Lack of compensatory increase in islet blood flow and islet mass in GK rats following 60% partial pancreatectomy

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Abstract

The effects of a 60% partial pancreatectomy were studied in hyperglycemic GK (Goto–Kakizaki) rats. Partial pancreatectomy or a sham operation was performed on 12-week-old female Wistar rats, GK rats or hybrids between male GK rats and female Wistar rats. Measurements of pancreatic blood flow and islet blood flow were performed by a microsphere technique 2 weeks after surgery. Glucose tolerance was decreased in hybrid compared with Wistar rats, and in GK rats compared with both hybrid and Wistar rats before surgery. Partial pancreatectomy induced minor changes in glucose tolerance. Wistar rats had a decreased islet mass following partial pancreatectomy. Both hybrid

and GK rats showed a significant decrease in relative islet volume, but only GK rats in total islet mass, compared with Wistar rats 2 weeks after surgery. Pancreatic blood flow and islet blood flow did not significantly differ between sham-operated Wistar, hybrid or GK rats. After partial pancreatectomy, islet blood flow in relation to islet mass increased 3-fold in Wistar rats and 2-fold in hybrid rats. In contrast, GK rats showed no increase in islet blood flow following partial pancreatectomy. It is concluded that compensatory mechanisms after partial pancreatectomy are operating less efficiently in hybrid and GK rats.

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Introduction

The regulation of islet blood flow is distinct from that of the exocrine pancreatic blood flow. A number of possibly interdependent neural and local factors have been suggested to influence islet blood perfusion (Jansson 1994, Brunnicardi *et al.* 1996). Our earlier investigations have pointed to an association between increased functional load on the islets and increased islet blood flow in different experimental systems, namely 48 h continuous high-glucose load, partial pancreatectomy and diet-induced and inherited obesity (Jansson & Sandler 1989, Styrd *et al.* 1992, Jansson 1994, Svensson *et al.* 1996). Although the mechanisms underlying these aberrations remain obscure, it could be envisaged that increased islet blood flow is a compensatory mechanism that may contribute to increased hormone output.

The GK (Goto–Kakizaki) rat is a non-obese animal model of hereditary non-insulin-dependent diabetes mellitus with mild hyperglycemia, initially derived from normal Wistar rats by repeatedly selecting animals with slightly aberrant glucose-tolerance tests for breeding (Goto

& Kakizaki 1981, Kimura *et al.* 1982, Suzuki & Goto 1987). The exact mechanism behind the impaired glucose-induced insulin release in the GK rat is unclear. However, it seems to be related to abnormalities in glucose metabolism and stimulus-secretion coupling within the β -cells (Giroix *et al.* 1993, Östenson *et al.* 1993a, 1993b, Hughes *et al.* 1994, MacDonald *et al.* 1996, Ling *et al.* 1998). F₁ hybrids between GK rats and Wistar rats are glucose-intolerant with impaired glucose-stimulated insulin release (Abdel-Halim *et al.* 1994).

We have previously shown increased islet and pancreatic blood flow in normoglycemic rats following a 60% pancreatectomy (Jansson & Sandler 1989, 1991). This pancreatectomy procedure includes removal of the splenic part (tail region) of the pancreas, leaving the parts attached to the duodenum and stomach (duodenal region) intact, i.e. the regeneration of pancreatic tissue is observed exclusively in the duodenal region. The present study was designed to investigate the effects on islet mass and pancreatic and islet blood flow by a further increase in functional load on hyperglycemic GK and hybrid rats achieved by a similar reduction in β -cell mass. Furthermore,

we addressed the issue of possible heterogeneity in islet mass and blood perfusion between the duodenal and splenic regions of the pancreas, to exclude regional contributions to the observed differences.

Materials and Methods

Animals

Female Wistar rats were purchased from B & K Universal AB (Sollentuna, Sweden). Female GK rats and F₁ hybrids, which were offspring of female Wistar and male GK rats, were from the Stockholm GK colony (Department of Endocrinology, Karolinska Hospital, Stockholm, Sweden), established in 1989 with breeding couples from Tohoku University School of Medicine, Sendai, Japan. Animals were 12 weeks old at the start of the experiment. All animals had free access to tap water and pelleted food, with the exception of a 12 h fast preceding the glucose-tolerance tests (see below). All experiments were approved by the local animal ethics committee.

