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Intrinsic Regulation of the Blood Flow to the Endocrine and Exocrine Parts of the Rat Pancreas

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ABSTRACT

To evaluate possible differences in the local regulation of blood flow between the endocrine and exocrine pancreatic parenchyma, the blood perfusion of the pancreas and the pancreatic islets has been measured after a 90-second period of anoxia or a 5-min period of increased venous pressure.

After anoxia, caused by interruption of arterial blood flow, there was a significant increase ($P<0.01$) in islet blood flow (IBF) while whole pancreatic blood flow (PBF) remained unchanged. Arterial occlusion also increased the serum glucose ($P<0.01$) and serum insulin concentrations ($P<0.001$). Vagotomy prevented the increase in IBF but did not affect the increase in serum glucose or serum insulin concentration, which suggests that the increase in IBF was due to the increased serum glucose concentration. An increased venous pressure in the portal vein did not affect IBF, PBF, serum glucose or serum insulin concentrations.

It is concluded that, in the rat pancreas, the local control of PBF and IBF is of minor importance in the regulation of blood flow.

INTRODUCTION

The microvasculature is the site of control of tissue blood perfusion, blood-tissue exchanges and ultimately the tissue blood volume. To achieve fine tuning of the regulation of these functions the vascular bed is not only under the control of nervous and humoral signals, but is also endowed with mechanisms with which it can independently regulate its own microcirculation (4). These intrinsic control systems allow the microcirculation of each organ to be adapted to the specific needs of the tissue it subserves.

It now seems clear that local regulation of the microcirculation may be effected by two different mechanisms. In one of these the tension of the vascular wall is the determinant for the degree of contraction of the vascular smooth muscle cells (1,2,11,14). In the other, a feedback linkage seems to exist between cell metabolism and the local blood flow. Either oxygen itself or, more probably, metabolites associated with parenchymal oxidative processes, e.g. adenosine or potassium, represent factors which may control the microcirculation (3). It also seems likely that the relative importance of each of these local regulatory mechanisms is different in different vascular beds.

We have previously demonstrated that the regulation of the blood flow differs between the endocrine and exocrine parts of the pancreas (5,7). This is particularly well illustrated by the effects of D-glucose, which produces a preferential increase in the blood flow to the endocrine part (7). Glucose regulation of islet blood flow seems, however, to be governed by a reflex arc via the central nervous system, rather than by any local effects of glucose on the pancreas (10). In order to elucidate the possible existence of local mechanisms for the regulation of islet microcirculation, we have studied the islet blood perfusion and the flow distribution in the pancreas after temporary arterial occlusion or during venous hypertension. To exclude glucose-effects, mediated via the central nervous system, similar experiments were performed on animals which had been vagotomized and/or deprived of pancreatic sympathetic innervation.

MATERIALS AND METHODS

Male Sprague - Dawley rats weighing approximately 350 g with free access to tap water and pelleted food (Ewos Type R3; Ewos, Anticimex, Södertälje, Sweden) were used in all experiments. The animals were anaesthetized with thiobutabarbital sodium (Inactin Byk^{R}; Byk Gulden, Konstanz, FRG; 130 mg/kg BW, IP) and heparinized (Heparin 5 000 IU/ml; Lövens Läkemedel, Malmö, Sweden; 200 IU, IV). Polyethylene catheters (inner diameter about 0.30 mm) were placed into the left ventricle of the heart (via the right carotid artery) and into the lower part of the abdominal aorta. The mean arterial blood pressure was recorded throughout the experiments. The abdominal cavity was opened by a V-shaped incision, with the point downwards, and the abdominal organs exposed. The experiments then proceeded according to one of the following protocols.

