Blood lipids affect rat islet blood flow regulation through $\beta_3$-adrenoceptors

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Lai E, Pettersson U, Verdugo AD, Carlsson PO, Bodin B, Källskog Ö, Persson AE, Sandberg M, Jansson L. Blood lipids affect rat islet blood flow regulation through $\beta_3$-adrenoceptors. Am J Physiol Endocrinol Metab 307: E653–E663, 2014. First published August 19, 2014; doi:10.1152/ajpendo.00680.2013.—Pancreatic islet blood perfusion varies according to the needs for insulin secretion. We examined the effects of blood lipids on pancreatic islet blood flow in anesthetized rats. Acute administration of Intralipid to anesthetized rats increased both triglycerides and free fatty acids, associated with a simultaneous increase in total pancreatic and islet blood flow. A preceding abdominal vagotomy markedly potentiated this and led acutely to a 10-fold increase in islet blood flow associated with a similar increase in serum insulin concentrations. The islet blood flow and serum insulin response could be largely prevented by pretreatment with propranolol and the selective $\beta_3$-adrenergic inhibitor SR-59230A. The nitric oxide synthase inhibitor NOS-nitro-l-arginine methyl ester prevented the blood flow increase but was less effective in reducing serum insulin. Increased islet blood flow after Intralipid administration was also seen in islet and whole pancreas transplanted rats, i.e., models with different degrees of chronic islet denervation, but the effect was not as pronounced. In isolated vascularly perfused single islets Intralipid diluted islet arterioles, but this was not affected by SR-59230A. Both the sympathetic and parasympathetic nervous system are important for the coordination of islet blood flow and insulin release during hyperlipidemia, with a previously unknown role for $\beta_3$-adrenoceptors.

Pancreatic islets

Pancreatic islet blood flow (IBF) is regulated by complex interactions between locally produced endothelium-derived mediators such as nitric oxide (NO) and endothelin, as well as metabolically produced substances like adenosine and ATP (18, 20). In addition to this, the autonomic nervous system also modulates the islet blood perfusion (8, 18). An increased insulin release is usually associated with an augmented IBF, initially by vagus-mediated effects, and later, i.e., after 5–10 min, mainly by adenosine formed from the increased $\beta$-cell metabolism (12). To what extent disturbances in islet blood perfusion is associated with impaired glucose tolerance is not known (8), but it has been suggested to be a modulating factor in the development of type 2 diabetes (T2D) (5, 33, 46). A consistent finding in impaired glucose tolerance (IGT) and early T2D is a hyperperfusion of blood through the islets, followed by a decrease as overt diabetes ensues.

Chronic hyperlipidemia has been considered to be an important contributing factor for development of IGT and T2D (51). Thus, there is a dose-dependent correlation between systemic free fatty acid (FFA) concentrations and impaired peripheral glucose uptake (7), suggesting that hyperlipidemia as such contributes to IGT. Furthermore, the hypothalamus is believed to play a key role in the regulation of hepatic glucose metabolism by monitoring FFA concentrations and then adjusting hepatic carbohydrate and lipid metabolism according to this information (32). To what extent such signals directly affect islet endocrine function is largely unknown, but, besides the metabolic effects, infusion with triglycerides lowers sympathetic activity (34), which then may affect islet endocrine function (1).

To further study the effects of lipids on islet function in relation to their blood perfusion, we used injection of Intralipid (an emulsion of refined soy oil), together with heparin, to increase both serum triglycerides and FFA in normoglycemic rats. In addition to metabolic effects, this procedure induces an acute endothelial dysfunction that most likely also affects the islets (14, 35, 50).

These experiments allowed us to confirm (4, 40) and further elucidate a previously unexpected role for the sympathetic nervous, especially $\beta_3$-adrenergic receptors as important mediators of islet blood flow. To further investigate the role of the nervous system, we also evaluated IBF effects in pancreatic-duodenal and islet transplanted rats. This enabled us to study in the former case an externally denervated pancreas with an intact intrinsinc nervous system, and in the latter islets completely devoid of innervation (28, 29). Finally, we also investigated lipid effects on arteriolar responses in vascularly perfused, isolated single islets ex vivo. In the latter model, the observed effects are likely to be derived mainly from the islet or arteriolar endothelial cells. In combination, this experimental approach has allowed us to demonstrate that acute elevation of blood lipids induces profound and specific changes in IBF, largely influenced by the autonomic nervous system, especially $\beta_3$-adrenoceptors. We suggest that the nervous system may influence the islet hyperperfusion of blood seen in early T2D and IGT and that this may be liable to pharmacological intervention to prevent islet endocrine impairment.