Intraperitoneal glucose-tolerance test (*i.p.GTT*)

An *i.p.GTT* was performed 2 days before partial pancreatectomy and again 2 days before the blood-flow measurements. Following an overnight fast, the animals were injected intraperitoneally with a 30% (w/v) D-glucose solution (2 g glucose/kg body weight). Blood glucose concentrations were measured with test reagent strips (ExacTech; Baxter Travenol, Deerfield, IL, USA) from blood drawn from the cut tip of the tail immediately before and 10, 30, 60 and 120 min after glucose administration.

Partial pancreatectomy

The animals were anaesthetized with an intraperitoneal injection of ekviticine (a combination of pentobarbital and chloral hydrate). The splenic region of the pancreas, i.e. all parts of the pancreas unattached to the stomach or duodenum, was carefully dissected with cotton-tip applicators and removed. Any bleeding was controlled by diathermy. In previous experiments (Jansson & Sandler 1989), the part of the pancreas removed by this procedure has been shown to constitute approximately 60% of the whole gland. In sham-operated animals, the splenic portion was mobilized gently using cotton-tip applicators but left in place.

Measurements of blood flow

This procedure has been described in detail in previous publications (see Jansson & Hellerström 1983). Rats were anaesthetized with an intraperitoneal injection of thiobutabarbital (Inactin; Research Biochemicals, Natick, MA, USA; 120 mg/kg body weight), heparinized and

placed on an operating table maintained at body temperature (38 °C). Polyethylene catheters were inserted into the ascending aorta via the right carotid artery and into the left femoral artery. The aortic catheter was connected to a pressure transducer (PDCR 75/1; Druck, Groby, Leicestershire, UK) to monitor mean arterial blood pressure. After mean arterial blood pressure had been stable for at least 10 min, $(1.5-3.0) \times 10^5$ non-radioactive microspheres (diameter, 11 µm; NEN-Trac; DuPont Pharmaceuticals, Wilmington, DE, USA) were injected into the ascending aorta for 10 s. An arterial blood sample was collected by free flow from the catheter in the femoral artery starting 5 s before the microsphere injection and continuing for a total of 60 s. The withdrawal rate was determined by weighing the sample. Blood glucose was measured in a sample from the carotid catheter using test reagent sticks as above. Another arterial sample was drawn for measurement of serum insulin. The animals were killed and the pancreas and adrenal glands were removed, blotted, weighed and treated with a freeze-thawing technique to visualize the pancreatic islets and the microspheres (see below; Jansson & Hellerström 1981). Samples from the duodenum and colon were treated in parallel. The pancreases from the sham-operated animals were divided into the duodenal region (approximately 40% of the pancreas), corresponding to the parts of the pancreas adherent to the duodenum or stomach, and the splenic region, constituting the remainder of the pancreas (approximately 60% of the gland). Pancreases from partially pancreatectomized rats were treated *in toto*. The number of microspheres was determined in each organ and in the reference blood sample. The organ blood-flow values were calculated according to the formula $Q_{org} = Q_{ref} \times N_{org}/N_{ref}$ where Q_{org} is organ blood flow (ml/min), Q_{ref} is withdrawal rate of the reference sample (ml/min), N_{org} is number of microspheres present in the organ and N_{ref} represents the number of microspheres in the reference sample. The blood-flow values of the adrenals were compared and a difference of <10% in blood flow between the glands confirmed adequate mixing of the microspheres into the circulation. The adrenal glands were of similar size in all animals.

Measurements of pancreatic islet volume and mass

Upon removal, the pancreas was divided into a duodenal part, consisting of the parts of the gland adhering to the duodenum or stomach, and a splenic part, corresponding to the remainder of the pancreas. The pancreas was divided into small pieces, each weighing approximately 25 mg. These pancreatic pieces were compressed between two object slides and stored at -20 °C (Jansson & Hellerström 1981). The number of microspheres in these samples was then counted (see above) under a microscope equipped with both bright- and dark-field illumination. The visualization of the islets in these samples also enabled

Table 1 Values are obtained 2 weeks after a 60% partial pancreatectomy or sham operation in female Wistar, GK or F₁ hybrids between GK and Wistar rats