Measurements of pancreatic and islet blood flow after acute pancreatic ischemia

A total of 13 animals were subjected to a bilateral, cervical vagotomy approximately 1 cm above the upper thoracic aperture, while a total of 16 animals were sham-operated and left with both vagus nerves intact (10). In all animals the intestines were subsequently moved out of the abdominal cavity to the right side of the animal and wrapped in wet and warm compresses. This manouvre gave free access to the abdominal aorta, which was gently rubbed with dry gauze to remove the surrounding connective tissue and to visualize the origin of the coeliac artery and the superior mesenteric artery. In order to cut the perivascular nerves, the adventitia of these vessels was incised to the external muscle layer. The animals were then allowed to equilibrate for 15 min or until the blood pressure stabilized . The flow in both these arteries was simultaneously stopped for 90 s (7 vagotomized and 8 sham-operated animals) by compressing them from the outside with tweezers. Control animals (6 vagotomized and 8 sham-operated animals) were treated identically except that the tweezers were held loosely around the arteries without compressing them. After release of the arterial occlusion the islet and whole pancreatic blood flows were measured using a microsphere technique, as previously described in detail (9). Briefly, 15 s after restoring the arterial flow through the pancreas, 1.5×10^5 non-radioactive microspheres (diameter 10.2 ± 0.6 μm , New England Nuclear, Boston, MA, USA) were injected via the catheter into the left ventricle of the heart. An arterial reference blood sample was withdrawn from the abdominal aorta into a preweighed test tube starting 5 s before the microsphere injection and continuing for 55 s after the injection. The sample were weighed and 0.3 ml (1,500 IU) of heparin added before the sample was stored at +4°C to await further processing (see below). Immediately after the injection of the microspheres arterial blood samples (200 μl) were collected and later analyzed for glucose content using a glucose oxidase-technique (Glucose Analyzer 2; Beckman, Fullerton, CA, USA) and for insulin content by radioimmunoassay (5).

After the blood samples had been collected the pancreas was removed and treated with a freezing technique (7) to enable visualization of the pancreatic islets and the microspheres. The same procedure was used to count the number of microspheres in the adrenal glands, while the microsphere contents of the arterial reference samples were determined

by transferring the samples to glass microfiber filters with a pore size less than 10 μm, and counting the number of microspheres in transmitted light.

The blood flow values were then calculated according to the formula

$$Q_{org} = \frac{N_{org} \times Q_{ref}}{N_{ref}}$$

where Q_{org} = organ blood flow (ml/min); Q_{ref} = withdrawal rate of the reference sample (ml/min); N_{org} = number of microspheres in the organ; N_{ref}= number of microspheres in the reference sample.

The numbers of microspheres in the adrenal glands were used to confirm an adequate mixing of microspheres in the circulation. When an animal showed a difference in microsphere content of more than 10 % between the two adrenals it was excluded (n=3) from the study.

Measurements of pancreatic and islet blood flow during increased venous pressure

In these experiments no vagotomy was performed, but all perivascular nerves to the pancreas were cut at the origin of the pancreatic arteries, as above. The duodenum was then gently lifted and rotated to the left to expose the distal end of the portal vein immediately before its entrance into the liver. A ligature was loosely passed around the vein and the animals were allowed to stabilize for 15 min. In 7 experimental animals the ligature was then tightened so that the portal blood pressure increased from 2 to approximately 10 mm Hg. In the 8 control animals the ligature was placed around the vein but was not tightened. Five minutes after the increase in the portal venous blood pressure the whole pancreatic and islet blood flows were measured as described above.

Statistical computations

Values are expressed as means ± SEM. Probabilities (P) of significant statistical differences between groups were estimated by Student's two-tailed t-test.

TABLE 1. Concentrations of glucose and insulin in the serum, and rates of pancreatic and islet blood flow in non-vagotomized and vagotomized rats, with an otherwise denervated pancreas, after a 90 sec interruption of pancreatic arterial blood flow.

	Non-vagotomized animals		Vagotomized animals	
	Control animals (8)	Experimental animals (8)	Control animals (6)	Experimental animals (7)
Serum glucose concentration (mmol/l)	11.8 ± 0.4	13.6 ± 0.4**	13.0 ± 0.7	14.0 ± 0.4
Serum insulin concentration (ng/ml)	2.38 ± 0.39	7.51 ± 0.92***	2.18 ± 0.84	6.08 ± 1.01**
Pancreatic blood flow (ml/min x g pancreas)	0.64 ± 0.10	0.77 ± 0.09	0.45 ± 0.05	0.55 ± 0.09
Islet blood flow (μg/min x g pancreas)	81 ± 13	152 ± 13***	87 ± 14	129 ± 22
Islet blood flow (% of pancreatic blood flow)	12.7 ± 1.1	20.9 ± 1.9**	20.3 ± 3.0	24.9 ± 2.9

Values are expressed as means ± SEM. The number of experiments in each group is given within parentheses.