METHODS

Animals. Male Wistar–Furth rats aged 3–4 mo were purchased from Scanbur (Sollentuna, Sweden). For single-islet perfusions, we used male C57BL6 mice purchased from M&B (Ry, Denmark). The animals had free access to food (type R3; Scanbur) and water throughout the experiments. A summary of all experimental groups referred to below is given in Table 1. All experiments were approved by the local animal ethics committee for Uppsala University (Uppsala, Sweden).

Drugs. Intralipid was from Fresenius Kabi (Intralipid 200 mg/ml; Uppsala, Sweden), norepinephrine and propranolol were from Sigma-Aldrich Chemicals (St. Louis, MO, USA), SR-59230A was from...
Table 1. Blood glucose concentrations, mean arterial blood pressure, and different organ blood flow values in anesthetized rats after different experimental procedures as outlined in Methods

<table>
<thead>
<tr>
<th>Intralipid or Saline</th>
<th>Bolus or Infusion</th>
<th>Vagotomy</th>
<th>Other Drugs or Actions</th>
<th>Dose of Drugs, mg/kg</th>
<th>Time after Intralipid/Saline, min</th>
<th>Blood Glucose, mmol/l</th>
<th>Mean Arterial Blood Pressure, mmHg</th>
<th>Duodenal Blood Flow</th>
<th>Colonic Blood Flow</th>
<th>Renal Blood Flow</th>
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<tr>
<td>Saline Bolus</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>3</td>
<td>6.1 ± 0.1</td>
<td>129 ± 3</td>
<td>1.88 ± 0.35</td>
<td>1.02 ± 0.14</td>
<td>4.07 ± 0.62</td>
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<td>Intralipid Bolus</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>3</td>
<td>6.0 ± 0.2</td>
<td>122 ± 5</td>
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<td>1.17 ± 0.22</td>
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<td>No</td>
<td>NA</td>
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<td>5.7 ± 0.3</td>
<td>119 ± 7</td>
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<td>0.89 ± 0.26</td>
<td>4.24 ± 1.46</td>
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<td>No</td>
<td>NA</td>
<td>3</td>
<td>6.0 ± 0.2</td>
<td>114 ± 5</td>
<td>1.91 ± 0.21</td>
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<td>NA</td>
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<td>4.8 ± 0.1</td>
<td>125 ± 5</td>
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<td>7.0 ± 0.2</td>
<td>113 ± 6</td>
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<td>0.94 ± 0.17</td>
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<td>No</td>
<td>NA</td>
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<td>NA</td>
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<td>119 ± 3</td>
<td>3.00 ± 0.59</td>
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<td>No</td>
<td>Propranolol</td>
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<td>96 ± 5</td>
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<td>Propranolol</td>
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<td>88 ± 5</td>
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<td>Propranolol</td>
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<td>88 ± 3</td>
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<td>82 ± 4</td>
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<tr>
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<td>No</td>
<td>SR-59230A</td>
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<td>10</td>
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<td>115 ± 6</td>
<td>49.1 ± 5.3</td>
<td>0.70 ± 0.11</td>
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<td>SR-59230A</td>
<td>1</td>
<td>10</td>
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<td>84 ± 3</td>
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<td>99 ± 2</td>
<td>33.4 ± 5.5</td>
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<td>No</td>
<td>No</td>
<td>NA</td>
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<td>110 ± 4</td>
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<td>NA</td>
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<td>NA</td>
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<td>4.8 ± 0.1</td>
<td>87 ± 2</td>
<td>73.1 ± 11.3</td>
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<td>3.19 ± 0.34</td>
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<td>Intralipid Infusion, portal vein</td>
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<td>No</td>
<td>NA</td>
<td>10</td>
<td>5.0 ± 0.2</td>
<td>93 ± 3</td>
<td>76.9 ± 7.2</td>
<td>1.46 ± 0.32</td>
<td>2.94 ± 0.41</td>
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<tr>
<td>Saline Bolus</td>
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<td>Whole pancreas transplanted</td>
<td>NA</td>
<td>10</td>
<td>6.3 ± 0.2</td>
<td>115 ± 5</td>
<td>See Fig. 5C</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Intralipid Bolus</td>
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<td>Islet transplanted</td>
<td>10</td>
<td>6.1 ± 0.2</td>
<td>115 ± 5</td>
<td>See Fig. 5C</td>
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<td>NA</td>
<td>NA</td>
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<tr>
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<td>Islet transplanted</td>
<td>NA</td>
<td>10</td>
<td>5.6 ± 0.3</td>
<td>108 ± 7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Intralipid Bolus</td>
<td>NA</td>
<td>Islet transplanted</td>
<td>NA</td>
<td>10</td>
<td>5.8 ± 0.4</td>
<td>103 ± 9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>

