused in comparison of the exocrine pancreas [14,17]. On the basis of observations showing the presence of a subgroup of highly perfused islet, it has been proposed that islets receiving lower blood flow could constitute a reserve mobilized upon demand (see Jansson [17]). Furthermore the islet blood flow and its regulation are independent of that of the exocrine part. This regulation is mainly under the control of hormones (somatostatin, glucagon like peptide 1, pancreatic polypeptide, glucagon, cholecystokinin), mediators produced in the islet itself (NO and ATP) nutrients (mainly glucose, lipids) and the autonomic nervous system [16,17,31,32]. As mentioned above the nerves endings are very often observed at the proximity of the microvessels and exert their effect directly on smooth muscle cells [26,27,31,32].

It has been shown in rats that islet blood flow is increased after a glucose load and that increase is under the influence of both parasympathetic and sympathetic activity. Indeed, this enhanced islet blood flow is abolished by vagotomy and by previous injection of alpha-2 adrenergic receptor agonist [4,33–35]. Treatment with a specific ß3-agonist induces a market increase in islet blood flow which was abolished by pre-treatment with bupranolol (ß1,ß2,ß3 antagonist). An acute increase in blood lipids induces an

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