** denotes $P < 0.01$ and *** $P < 0.001$ vs. the corresponding control animals.

RESULTS

All animals maintained a stable circulation throughout the experiments. The vagotomized animals had significantly higher blood pressure values (125 ± 3 mm Hg) than the sham--operated control animals (102 ± 3 mm Hg; $P<0.05$) while the other groups had values similar to those of the control group (data not shown).

Blood flow after acute pancreatic ischemia

After interruption of pancreatic arterial blood flow for 90 sec the serum glucose and the serum insulin concentrations were significantly higher both in the vagotomized and non-vagotomized experimental groups compared to those of the corresponding control animals (Table 1).

Whole pancreatic blood flow did not differ from that of the control animals in any of the groups (Table 1). Islet blood flow, however, was significantly increased in the non-vagotomized experimental animals and this was the case when the islet blood flow was expressed as a fraction of the whole pancreatic blood flow (fIBF) (Table 1). In the vagotomized animals, however, no increase in either IBF or fIBF could be observed (Table 1).

Blood flow during increased venous pressure

No significant differences in serum glucose or serum insulin concentrations between the experimental and the control groups ($P>0.05$) could be observed (data not shown). With respect to the blood flow values, neither the whole pancreatic blood flow nor the fractional islet blood flow were significantly changed after venous hypertension (Table 2).

DISCUSSION

Studies on the intrinsic regulation of the pancreatic blood circulation are scarce in contrast to that of the other gastro-intestinal organs. It has, however, been demonstrated by Kvietys et al (12) that changes in pancreatic capillary exchange capacity could be dissociated from vascular transmural pressure which would indicate that metabolic, rather than myogenic factors, are important for the regulation of capillary exchange

TABLE 2

Whole pancreatic and islet blood flow 5 min after an increase of the portal venous pressure from 2 to 10 mm Hg in the rat.

	Control animals (8)	Experimental animals (7)
Pancreatic blood flow (ml/min x g pancreas)	1.05 ± 0.20	0.61 ± 0.09
Islet blood flow (µl/min x g pancreas)	104 ± 19	63 ± 7
Islet blood flow (% of pancreatic blood flow)	10.4 ± 0.7	10.9 ± 1.4

All values are expressed as means ± SEM. The number of experiments in each group is given within parentheses.

(12). However, in the same study support was also found for the presence of myogenic vasoregulatory mechanisms. Although the latter finding could not be confirmed in the present study, it should be noted that Kvietys et al (12) used a totally isolated, blood--perfused dog pancreas. Since the aim of the present study was to investigate differences in regulation between the endocrine and exocrine parenchyma we did not disconnect the other splanchnic organs from the mesenteric circulation, which makes redistribution to these organs possible. We have also used the pancreas of the rat, which differs in several respects from that of the dog.

Both PBF and IBF appeared elevated in the control animals of the group exposed to venous hypertension. This was presumably caused by the more extensive manipulation of the pancreas in these experiments. Since no significant difference in fIBF could be observed the endocrine and the exocrine pancreas were affected similarly. It is also likely that both these compartments have a very low degree of myogenic reactivity in their vasculature since a decrease in these flows would otherwise be expected.

Interruption of arterial blood flow caused a reactive hyperemia in the islets but not in the whole pancreas. The latter finding is in contrast to the findings by Kvietys et al. (12) but may be due to the differences in experimental designs mentioned above. It is of interest in this context that a similar dissociation between IBF and PBF can also be seen after administration of glucose (8). It is indeed likely that the stimulation of IBF in this study was due to an increase in serum glucose concentration since vagotomy, which is known to inhibit this response (10), blocked the reactive hyperemia of the islets. It should be noted that fIBF in vagotomized control animals was very high (approximately 20%) compared to that of the corresponding non-vagotomized animals. This contrast to our previous findings (10) but it is likely that this effect is also due to manipulation of the pancreas, although the exact mechanism remains unknown.

Acute pancreatic ischemia elevated the serum insulin concentrations in both non-vagotomized and vagotomized animals. The reason for this is unknown but may reflect a continuing insulin secretion in spite of the interrupted blood flow, followed by a washout effect when blood flow is restored.

Altogether these findings indicate that, in the rat, there is no metabolic regulation of the blood flow to the endocrine and exocrine parenchyma of the pancreas. The lack

of myogenic and metabolic regulation in the islets and in the acini of the pancreas are in accord with the findings that D-glucose preferentially increases IBF via extra-pancreatic mechanisms (10).

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