Values are means ± SE for 7–9 observations. All organ blood flow values are given as ml·min⁻¹·g organ wt⁻¹. Pertinent statistical differences are referred to in RESULTS. NA, not applicable.

Bachem (St. Helen’s, Merseyside, UK), and heparin was from Lövens Läkemedel (Malmö, Sweden).

Analysis of blood. Immediately after induction of anesthesia and at the end of each experiment, arterial blood samples were secured and later analyzed for hematocrit, blood glucose concentrations with test reagent strips (Medisense Svenska, Sollentuna, Sweden), and for serum insulin concentrations with an ELISA (Rat Insulin ELISA; Mercodia, Uppsala, Sweden) for serum losses. Some of the animals were subjected to a vagotomy at the level of the esophagus where both the left and right crura were cut. Controls for the vagotomized rats were sham operated. This procedure has previously been described in detail (21) and is known to prevent the nervously mediated IBF response to nutrient stimulation (12).

Time-dependent effects of a bolus dose of Intralipid. When the blood pressure had remained stable for at least 20 min, Intralipid (1 ml) or saline (1 ml) was administered intravenously as a bolus dose. Blood flow measurements (see below) were then performed 3, 10, or 30 min later in vagotomized and nonvagotomized rats. Thus, at each time point, four groups of animals were studied, namely saline- or Intralipid-injected nonvagotomized rats and saline- or Intralipid-injected vagotomized rats.

Effects of β-adrenergic antagonists and N⁵-nitro-L-arginine methyl ester on blood perfusion after acute Intralipid administration. Because the most pronounced effects on blood perfusion occurred 10 min after administration of Intralipid, we chose to further study such animals by intravenously administering the nonselective β-adrenoceptor antagonist propranolol (5 mg/kg body wt 15 min before blood flow measurements) or the β₁-adrenoceptor selective antagonist SR-
59230A (1 mg/kg body wt 15 min before blood flow measurements). These substances were given to saline- or Intralipid-injected nonvagotomized rats and saline- or Intralipid-injected vagotomized rats (see Table 1).

In a separate set of experiments, we instead intravenously administered $N^\omega$-nitro-L-arginine methyl ester (l-NAME, 25 mg/kg body wt; Sigma-Aldrich) 15 min before the blood flow measurements. This drug was given only to vagotomized control rats and vagotomized Intralipid-injected animals.

**Infusion of Intralipid in the portal vein.** The animals were prepared for blood flow measurements as given above, and some of the animals were vagotomized. The midline incision in the upper part of the abdominal cavity was used to visualize the portal vein immediately before its entering the liver hilus by gently moving the intestines upward to the left of the animal (9). A catheter was then placed in the portal vein and used to infuse 0.1 ml saline or 20% Intralipid during 10 min. After this, blood flow measurements were performed as outlined below. Before and after the infusion, blood samples for analysis of glucose, insulin, FFAs, and triglycerides were secured.