Strain Pancreatectomy No. of animals	Wistar No 7	Wistar Yes 8	Hybrid No 7	Hybrid Yes 7	GK No 7	GK Yes 8
Body weight (g)						
Before surgery	229 ± 4	231 ± 2	225 ± 7	232 ± 4	218 ± 7	227 ± 4
2 weeks after surgery	232 ± 4†	234 ± 4	227 ± 7	237 ± 5	224 ± 8††	232 ± 4
Pancreas removed at pancreatectomy (mg)	—	524 ± 21	—	486 ± 18	—	466 ± 17
Pancreas weight (mg)	889 ± 45	440 ± 25***	937 ± 42	537 ± 27***	815 ± 25	479 ± 14***
Blood glucose (mM)	5.9 ± 0.3	6.4 ± 0.2	8.0 ± 0.5§§	8.5 ± 0.5§§	9.3 ± 0.3§§§	12.3 ± 0.3§§§
Serum insulin (ng/ml)	2.64 ± 0.46	2.14 ± 0.31	2.42 ± 0.16	2.55 ± 0.30	2.18 ± 0.26	1.45 ± 0.26
Mean arterial blood pressure (mmHg)	120 ± 5	122 ± 4	120 ± 5	121 ± 3	123 ± 3	124 ± 3

Values are means ± S.E.M. *** $P < 0.001$ compared with non-pancreatectomized rats of the same strain. §§ $P < 0.01$ and §§§ $P < 0.001$ compared with the corresponding group of Wistar rats. † $P < 0.05$ and †† $P < 0.01$ compared with the corresponding value before surgery.

us to estimate the pancreatic islet volume within the pancreatic regions, and thereby also the islet mass, by a point-counting method (Weibel 1979) adapted for use in freeze-thawed samples (Carlsson *et al.* 1996). The islet mass was then calculated assuming a similar density of the endocrine and exocrine parenchyma. Islets with a diameter less than 50 µm were not analyzed with this method, since the visualization technique makes their identification difficult. The estimated islet mass was obtained by multiplying the islet volume with the total pancreatic weight.

Measurement of serum insulin concentrations

Blood samples were drawn from the tail vein of non-fasting animals. The samples were centrifuged and the serum portion was separated and stored at -20°C . The insulin content was determined with ELISA (Insulin ELISA; Mercodia AB, Uppsala, Sweden) using rat insulin (Novo Nordic, Bagsværd, Denmark) as a standard.

Statistical analysis

All values are expressed as means ± S.E.M. Statistical comparisons were made with Student's paired *t*-test or repeated-measurement ANOVA, with Bonferroni's correction (Sigmastat; SSPD, Erlangen, Germany).

Results

Body weight and mean arterial blood pressure

Before surgery there were no significant differences in body weight between Wistar, hybrid and GK rats (Table 1). A slight increase in body weight was seen 2 weeks following the procedure in sham-operated Wistar and GK rats, while no significant increase was seen in any of the

other groups (Table 1). Mean arterial blood pressure (Table 1) and hematocrit values (results not shown) were similar in all animals.

Pancreatic wet weight

Sham-operated Wistar, hybrids and GK rats had similar total pancreatic wet weights (Table 1). Likewise, partially pancreatectomized Wistar, hybrids and GK rats had similar pancreatic weights 2 weeks after surgery. As expected, the weight of the pancreas was markedly lower in all animals subjected to a partial pancreatectomy compared with sham-operated rats of the same strain.

Glucose tolerance (Fig. 1)

Intraperitoneal glucose tolerance tests were performed 2 days before partial pancreatectomy and again 2 days

Figure 1 Blood glucose concentrations after an ipGTT (2 g/kg body weight) 12 days after a 60% partial pancreatectomy (open symbols) or sham operation (filled symbols) on female Wistar (circles), F₁-hybrid (triangles) or GK (squares) rats. Values are means ± S.E.M. from seven or eight experiments.

before blood-flow measurements. Both hybrids and GK rats had impaired glucose tolerance compared with Wistar rats both before and after surgery. After partial pancreatectomy, there was a slight deterioration in glucose tolerance in Wistar rats ($P<0.05$ for blood glucose concentrations at 30 and 60 min) and in hybrids ($P<0.05$ at 60 min) compared with sham-operated rats of the same strain. In GK rats however, the values obtained 2 days before surgery did not differ from those seen 12 days after surgery, i.e. no worsening of the glucose tolerance was imposed by the partial pancreatectomy.

