Influence of age, hyperglycemia, leptin, and NPY on islet blood flow in obese-hyperglycemic mice

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Carlsson, Per-Ola, Arne Andersson, and Leif Jansson. Influence of age, hyperglycemia, leptin, and NPY on islet blood flow in obese-hyperglycemic mice. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E594–E601, 1998.—This study aimed to elucidate possible age-related changes in islet blood perfusion in lean and obese C57BL/6 mice. Obese mice aged 1 mo were hyperglycemic and hyperinsulinemic and had an increased islet blood flow compared with age-matched lean mice. This augmented blood flow could be abolished by pretreatment with leptin. The islet blood perfusion was, in contrast to this, markedly decreased in obese 6- to 7-mo-old animals compared with age-matched lean mice. Reversal of hyperglycemia, but not hyperinsulinemia, in these obese mice with phlorizin normalized the islet blood flow. Spontaneous reversal of hyperglycemia, but not hyperinsulinemia, was seen in the 12-mo-old obese mice. Islet blood perfusion in obese mice at this age did not differ compared with lean mice. It is suggested that the initial increase in islet blood flow in obese mice is due to the leptin deficiency. The subsequent decrease in islet blood perfusion is probably caused by the chronic hyperglycemia. The described islet blood flow changes may be of importance for impairment of islet function in obese-hyperglycemic mice.

non-insulin-dependent diabetes mellitus; microcirculation; phlorizin; neuropeptide Y

OBESE-HYPERGLYCEMIC, HYPERINSULINEMIC MICE (gene symbol ob/ob; obese mice) have a mutation in the ob gene that prevents normal leptin production in adipose tissue (39). Already at 3–5 wks of age, these mice are obese and have significantly increased blood glucose and serum insulin concentrations compared with lean litter mates (37). The highest blood glucose and serum insulin concentrations are seen in 3- to 5-mo-old obese mice, after which the blood glucose concentrations tend to decrease (37). By 11–12 mo of age, most animals are normoglycemic but remain hyperinsulinemic (37). These changes are mirrored by an increase in β-cell volume in obese-hyperglycemic mice, which depends on an initially augmented cell replication followed by a subsequent decrease (2).

An adequate islet blood perfusion is pivotal, both for the oxygen and nutrient supply of the endocrine cells and for dispersal of islet hormones to target organs (17). This is of particular importance when an increased requirement of insulin is imposed on the β-cells. Thus most conditions associated with increased insulin secretion are initially accompanied by an increased islet blood flow (17). However, the islet blood hyperperfusion, which is associated with a capillary hypertension, may damage the islet vasculature with time and finally cause a decrease in islet blood flow (see Refs. 5, 34). Interestingly, we have recently found that 7-mo-old obese mice have a 50% decrease in islet blood flow compared with age-matched lean mice, when blood flow is corrected for differences in islet volume (4).

The aim of the present study was therefore to further evaluate the islet blood flow changes that occur in obese mice. For this purpose, measurements of islet blood perfusion were performed immediately after onset of hyperglycemia (1-mo-old mice), during the fully developed syndrome, i.e., after exposure to hyperglycemia for several mo (6- to 7-mo-old mice), and, finally, when spontaneous reversal of hyperglycemia has occurred (12-mo-old mice). Because pronounced differences in islet blood perfusion were seen when lean and obese mice were compared at 1 and 6–7 mo of age, we tried to elucidate the underlying mechanisms by investigating the influence of reversal of hyperglycemia, the correction of leptin deficiency, and, finally, the addition of a neuropeptide Y1 (NPY1) receptor antagonist.

MATERIALS AND METHODS

Animals. Inbred obese (ob/ob) and lean (+/+) C57BL/6 mice, originally obtained from the Jackson Laboratories (Bar Harbor, ME), were used in all experiments. The animals were purchased from Bomholtgaard (Ry, Denmark) and had free access to autoclaved tap water and pelleted food throughout the course of the study, except when stated otherwise. All lean and obese mice were randomly assigned to the different experiments and were obtained from the same population of mice. The experiments were approved by the local animal ethics committee at Uppsala University.