**Blood flow measurements with microspheres.** Blood flow measurements were then performed with a microsphere technique as previously described (10). Briefly, a total of $3.0 \times 10^5$ black, nonradioactive microspheres (EZ-Trac; Triton Microspheres, San Diego, CA) with a diameter of 10 $\mu$m were injected via the catheter with its tip in the ascending aorta during 10 s. Starting at the microsphere injection, and continuing for a total of 60 s, an arterial blood sample was collected by free flow from the catheter in the femoral artery at a rate of $\sim 0.6$ ml/min. The exact withdrawal rate was confirmed in each experiment by weighing the sample. Arterial blood was collected from the carotid catheter for determination of hematocrit and blood glucose and serum insulin concentrations as given above.

The animals were then killed, and the pancreas and adrenal glands were removed in toto, blotted, and weighed. Samples of both glands, and the endogenous and transplanted duodenum were measured with the microsphere technique referred to above.

**Islet transplantations.** Pancreatic islets were isolated and cultured as previously described (45). The islets were cultured free-floating, with 150 islets in each culture dish, in 5 ml culture medium, RPMI 1640 (Sigma-Aldrich, Stockholm, Sweden) supplemented with L-glutamine (Sigma-Aldrich), 11.1 mmol/l D-glucose, benzylpenicillin (100 U/ml; Roche Diagnostics Scandinavia, Bromma, Sweden), streptomycin (0.1 mg/ml; Sigma-Aldrich), and 10% (vol/vol) fetal calf serum (Sigma-Aldrich). The medium was changed every second day.

Male Wistar-Furth rats were used as recipients. These animals were anesthetized with an intraperitoneal injection of evkivitine (see above). The left kidney was exposed through a flank incision, and 250 islets were implanted as an aggregate under the renal capsule.

Four weeks later the transplanted rats were anesthetized with an intraperitoneal injection of thiobutabarbitar (Inactin). The animals were placed on a servo-controlled heated operating table to maintain body temperature, and breathed spontaneously through a tracheostomy. Polyethylene catheters were inserted in the femoral artery and vein. The arterial catheter was connected to a pressure transducer (PDCR 75/1; Druck) to allow constant monitoring of the mean arterial blood pressure, whereas the venous catheter was used to continuously infuse Ringer solution (6 ml/kg body wt $^{-1}$ h$^{-1}$).

A subcutal left flank incision was made to visualize the graft-bearing left kidney. The kidney and its vascular stalk were gently dissected free from surrounding tissues and immobilized in a Lucite cup. The kidney was then embedded in pieces of cotton wool soaked in Ringer solution and covered with mineral oil (Apoteksbolaget, Uppsala, Sweden) heated to body temperature to prevent evaporation and thereby keep the kidney moist and at body temperature.

**Laser-Doppler flow probes (Transonic BLF 21 series, probe diameter 1.2 mm; Transonic, Ithaca, NY) were positioned with the aid of micromanipulators to measure the blood flow of the islet graft and the adjacent renal cortex as previously described in detail (11). Continuous measurements of renal cortical and islet graft blood flow after a bolus injection of 1 ml saline followed by 1 ml of Intralipid 20 min later were continuously recorded in a computer (Chart 5 for Windows; AD Instruments, Colorado Springs, CO).

**Isolation and preparation of islets for single-islet perfusion.** C57BL mice were killed by cervical dislocation, and the pancreas was quickly removed and placed in cold (4°C) albumin-enriched (1% Dulbecco’s minimal enriched medium (Sigma-Aldrich, Stockholm, Sweden). Islets were dissected with their arterioles intact (30) using a modification of a previously described technique for renal glomeruli (38, 39). The time for dissection was limited to 60 min, and most of the obtained islets were large (diameters $\sim 400 \mu$m). For further details, see our previous publications (30, 31).

The experimental set-up allowed us to measure the diameter of the afferent islet arterioles continuously and to record changes at a resolution of $< 0.2 \mu$m. Criteria for using an islet arteriole were remaining basal tone, no pronounced vasodilatation, and a fast and complete constriction in response to administration of KCl solution (100 mmol/l) at the end of the experiments.
Each experiment began with a 15-min equilibrium period with buffer containing 5.5 mmol/l glucose in both the bath and perfusion solution. Thereafter, 1% (vol/vol) of Intralipid was added to the buffer, and the islets were perfused with this for 30 or 60 min. In some of the experiments, SR-59230A (10^{-6} M) was added to the buffer during the last 30 min. In a separate group of islets, the blood vessels were preconstricted by adding norepinephrine (10^{-6} M) to the buffer throughout the experiments. After a 15-in equilibrium period, 1% Intralipid was added to the medium during 30 min, and then also SR-59230A was added for an additional 30 min. Each perfusion was terminated by administration of KCl (100 mmol/l) to ascertain that the arterioles were able to contract.