Blood glucose and serum insulin concentrations (Table 1)

Blood glucose concentrations at the time of the blood-flow measurements were increased in both hybrids and GK rats compared with Wistar rats. However, there were no significant differences between sham-operated and partially pancreatectomized animals when comparisons were made within the respective strains. Serum insulin concentrations were similar in all groups.

Relative islet volume density (Fig. 2) and estimated total islet mass (Fig. 3)

There were no differences in relative islet volume densities when comparing sham-operated Wistar, hybrid and GK rats. The relative islet volume density 2 weeks after partial pancreatectomy was higher in Wistar rats when compared with sham-operated animals of the same strain. The relative islet volume density in partially pancreatectomized hybrid and GK rats was lower when compared with the corresponding value in Wistar rats, but did not differ from the values in sham-operated rats of the same strain. However, the relative islet volume density of both partially pancreatectomized hybrid and GK rats was lower than that of sham-operated Wistar rats.

When total islet mass was estimated in the whole pancreas 2 weeks after surgery a lower value was seen in sham-operated GK rats compared with sham-operated Wistar rats, whereas no differences were seen when hybrid and Wistar rats were compared. As expected, all partially pancreatectomized rats showed decreased total islet mass compared with sham-operated rats of the same strain when calculated per whole gland ($P<0.001$ for all comparisons against sham-operated control rats).

Regional differences in islet volume density (Fig. 2) and islet mass (Fig. 3)

The duodenal and splenic regions of the pancreas were analyzed separately in sham-operated animals with respect to islet volume density and islet mass. The splenic portion of the pancreas showed higher islet volume density compared with the duodenal part in both Wistar and hybrid rats. In GK rats, however, no such difference was seen ($0.1>P>0.05$ with ANOVA). Furthermore, the islet

Figure 2 Islet volume density in the whole pancreas and in the duodenal and splenic regions of the pancreases in Wistar, F₁-hybrid or GK rats 2 weeks after sham surgery or a 60% partial pancreatectomy (Px). Values are means $\pm$ S.E.M. from seven or eight experiments. * $P<0.05$ and ** $P<0.01$ when compared with the corresponding value in the whole pancreas of partially pancreatectomized Wistar rats. § $P<0.05$ when compared with the corresponding value in sham-operated Wistar rats. Statistical comparisons were made with Student's paired *t*-test for comparisons between the duodenal (Duo) and splenic (Sple) region in the same strain, and with variance analysis for the other comparisons.

volume density in the splenic part of the pancreas was lower in GK rats compared with Wistar rats.

When islet mass was analyzed, a higher value was noted for the splenic portion compared with the duodenal part in all groups of sham-operated rats ($P<0.05$ for Wistar and hybrid rats and $P<0.01$ for GK rats with ANOVA). The islet mass in the duodenal part of the pancreas of sham-operated rats was similar in all strains of animals. However, the islet mass in the splenic part of the gland in sham-operated rats was lower in GK rats when compared with the other strains.

Total pancreatic blood flow (Fig. 4)

Total pancreatic blood flow in Wistar rats, hybrids and GK rats was similar when sham-operated or partially pancreatectomized rats of the same strain were compared. Pancreatic blood flow was also measured in the duodenal and splenic parts of the gland in sham-operated rats, but no differences were seen when the different strains were compared. After partially pancreatectomy no differences between the strains were seen, even though there was a tendency towards a decrease in the GK rats ($P=0.07$).

Figure 3 Islet mass in the whole pancreas and in the duodenal (Duo) and splenic (Sple) regions of the pancreases in Wistar, F₁-hybrid or GK rats 2 weeks after sham surgery or a 60% partial pancreatectomy (Px). Values are means $\pm$ S.E.M. from seven or eight experiments. \$ P <0.05 and ** P <0.01 when compared with the corresponding value for the other two strains as calculated with variance analysis.