Phlorizin treatment. One-month-old and 6- to 7-mo-old lean and obese mice were injected subcutaneously twice daily (8 AM and 8 PM) with phlorizin (0.4 g·kg body wt−1·day−1; Sigma, St Louis, MO) dissolved in propylene glycol for 10–12 days. Phlorizin inhibits renal tubular glucose transport, which enhances renal glucose excretion to such an extent that normoglycemia can be achieved in diabetic animals (5, 20, 29). Pair-fed obese mice injected with vehicle only were used as controls. The amount of food provided to these control pair-fed animals each day was equal to the amount consumed by their phlorizin-treated partners during the previous 24-h period. Body weight and blood glucose concentrations were determined at 8 AM, i.e., immediately before administration of phlorizin or vehicle, on days 1, 3, 7, and 10 or 12 of treatment. Blood glucose concentrations were measured with test reagent strips (Medisense; Baxter Travenol, Deerfield, IL).

Leptin treatment. One-month-old and 6- to 7-mo-old lean and obese mice were injected intraperitoneally once daily for 5 days with leptin (2.5 µg/g body wt; PeproTech EC, London, UK) dissolved in Tris buffer (pH 9.5). Pair-fed obese mice were injected with vehicle alone. Body weight and blood glucose concentrations were measured on days 1, 3, 7, and 10 or 12 of treatment.
concentrations of control lean and obese C57BL/6 mice aged 1, 6–7, or 12 mo.

Table 1. Body weights, pancreatic weights, blood glucose concentrations, and serum insulin concentrations of control lean and obese C57BL/6 mice aged 1, 6–7, or 12 mo.

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>Body Weight, g</th>
<th>Pancreatic Weight, mg</th>
<th>Blood Glucose Concentration, mmol/l</th>
<th>Serum Insulin Concentration, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lean</td>
<td>Obese</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>Obese</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23 ± 1</td>
<td>31 ± 1*</td>
<td>211 ± 12</td>
<td>7.7 ± 0.8</td>
</tr>
<tr>
<td>6–7</td>
<td>28 ± 2b</td>
<td>57 ± 2c</td>
<td>275 ± 14a</td>
<td>6.0 ± 0.2</td>
</tr>
<tr>
<td>12</td>
<td>35 ± 2d</td>
<td>71 ± 2df</td>
<td>319 ± 15e</td>
<td>6.9 ± 0.2</td>
</tr>
</tbody>
</table>

All values are given as means ± SE for 7–12 animals. *P < 0.05, **P < 0.01, and ***P < 0.001 vs. age-matched lean mice; †P < 0.05, ‡P < 0.01, and §P < 0.001 vs. 1-mo-old mice of the same strain; ¶P < 0.05, ¶¶P < 0.01, and ¶¶¶P < 0.001 vs. 6- to 7-mo-old mice of the same strain. All comparisons were made with ANOVA and Fisher's protected least significant difference (PLSD) test.
vehicle did not affect the body weight of the animals (data not shown).

The pancreas weight increased with age in lean mice, whereas the weight remained constant in obese mice. This means that the pancreas weight was lower in 6- to 7-mo-old and 12-mo-old obese mice compared with age-matched lean mice. The pancreas weights were not affected by pretreatment with phlorizin, leptin, or their corresponding vehicles in either lean or obese 1- or 6- to 7-mo-old mice (data not shown).

Blood glucose concentrations. There were no differences in blood glucose concentrations between 1-mo-old, 6- to 7-mo-old, and 12-mo-old saline-treated lean mice (Table 1). Obese mice aged 1 and 6–7 mo were hyperglycemic, with a markedly higher blood glucose concentration than in age-matched lean mice, whereas 12-mo-old obese mice did not differ in their blood glucose concentration from lean mice. When obese mice were compared, 1-mo-old animals had a slightly higher blood glucose concentration than 6- to 7-mo-old obese mice and a markedly higher concentration than that seen in 12-mo-old animals. Pretreatment of obese mice with the NPY1 antagonist BIBP 3226 did not affect blood glucose levels compared with age-matched saline-treated animals (data not shown).