Statistical calculations. All values are given as means ± SE. Probabilities (P) of chance differences were calculated with Student’s unpaired t-test or with one-way repeated-measurement ANOVA with Tukey’s correction (SigmasStat; SSPD, Ertalf, Germany). For calculation of statistical differences between fractions, nonparametric ANOVA with Tukey’s correction was used. A value of P < 0.05 was considered to be statistically significant.

RESULTS

A summary of all experimental groups is given in Table 1. A total of 12 animals were excluded from the study because of reduced mean arterial blood pressure (<80 mmHg; n = 9) or inadequate mixing of the microspheres with the arterial circulation (n = 3). Hematocrit values were similar (~44%) in all experimental groups (data not shown).

The serum triglyceride concentrations were increased approximately fourfold, and FFA doubled 10 min after Intralipid administration in both nonvagotomized and vagotomized rats (Table 2). At both 3 and 30 min after administration, triglyceride and FFA values were approximately doubled (Table 2).

Time-dependent effects of Intralipid. No significant changes in mean arterial blood pressure were induced by Intralipid administration or vagotomy at any of the time points studied (Table 1). The rationale for using vagotomy in our experiments is that it has previously been shown to prevent nutrient-induced nervously mediated IBF increase but not that mediated by islets (12). Intralipid administration increased total pancreatic blood flow (PBF) 10 and 30 min after administration (Fig. 1A) and IBF 3, 10, and 30 min after injection in nonvagotomized rats (Fig. 1B). When Intralipid was administered to vagotomized rats, neither total PBF nor IBF was affected after 3 min, whereas the latter was slightly increased 30 min postinjection. However, there was a pronounced increase in total PBF at 10 min and an even more pronounced ~10-fold increase in IBF.

Also duodenal and renal blood flow values were increased 10 min after Intralipid administration to vagotomized rats, whereas no differences were seen in colonic blood flow (Table 1). The corresponding blood flow values were unaffected in the other groups (Table 1).

The marked Intralipid-induced increase in islet blood perfusion in vagotomized rats coincided with a pronounced increase in serum insulin concentrations (Fig. 1C). This was paradoxically associated with a slightly increased blood glucose concentration (Table 1). An increased insulin concentration could also be seen 30 min after Intralipid administration, in both vagotomized and nonvagotomized rats, without any associated changes in blood glucose concentrations (Table 1).

Effects of β-adrenergic antagonists. The nonselective β-adrenoceptor inhibitor propranolol decreased total PBF (Fig. 2A), whereas both propranolol and the β_{2}-adrenoceptor selective inhibitor SR-59230A decreased IBF (Fig. 2B) in control saline-treated Wistar-Furth rats. The Intralipid-induced PBF and IBF increase 10 min after administration in nonvagotomized rats was prevented by SR-59230A, but not by propranolol. Both propranolol and SR-59230A markedly decreased the total pancreatic and islet hyperperfusion with blood seen after Intralipid administration in vagotomized rats.

 Pretreatment with propranolol or SR-59230A did not affect colonic, renal, or adrenal blood flow in any of the treatment groups (Table 1). The increase in duodenal blood flow elicited by Intralipid could be prevented by pretreatment with SR-59230A (1.60 ± 0.31 vs. 2.79 ± 0.31 ml·min^{-1}·g^{-1}; P = 0.020 with ANOVA).

Propranolol decreased the blood pressure to the same degree in all groups of rats, whereas SR-59230A had only minor effects in nonvagotomized rats (Table 1). The latter substance, however, decreased blood pressure in vagotomized rats given Intralipid (Table 1).

Blood glucose concentrations were only marginally affected by the pharmacological treatment and varied between 5 and 7 mmol/l (Table 1). The increase in serum insulin concentrations elicited by Intralipid in itself and the marked potentiation of this release were prevented by pretreatment with both investigated substances in vagotomized rats (Fig. 2C).