Islet blood flow (Fig. 5)

Islet blood flow expressed per mg islet tissue was higher in Wistar rats compared with hybrid and GK rats (P <0.05 for both comparisons; variance analysis). Furthermore, the blood perfusion of the islets in the splenic part of the gland of Wistar rats was almost twice as high as that to the duodenal part, whereas no such regional difference was seen in hybrid or GK rats. Partial pancreatectomy induced a pronounced increase in islet blood flow in Wistar rats, a less-marked augmentation in hybrid rats, and no change in GK rats when compared with sham-operated animals of the same strain.

When the blood perfusion of the whole islet organ, expressed as μ l/min, was calculated, the flow values were similar in all groups of animals, with the exception of partially pancreatectomized GK rats, which had notably (P <0.001 with ANOVA) lower blood-flow values (results not shown).

Other regional blood-flow values (Table 2)

There were no differences in colonic or duodenal blood flow between any of the groups. Adrenal blood flow was increased in sham-operated GK rats compared with Wistar rats, while the value for hybrid rats did not differ from that of the Wistar rats. Following pancreatectomy, an increase in adrenal blood flow was seen in the Wistar rats, while a decrease was demonstrated in GK rats.

Figure 4 Pancreatic blood flow in the whole gland 2 weeks after a sham operation or a 60% partial pancreatectomy (Px) in female Wistar, F₁-hybrid or GK rats. The blood-flow value is also provided separately for the duodenal (Duo) and splenic (Sple) portions of the pancreas in sham-operated rats. Values are means $\pm$ S.E.M. from seven or eight experiments.

Discussion

The present study focused on the effects of increased demand for insulin secretion on pancreatic islet mass and blood flow following a reduction of functioning islets after partial pancreatectomy. Several models for partial obliteration of the β -cell mass are available. In addition to different protocols involving systemic administration of β -cell toxins, surgical techniques including 40, 70 or 90% pancreatectomy have been described (see e.g. Pearson *et al.* 1977, Brockenbrough *et al.* 1988, Leahy *et al.* 1988, Lee *et al.* 1989, Jansson & Sandler 1989, Tanigawa *et al.* 1996). Removal of 90% of the pancreas in normal rats results in greatly increased blood glucose levels, which may in turn affect the differentiation and function of β -cells *per se* (Jonas *et al.* 1999). Both the exocrine and endocrine tissue has been shown to regenerate β -cells by differentiation of duct precursor cells as well as by mitosis in pre-existing islets (Bonner-Weir *et al.* 1993). On the other hand, a 40% pancreatectomy does not lead to changes in glucose tolerance or glucose-induced insulin response 3 weeks after surgery (Leahy *et al.* 1988). Effects of a more pronounced reduction of the β -cell mass on insulin secretion have been evaluated previously in other animal models for glucose intolerance, and a decreased insulin response has been shown after increased

Figure 5 Islet blood flow 2 weeks after a sham operation or a 60% partial pancreatectomy (Px) in female Wistar, F₁-hybrid or GK rats. The islet blood-flow value is also provided separately for the duodenal (Duo) and splenic (Sple) portions of the pancreas in sham-operated rats. Values are means $\pm$ S.E.M. from seven or eight experiments. *** P <0.001 when compared with the corresponding value for sham-operated rats of the same strain and α P <0.01 when compared with the values for partially pancreatectomized Wistar and hybrid rats. # P <0.05 and ## P <0.01 when compared with the corresponding value for the whole pancreas of the same strain. All comparisons were made with variance analysis.

load was applied (Leahy *et al.* 1988, Tanigawa *et al.* 1996).

In the present study a 60% pancreatectomy was performed. This can easily be accomplished by blunt dissection and removal of the splenic portion of the pancreas (for further details, see Jansson & Sandler 1989). One inherent potential source of error with this model is that the only part that can be analyzed for regeneration following the procedure is the duodenal region, which has a relative lack of glucagon-producing α -cells and a relatively high number of pancreatic polypeptide (PP) cells (Baetens *et al.* 1979). However, in several studies this has been shown to be of minor importance for growth and endocrine function (see Bonner-Weir 2000). In the present study we found that the splenic region contained more islets but had a

blood perfusion similar to that of the duodenal region in control Wistar rats as well as hybrid rats, i.e. findings similar to those obtained previously in control rats (Jansson & Hellerström 1987). No differences in either islet mass or blood perfusion between the two regions were seen in the GK rats. Thus, we deem this factor to be of minor importance for our findings.