Phlorizin had no effects on the blood glucose concentrations in lean 1- or 6- to 7-mo-old mice (data not shown). All obese animals assigned to phlorizin treatment and the pair-fed control mice were hyperglycemic before treatment (11.1 ± 0.8 mmol/l, n = 16, obese 1 mo; 10.2 ± 0.5 mmol/l, n = 16, obese 6 mo). Phlorizin reversed hyperglycemia in both the 1- and 6- to 7-mo-old obese mice, i.e., blood glucose values did not differ between lean and obese mice given phlorizin from treatment day 3 and onward [day 3: 6.0 ± 0.3 mmol/l (n = 8, lean 1 mo) vs. 6.4 ± 0.8 mmol/l (n = 8, obese 1 mo); 5.1 ± 0.3 mmol/l (n = 11, lean 6 mo) vs. 5.5 ± 0.2 mmol/l (n = 8, obese 6 mo)]. Vehicle treatment did not affect the blood glucose concentrations of the pair-fed obese mice (data not shown). Finally, treatment with leptin or its vehicle did not affect the blood glucose concentrations in 1-mo-old lean (data not shown) or obese mice [10.1 ± 0.6 mmol/l (before leptin) vs. 9.9 ± 1.0 mmol/l (after leptin), 10.6 ± 1.0 mmol/l (before Tris buffer) vs. 10.6 ± 0.7 mmol/l (after Tris buffer), n = 7 in each group]. Neither could any effects on blood glucose concentrations be seen in 6- to 7-mo-old lean (data not shown) or obese mice [11.5 ± 0.7 mmol/l (before leptin) vs. 8.7 ± 0.6 mmol/l (after leptin), 11.8 ± 0.9 mmol/l (before Tris buffer) vs. 10.1 ± 0.8 mmol/l (after Tris buffer), n = 8 in each group).

Serum insulin concentrations. The serum insulin concentrations of 1-, 6- to 7-, and 12-mo-old saline-treated lean mice did not differ (Table 1). However, the obese mice were markedly hyperinsulinemic, roughly a tenfold increase, compared with lean mice of corresponding age. The 1-mo-old obese mice had a higher serum insulin concentration than 12-mo-old obese animals. Serum insulin concentrations were not affected by the NPY1 antagonist BIBP 3226 in either lean or obese mice (data not shown). Likewise, there were no effects on serum insulin concentrations after pretreatment with phlorizin in either lean (data not shown) or obese mice [21.7 ± 4.5 ng/ml (phlorizin) vs. 38.1 ± 11.0 ng/ml (vehicle), n = 8 in each group, 1-mo-old animals; 139.2 ± 40.1 ng/ml (phlorizin) vs. 108.2 ± 17.1 ng/ml (vehicle), n = 8 in each group, 6- to 7-mo-old animals]. In addition, there were no differences in serum insulin concentrations between 1- and 6- to 7-mo-old obese animals treated with the vehicle for phlorizin and nonpretreated age-matched obese animals (see previous paragraph and Table 1). Pretreatment with leptin did not affect the serum insulin concentrations in lean mice (data not shown). However, in obese mice, the serum insulin concentration decreased [9.8 ± 3.9 ng/ml (leptin) vs. 41.4 ± 8.0 ng/ml (Tris buffer), n = 7 in each group, obese 1 mo, P < 0.05 Student’s paired t-test; 14.9 ± 6.2 ng/ml (leptin) vs. 74.1 ± 16.7 ng/ml (Tris buffer), n = 7 in each group, obese 6-7 mo, P < 0.01 Student’s paired t-test]. In the 6- to 7-mo-old, but not in 1-mo-old, obese mice treated with the vehicle for leptin, the serum insulin concentration was increased compared with nonpretreated saline-injected age-matched obese mice (see Table 1, P < 0.01 by Student’s unpaired t-test).

Fractional pancreatic islet volume. The islet volume percentage was increased in obese mice already at 1 mo of age compared with lean mice, and this increase was even more pronounced in 6- to 7- and 12-mo-old animals (Fig. 1). In the obese mice, but not in the lean animals, islet volume percentage increased between 1 and 6–7 mo of age. The islet volume percentages of the 12-mo-old obese mice were, however, lower than those of the 6- to 7-mo-old animals, whereas in lean mice the islet volume percentage had increased in the oldest animals examined. There were no effects of administration of leptin, phlorizin, or BIBP 3226 on the islet volume percentage.
volume percentage in either lean or obese mice at 1 or 6–7 mo of age (data not shown).

Pancreatic and islet blood flows. Mean arterial blood pressure was ~90 mmHg in all animals and did not differ among any of the experimental groups (data not shown).