Effects of l-NAME. These experiments were performed because we have previously shown that an intact NO production is a prerequisite to maintain high basal islet blood perfusion and is involved in IBF increases in itself (47). Administration of the nitric oxide synthase (NOS) inhibitor l-NAME decreased both total PBF (Fig. 3A) and IBF (Fig. 3B) in control saline rats. Furthermore, the substance totally prevented any increase whatsoever in the total PBF or IBF values in vagotomized Intralipid-injected rats. Mean arterial blood pressure was increased, and the other regional blood flow values decreased, after l-NAME injection (Table 1). Blood glucose and serum insulin concentrations were unaffected by l-NAME in control rats, whereas the increase seen after Intralipid admin-

### Table 2. Serum triglyceride and free fatty acid (FFA) concentrations in anesthetized Wistar-Furth rats at different times after an intravenous bolus injection of 1 ml of saline or Intralipid

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time, min</th>
<th>Plasma Triglycerides, mmol/l</th>
<th>Serum FFA, mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline, no vagotomy</td>
<td>3</td>
<td>0.93 ± 0.12</td>
<td>490 ± 61</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.966 ± 0.14</td>
<td>470 ± 49</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>0.991 ± 0.15</td>
<td>491 ± 62</td>
</tr>
<tr>
<td>Intralipid, no vagotomy</td>
<td>3</td>
<td>1.94 ± 0.23</td>
<td>790 ± 90</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>4.13 ± 0.60*</td>
<td>1,806 ± 244*</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>1.75 ± 0.20</td>
<td>906 ± 116</td>
</tr>
<tr>
<td>Saline, vagotomy</td>
<td>3</td>
<td>1.01 ± 0.17</td>
<td>430 ± 65</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.95 ± 0.17</td>
<td>432 ± 70</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>0.92 ± 0.18</td>
<td>478 ± 57</td>
</tr>
<tr>
<td>Intralipid, vagotomy</td>
<td>3</td>
<td>2.05 ± 0.30</td>
<td>926 ± 109</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>4.67 ± 0.56*</td>
<td>1,990 ± 238*</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>1.84 ± 0.26</td>
<td>799 ± 120</td>
</tr>
</tbody>
</table>

All values are means ± SE for 6 experiments in each group. FFA, free fatty acid. Some of the animals were vagotomized before injection of saline or Intralipid. All values in the Intralipid-infused animals are higher (P < 0.01) compared with saline-infused rats at the same time point. *P < 0.005 compared with the values in Intralipid-infused rats at 3 and 30 min.
Infusion of Intralipid in the portal vein. We have previously demonstrated that portal receptors for hormones and glucose can markedly affect IBF (9) and therefore wanted to determine if increased lipid concentrations could be sensed directly by the liver. Infusion of Intralipid or saline in the portal vein of control or vagotomized rats did not affect total pancreatic (Fig. 4A) or islet (Fig. 4B) blood flow, and neither were the mean arterial blood pressure or any of the other regional blood flow values affected (Table 1). Serum insulin concentrations were, however, increased in nonvagotomized Intralipid-injected rats (Fig. 4C). It should be noted that this infusion did not alter serum triglyceride concentrations in these rats (125 ± 30 vs. 108 ± 14 mg/dl in Intralipid- and saline-infused rats, respectively).

Pancreas-duodenum transplantations. This represents a model where the pancreas is externally denervated, whereas the internal nervous system remains intact. The latter is of importance for modulation of both islet function and IBF (29).

We show that an induced acute elevation of blood lipids by Intralipid administration increases blood flow to especially the pancreas-duodenum transplantations. This represents totally denervated islets at the time point used for our study (26) (Fig. 6). Administration of a bolus dose of saline (time 0) affected neither renal cortical nor islet graft blood perfusion. Intralipid (given at time 20 min) induced only minor and nonsignificant changes in renal cortical blood flow. Islet graft blood flow, on the other hand, increased ~50% after Intralipid injection and remained high (P < 0.05 at all time points) for at least 30 min. These animals demonstrated similar mean arterial blood pressure and blood glucose concentrations as similarly treated Wistar rats exposed to microsphere blood flow measurements (Table 1). The serum insulin concentrations were increased by ~100% after Intralipid administration (2.50 ± 0.59 vs. 5.78 ± 1.34 ng/ml, respectively, P < 0.01, n = 7 and 8, respectively).