In a preceding study, 60% pancreatectomy carried out in normoglycemic male Sprague–Dawley rats had only minor effects on glucose homeostasis (Jansson & Sandler 1989). These results were confirmed in the present study, which showed unchanged serum insulin concentrations and minor changes in ipGTT in the normal Wistar rats following pancreatectomy. Also in hybrid rats the changes in glucose tolerance were of a small magnitude, while virtually no effects were noted in the GK rats.

Previous reports have shown progressive proliferation of fibrous tissue in the islets of GK rats, ultimately leading to the formation of irregularly shaped, so-called starfish islets, with a decreased number of β -cells (Goto & Kakizaki 1981, Höög *et al.* 1996, 1997). However, in previous investigations involving 8-week-old Wistar, GK and hybrid rats from the Stockholm colony, a majority of the islets appeared histologically normal and only a few starfish-shaped islets were found (Abdel-Halim *et al.* 1994, Guenifi *et al.* 1995). In other studies, no differences in islet β -cell density or insulin content were seen between GK rats and Wistar rats at 12 weeks of age (Ohneda *et al.* 1993, Höög *et al.* 1996, 1997, Metz *et al.* 1999). The animals studied in the present experiments were 14 weeks old, and were thus not expected to show significant aberrations in islet architecture or β -cell mass. Although the islet mass was found to be slightly lower in the sham-operated GK rats compared with Wistar and hybrid rats, the relative islet volumes were similar in all groups of sham-operated animals. Thus, although the β -cell mass may be slightly reduced in the GK rats, this change would not explain the metabolic aberrations in these animals. It should be noted that, in contrast to our findings, rats from the Paris colony of GK rats have demonstrated a pronounced decrease in islet volume at a very early age (Movassat *et al.* 1995). It could be assumed that such a decrease contributes to the glucose intolerance in these animals (Giroix *et al.* 1993).

Table 2 Organ blood flow values 2 weeks after a 60% partial pancreatectomy or sham operation in female Wistar, GK or F₁ hybrids between GK and Wistar rats

Strain	Wistar	Wistar	Hybrid	Hybrid	GK	GK
Pancreatectomy	No	Yes	No	Yes	No	Yes
No. of animals	7	8	7	7	7	8
Duodeanal blood flow (ml/min $\times$ g)	1.09 $\pm$ 0.23	1.40 $\pm$ 0.26	0.97 $\pm$ 0.14	0.84 $\pm$ 0.10	1.24 $\pm$ 0.28	1.17 $\pm$ 0.29
Colonic blood flow (ml/min $\times$ g)	0.45 $\pm$ 0.15	0.44 $\pm$ 0.12	0.21 $\pm$ 0.06	0.20 $\pm$ 0.06	0.29 $\pm$ 0.12	0.21 $\pm$ 0.04
Adrenal blood flow (ml/min $\times$ g)	1.83 $\pm$ 0.31	2.61 $\pm$ 0.29	2.39 $\pm$ 0.30	2.64 $\pm$ 0.23	3.64 $\pm$ 0.70*	1.91 $\pm$ 0.27

Values are means $\pm$ S.E.M. * P <0.05 when compared with the corresponding group of Wistar rats.

Following partial pancreatectomy, a marked reduction in islet mass was seen in all groups of rats. When pancreatectomized rats were compared, GK rats had significantly lower islet mass than both Wistar and hybrid rats. Taken together, our results suggest that after a 60% partial pancreatectomy Wistar rats are able to functionally compensate for the loss of insulin-producing tissue. In contrast, GK rats do not seem to be able to respond to the same degree, as reflected not only in the higher blood glucose concentrations of these animals, but also by a decrease in relative islet volume and a decreased islet mass compared with Wistar rats following pancreatectomy. This may indicate a relative impairment of the β -cell replication (see Brockenbrough *et al.* 1988, Lee *et al.* 1989). However, replication *per se* has not been evaluated in the present study. As expected (see Hellman 1959, Saito *et al.* 1978, Hellerström *et al.* 1988), islet cell mass was higher in the splenic portion of the pancreas in Wistar rats. This pattern of distribution was also present in hybrid and GK rats.