Whole pancreatic blood flow significantly increased with age in lean, but not in obese, mice (Fig. 2A). Lean mice aged 6–7 and 12 mo had a higher whole pancreatic blood flow than the corresponding age-matched obese mice (Fig. 2A). This was not observed in 1-mo-old mice (Fig. 2A). Islet blood flow (expressed per gram pancreas) increased with age in both lean and obese mice (Fig. 2B). In the obese mice, islet blood flow expressed per gram pancreas was higher than that in lean mice in all age groups (Fig. 2B).

After compensation for age-related changes in islet volume, there was an increased islet blood flow in lean mice 6–7 mo of age compared with lean 1-mo-old mice (Fig. 2C). On the contrary, obese mice showed a decrease in islet blood flow during this time period (Fig. 2C). The islet blood flow, when expressed per milligram islet weight, was increased at 1 mo of age in obese mice compared with lean mice (Fig. 2C). In the 6- to 7-mo-old obese mice, however, there was a lower islet blood perfusion than in the age-matched lean mice (Fig. 2C). In 12-mo-old animals there were no differences in islet blood flow between lean and obese mice (Fig. 2C).

In 1-mo-old lean and obese mice, pretreatment with phlorizin or leptin or acute administration of the NPY$_1$ receptor antagonist BIBP 3226 had no effects on whole pancreatic blood flow (Table 2). Likewise, neither phlorizin nor BIBP 3226 affected the islet blood flow in 1-mo-old lean and obese mice (Table 2, Figs. 3, A and B). However, in the obese but not the lean mice, leptin markedly decreased islet blood flow when expressed either per gram pancreas (Table 2) or per milligram islet weight (Fig. 3, A and B).

In 6- to 7-mo-old lean mice, pretreatment with phlorizin or leptin or acute administration of BIBP 3226 did not affect whole pancreatic or islet blood flow (Table 2, Fig. 4A). Leptin and BIBP 3226 had no effects on whole pancreatic or islet blood flow in age-matched obese mice (Table 2, Fig. 4B). However, in the obese mice, phlorizin treatment increased both whole pancreatic (Table 2) and islet blood flow, the latter when expressed either per gram pancreas (Table 2) or per milligram islet weight (Fig. 4B).

DISCUSSION

In agreement with previous studies (2, 4, 37), the islet volume percentage of obese mice was markedly increased in 1- and 6- to 7-mo-old animals. The decrease in islet volume percentage between 6–7 and 12 mo of age in obese mice has also previously been described, and most certainly a decreased islet cell replication contributes to this (2). Also, the time frame of the development of hyperglycemia and hyperinsulinemia, and the spontaneous reversal of the hyperglycemia due to decreased peripheral insulin resistance (see Fig. 2. Whole pancreatic blood flow (A) and islet blood flow expressed per g pancreas (B) or per mg islet weight (C) in control lean and obese 1-, 6- to 7-, and 12-mo-old C57BL/6 mice. All values are means ± SE for 8–12 experiments. *P < 0.05 and **P < 0.001 vs. age-matched lean mice; P < 0.05, **P < 0.01, and ***P < 0.001 vs. 1-mo-old mice of the same strain. All comparisons were made with ANOVA and Fisher’s PLSD test.
Ref. 30) with a persistent hyperinsulinemia, are in accordance with previous investigations (2, 37).

In the present study, whole pancreatic blood flow increased with age in the lean mice but remained constant in the obese mice. However, previous studies in lean rats have shown an age-related decrease in whole pancreatic blood flow, mainly due to an atrophy of the exocrine parenchyma (19). The reason for this discrepancy is probably due to species-related differences in the deterioration of exocrine function, and thereby also blood perfusion, with age.

When total islet blood flow per gram pancreas was studied, a marked age-dependent increase was seen in both lean and obese mice, even though it was more pronounced in the latter strain. This age-related increase in islet blood flow has previously been described in rats (19). In mice, the increase could, however, mainly be ascribed to the concomitant age-related increase in islet volume, i.e., the blood flow per endocrine cell mass remained fairly constant, or even decreased. After compensation for differences in islet volume by expression of islet blood flow per islet weight, an augmented islet blood flow was seen only when 1- and 6- to 7-mo-old lean mice were compared, whereas, in contrast, a decrease was seen in the obese mice when these age groups were compared.