Islet transplantations. This technique was applied to study a single islet without any influence from the nervous system, endocrine system, or paracrine regulators. When Intralipid was administered to vascularly isolated islets ex vivo where the blood vessels were preconstricted with norepinephrine, a rapidly occurring (within 5 min) vasodilatation that approached 60% was observed (Fig. 7). After 30 min, SR-59230A was added to the perfusate, but this did not affect the vascular response. When similar experiments in islets not treated with norepinephrine were perfused, the response was much less and amounted to a dilation of ~15% (Fig. 7).

**DISCUSSION**

We show that an induced acute elevation of blood lipids by Intralipid administration increases blood flow to especially the
pancreatic islets but also the upper gastrointestinal tract in general. A preceding acute abdominal vagotomy potentiates in particular pancreatic islets but also the upper gastrointestinal tract in general. These responses are mainly mediated through $\beta_3$-adrenoceptors and NO. The blood flow increased in concert with and to the same extent as serum insulin concentrations. In chronically denervated pancreatic islets, i.e., after whole pancreas or islet transplantation, Intralipid increases blood flow and insulin release but only to the same extent as after Intralipid administration to a control rat with intact vagus nerves. Thus, it seems as if an acute, but not a chronic, vagotomy potentiates the Intralipid-induced blood flow and insulin increase. In freshly isolated vascularly perfused islets, Intralipid induces a 60% dilation that cannot be prevented by simultaneous $\beta_3$-adrenoceptor inhibition. A brief mentioning of possible effects of anesthesia is warranted. We used thiobutabarbital, which we have previously shown to have little effect on glucose tolerance and regional blood flow values (17). To what extent, if any, triglycerides and FFAs may disturb the measurements is not known, but seems unlikely.

Acute Intralipid injection, in doses not increasing blood viscosity (25), increased as expected both serum triglycerides and FFA, an effect that was most pronounced after 10 min, and then gradually decreased. An acute increase in FFA and triglycerides of this magnitude is known to enhance insulin secretion both in vitro and in vivo (16, 51, 52), and we could confirm this. The insulin increase could to a large extent be prevented by inhibition of $\beta_3$-adrenoceptors, and completely by nonselective inhibition of $\beta$-adrenoceptors by propranolol. The latter also blocks $\beta_2$-adrenoceptors, which stimulate insulin release (2). Interestingly, when Intralipid was infused in the portal vein, which increased intrahepatic lipid concentrations without affecting those in serum, an increased insulin concentration was also seen. This probably reflects the presence of intrahepatic receptors for FFA, which convey signals through the vagus nerve to the hypothalamus (36). Efferent signals follow the same route and modulate hepatic glucose production and insulin release (32, 41). In line with this, we observed that a simultaneous vagotomy prevented the insulin release in this setting. We also saw an increase in serum insulin after Intralipid administration to whole pancreas or islet-transplanted rats, but since these animals also possessed an intact endogenous pancreas it precludes any conclusions on the origin of this insulin.

The findings referred to above on insulin secretion are, as mentioned, confirmatory to other studies (16, 51, 52) and probably reflect direct lipid-mediated metabolic effects on the $\beta$-cells, and receptors in the central nervous system and liver, since the blood glucose concentrations were similar in these groups. A very surprising finding was the extreme potentiation of the Intralipid effects by a simultaneous acute vagotomy, which caused a 10- to 15-fold increase in insulin concentrations, as well as IBF, the latter being further discussed below.