Previous studies have shown that a 60% pancreatectomy induces a marked increase in total pancreatic and islet blood perfusion during the first four post-operative weeks (Jansson & Sandler 1989). In the present study, we chose to study the animals 2 weeks after surgery, i.e. when the post-operative blood-flow increase reaches a maximum (Jansson & Sandler 1989) and there is still ongoing regeneration of the islets (Pearson *et al.* 1977, Brockenbrough *et al.* 1988).

Our previous study, using male Sprague–Dawley rats (Jansson & Sandler 1989), showed an increase in total pancreatic blood flow 2 weeks post-surgery. In contrast, the female Wistar rats in the present study did not attain an increased pancreatic blood flow ($0.05 < P < 0.1$). This inconsistency may be due to strain or sex differences.

Following partial pancreatectomy, a 2-fold increase in islet blood flow, as calculated in relation to islet volume, was seen in the Wistar rats. Thus, the islet blood flow in partially pancreatectomized Wistar rats increased to such a magnitude that the total blood perfusion to islets in these rats reached the same level as the islet blood flow in the whole pancreas in the sham-operated animals. This finding confirms previous observations linking augmented islet blood flow to settings with increased need for insulin secretion (see Jansson & Sandler 1989, Styrd *et al.* 1992, Atef *et al.* 1992, 1994, Svensson *et al.* 1996). Obviously, increased islet blood flow could constitute one mechanism for maintaining normal glucose homeostasis in the face of increased functional demand, i.e. a sudden decrease in islet mass. The physiological and/or metabolic events underlying the increase in islet blood flow under these circumstances are unknown. However, we believe that it could reflect an increased metabolism of the islets, since we have recently shown that this can lead to a pronounced increase in islet blood flow in other models, in which the major mediator of the response seems to be adenosine (Carlsson *et al.* 2002). It can also be speculated that growth factors

involved in the regeneration of islets (see Nielsen *et al.* 1999) can influence islet blood flow, but this notion remains hypothetical.

We and others previously demonstrated increased islet perfusion in adult GK and hybrid rats compared with Wistar rats (Atef *et al.* 1994, Svensson *et al.* 1994, 2000, Carlsson *et al.* 1997). However, in the present study, no significant differences in islet blood perfusion between sham-operated Wistar and sham-operated hybrid or GK rats were seen. The reason for this is unclear. Since the sham operation involves mobilization of the splenic part of the pancreas, it could be envisaged that this procedure *per se* affects blood perfusion. We have previously noted a decrease in islet blood flow 1 week after intra-abdominal sham operations in Sprague–Dawley rats (Jansson & Andersson 1997), which may reflect responses to changes in abdominal pressure or inflammatory reactions following laparotomy. GK and hybrid rats may be more sensitive to such events, in line with our previous observations that vagotomy and treatment with atropine decreases islet blood flow in hybrid rats to levels similar to those of normal Wistar rats (Svensson *et al.* 1996).

The most important finding in the current investigation is the decrease in islet blood flow following partial pancreatectomy seen in GK rats, after correction for differences in islet mass. This is in contrast to the normal Wistar rats which have a 3-fold increase in their islet blood flow following surgery, while hybrid rats show a 2-fold increase. This suggests that whereas normal rats may compensate for the surgical removal of endocrine tissue by regeneration and hyperperfusion of the islets, these mechanisms are much less efficient, or even absent, in GK rats. It is of interest that a similar decrease in islet blood flow is seen in aging GK rats, which have an even more impaired glucose tolerance (Svensson *et al.* 2000). The present findings lend support to the notion that, in this model, a decrease in islet blood flow may precede the functional impairment of the islets. It may be speculated that an increased functional load is initially associated with an augmented islet blood perfusion, providing nutrients and means of delivery of the secreted hormones to sustain normal glucose tolerance. However, an associated capillary hypertension, as seen in GK rats (Carlsson *et al.* 1997) may cause endothelial and organ damage (see Zatz & Brenner 1986, Toppee & Gimbrone 1999), leading to changes in islet blood-flow regulation and decreased blood perfusion, ultimately resulting in impairment of nutrient and hormone transport. This could contribute to the glucose intolerance seen in some animal models of type 2 diabetes.

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