Interestingly, in the 1-mo-old animals, islet blood flow, even when the increased islet mass was taken into account, was higher in the obese than in the lean mice. On the contrary, 6- to 7-mo-old obese mice had a markedly decreased islet blood perfusion compared with lean mice, which is consistent with previous findings (4). To elucidate the mechanisms behind these changes in islet blood perfusion in the obese mice, 1- and 6- to 7-mo-old animals were pretreated with leptin or phlorizin or were given the NPY₁ receptor antagonist BIBP 3226 acutely.

The rationale for these further investigations is that there is a mutation in the ob gene in the obese-hyperglycemic mice that leads to the production of a leptin defect (39). Leptin is normally released from adipose tissues and functions as a signal to the hypothalamic satiety center, ultimately regulating the size of the body fat deposits (10, 13, 23, 27). Leptin receptors have also been found on pancreatic β-cells (21), and the predominant effect of leptin seems to be an inhibition of insulin release (6, 8, 15, 22). In view of these findings, it has been suggested that an adipoinsular feedback loop exists, with high circulating concentrations of leptin inhibiting insulin release and preventing fat storage, and vice versa (21). In support of this, we found that leptin administration decreased serum insulin concentrations of the obese mice. In addition, however, the serum insulin concentration in 6- to 7-mo-old obese animals pretreated with the vehicle for leptin (Tris buffer) differed from that of nonpretreated saline-injected obese control mice. This may be due to the different treatment protocols for these two groups of animals. It should be noted that the latter animals were fed ad libitum and received no pretreatment, whereas the leptin controls were subject to calorie restriction (they were pair fed with age-matched mice receiving leptin) and received daily injections with the leptin vehicle.

In accordance with previous reports (13, 23, 27), correction of the leptin deficiency in the obese animals caused a more pronounced weight loss than that observed in the vehicle-treated pair-fed animals. Moreover, leptin treatment selectively and markedly decreased islet blood flow in 1-mo-old obese mice. This means that the selectively increased islet blood perfusion in obese, 1-mo-old animals compared with age-matched lean mice was fully reversed, thereby suggesting that this blood flow increase was due to leptin deficiency. It can be speculated that leptin deficiency is initially associated with an increased islet blood flow as a result of a deficient negative feedback of leptin on insulin release and blood perfusion. However, this notion awaits further experimental confirmation. Because a decreased islet blood flow in the pair-fed animals was not observed, the possibility that the present findings were due to decreased food intake can

### Table 2. Whole pancreatic blood flow and islet blood flow in lean and obese 1- and 6- to 7-mo-old C57BL/6 mice 15 min after various treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Whole Pancreatic Blood Flow, ml · min⁻¹ · g pancreas⁻¹</th>
<th>Islet Blood Flow, µl · min⁻¹ · g pancreas⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mo Lean  Obese 1 mo Lean  Obese 1 mo Lean  Obese 1 mo Lean  Obese</td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>1.26 ± 0.23  1.08 ± 0.13  1.59 ± 0.18  0.92 ± 0.14  16 ± 2  64 ± 9  35 ± 6  136 ± 22</td>
<td></td>
</tr>
<tr>
<td>BIBP 3226</td>
<td>1.43 ± 0.12  1.05 ± 0.21  1.90 ± 0.29  1.18 ± 0.11  14 ± 3  43 ± 7  42 ± 7  172 ± 13</td>
<td></td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>0.95 ± 0.15  0.96 ± 0.13  1.45 ± 0.13 +</td>
<td>11 ± 1  41 ± 7  26 ± 4  340 ± 51 +</td>
</tr>
<tr>
<td>Phlorizin</td>
<td>0.98 ± 0.12  0.75 ± 0.14  1.37 ± 0.15  0.86 ± 0.11  61 ± 14  169 ± 33</td>
<td></td>
</tr>
<tr>
<td>Tris buffer</td>
<td>1.25 ± 0.16  0.64 ± 0.13  2.10 ± 0.32  0.68 ± 0.14  16 ± 3  21 ± 5 +</td>
<td>38 ± 6  162 ± 22</td>
</tr>
<tr>
<td>Leptin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are means ± SE for 7–12 experiments. Measurements were performed after iv administration of 0.2 ml saline or the NPY₁ receptor antagonist BIBP 3226 (1 mg/kg) dissolved in saline, or after pretreatment with phlorizin (0.4 g/kg sc) for 10–12 days or leptin (2.5 µg/g) for 5 days. Pair-fed obese animals were treated with vehicles for phlorizin (propylene glycol) and leptin (Tris buffer). Values for saline-treated animals are the same as given in Fig. 2. *P < 0.01 vs. age-matched saline-treated animals of the same strain. All comparisons were made with ANOVA and Fisher’s PLSD test.
be excluded. It is also unlikely that the observed decrease in islet blood flow after leptin treatment was merely due to a more lean body composition in these animals, because the body weight of the leptin-treated and pair-fed vehicle-treated animals did not differ either before or after the treatment period. However, it cannot be excluded that the leptin-induced effects on islet blood flow result from changes secondary to leptin administration, e.g., alterations in metabolism. Leptin treatment in 6- to 7-mo-old obese mice had no effects on islet blood flow. This may be due to an induced resistance in leptin regulation of islet blood flow. It may also be related to the fact that the islet blood perfusion in these animals was already decreased compared with age-matched lean animals, and that autoregulation within the islet vasculature overrode any additional deterioration of islet blood flow. No effects of leptin on blood glucose concentrations were seen in the present study. The reason for this may be the relatively short treatment period (5 days) compared with other studies (13, 23, 25, 27). Nevertheless, secondary effects of leptin on islet blood perfusion mediated by reversal of hyperglycemia can be ruled out by these findings.

Phlorizin inhibits renal tubular glucose transport and thereby enhances renal glucose excretion to such an extent that hyperglycemia associated with diabetes may become normalized (5, 20, 29). In the present study, phlorizin fully reversed the hyperglycemia in both 1- and 6- to 7-mo-old obese animals but had, as expected, no effects in normoglycemic lean mice. Phlori-
pylorin had no effects on whole pancreatic and islet blood perfusion in 1-mo-old animals. This suggests that hypoglycemia is not involved in the regulation of whole pancreatic or islet blood flow in the obese mice at this time point. However, in 6- to 7-mo-old obese mice, phlorizin treatment caused a marked increase in both whole pancreatic and islet blood flow compared with age-matched lean mice. This means that reversal of hypoglycemia with phlorizin normalized both whole pancreatic and islet blood perfusion in these obese animals. The present findings therefore suggest that the decreased whole pancreatic and islet blood perfusion in the untreated 6- to 7-mo-old obese animals was due to persistent hyperglycemia. However, a direct effect of phlorizin on whole pancreatic and islet blood flow cannot be excluded, although we deem it less likely. Interestingly, also in another non-insulin-dependent diabetes mellitus model with moderate hyperglycemia, the GoCo Kakizaki (GK) rat, a markedly decreased islet blood flow is found in old animals when compared with age-matched Wistar Furth rats (34). In contrast to this, a marked increase in islet blood flow has been reported after short-term modest hyperglycemia (2–10 days; see Refs. 32, 33) and also in young GK rats (5, 35) and obese Zucker rats (3). The present findings, in addition to those in old GK rats, therefore suggest that hyperglycemia is associated with an initial hyperperfusion of the islets, and also with a capillary hypoperfusion (5), which with time is replaced by a capillary hypoperfusion. To what extent the latter is associated with a functional deterioration of the islets remains to be established. It should be noted that spontaneous reversal of hyperglycemia occurs in obese mice at an age of 10–12 mo, and no differences in either whole pancreatic or islet blood flow were seen in these old animals. In comparison, all obese animals in the present study, irrespective of age, were markedly hyperinsulinemic compared with lean animals. It is therefore unlikely that hyperinsulinemia per se is of any importance for the observed changes in islet blood perfusion.

NPY has vasoconstrictory effects that are mediated by the NPY₁ receptor (see Refs. 9, 12), e.g., in the pancreatic vascular bed (31). In confirmation of this, a decrease in pancreatic blood flow has been observed after administration of NPY (1). A major obstacle for investigations of the effects of NPY has been the lack of specificity for the observed changes in islet blood perfusion. The described islet blood flow changes may be of importance for impairment of islet function in this animal model, as well as in other animal models of impaired glucose tolerance.

The skilled technical assistance of Astrid Nordin is gratefully acknowledged.

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