**Fig. 2.** Total pancreatic (A) and islet (B) blood flow in Wistar-Furth rats injected iv with 1 ml Intralipid or saline 10 min before blood flow measurements. Some rats were subjected to a vagotomy before administration of the test substances. Some animals were pretreated by administering propranolol (5 mg/kg body wt) or SR-59230A (1 mg/kg body wt) iv 15 min before the blood flow measurements. In C, the serum insulin concentrations are given. Values are means ± SE for 7–8 experiments. *P < 0.05 compared with the control saline animals in the control group. #P < 0.05 compared with the corresponding control saline group. §§P < 0.05 compared with all other groups.
It should be noted that only minor or no effects on blood glucose were seen. The reason is somewhat unclear; the insulin values have only been elevated for a short time period. If we follow the glucose values at short intervals (data not shown from separate experiments), we can indeed see a drop to $\sim 3$

Fig. 3. Total pancreatic (A) and islet (B) blood flow in Wistar-Furth rats injected iv with 1 ml Intralipid or saline 10 min before blood flow measurements. Some rats were subjected to a vagotomy before administration of the test substances. Some animals were pretreated by administering $N^G$-nitro-$l$-arginine methyl ester ($l$-NAME; 25 mg/kg body wt) 15 min iv before the blood flow measurements. In C, the serum insulin concentrations are given. Values are means ± SE for 7–8 experiments. §$P < 0.05$ compared with the nonvagotomized control animals. *$P < 0.05$ compared with the corresponding vagotomized control animal.

Fig. 4. Total pancreatic (A) and islet (B) blood flow in Wistar-Furth rats infused in the portal vein with 0.1 ml of either saline or Intralipid (20% solution) for 10 min before blood flow measurements. Some rats were subjected to a vagotomy before the infusion. In C, the serum insulin concentrations are given. Values are means ± SE for 7–8 experiments. *$P < 0.05$ compared with the nonvagotomized control animals.

It should be noted that only minor or no effects on blood glucose were seen. The reason is somewhat unclear; the insulin values have only been elevated for a short time period. If we follow the glucose values at short intervals (data not shown from separate experiments), we can indeed see a drop to $\sim 3$
mmol/l at 15 min that then returns to normal at \( \sim 20 \) min. This potentiation of insulin secretion was completely abolished by simultaneous treatment with propranolol or SR-59230A, suggesting that an increased activity in the sympathetic nervous system (\( \beta_2 \)-adrenoceptors) was responsible. The possible association between islet blood perfusion and insulin release will be discussed further below.

Intralipid administration caused a time-dependent stimulation of both total pancreatic (PBF) and islet (IBF) blood flow in anesthetized normoglycemic rats. The effect prevailed for at least 30 min, and nonselective \( \beta \)-adrenoceptor inhibition with propranolol did not prevent this Intralipid-induced blood flow increase in nonvagotomized rats, whereas the \( \beta_3 \)-adrenoceptor antagonist SR-59230A did. The reason for this discrepancy is unknown and contrasts with our findings on insulin rerelease referred to above. However, we have earlier seen that a \( \beta_2 \)-adrenoceptor agonist decreases IBF in normal rats despite stimulation of insulin release (19). It may be that prevention of this effect by propranolol maintains IBF after the Intralipid administration. The inhibitor that we used, SR-59230A, is generally considered to be a specific \( \beta_3 \)-adrenergic receptor inhibitor. To confirm our findings, we also performed a few pilot experiments on vagotomized rats given Intralipid where we instead used another alleged \( \beta_3 \)-adrenergic receptor-specific inhibitor, namely L-748,337 (Tocris Biosciences, Leicester, UK), and confirmed our findings (data not shown).

When an acute vagotomy was performed, a marked increase in both PBF and IBF occurred 10 min after Intralipid administration. PBF was increased 5-fold and IBF more than 10-fold, i.e., IBF in these animals was similar to the total PBF in the control animals. Pretreatment with both propranolol and SR-PANCREATIC BLOOD FLOW (ml/min x g)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intralipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Transplanted</td>
<td>0.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Fig. 5. Total pancreatic (A) and islet (B) blood flow in the endogenous and transplanted pancreas of Wistar-Furth rats receiving a syngeneic pancreatic-duodenal transplant 4 wk earlier. The rats were injected iv with 1 ml Intralipid or saline 10 min before blood flow measurements. Values are means \( \pm SE \) for 7 experiments. * \( P < 0.05 \) compared with the endogenous gland in control rats (*) and the transplanted pancreas in control rats (§).

Fig. 6. Left kidney cortical and islet graft blood flow measured with laser-Doppler flow probes after surgical preparation in anesthetized syngeneically islet-implanted Wistar-Furth rats 4 wk after transplantation. At time 0, 1 ml saline was given intravenously, and at time 20 min (arrow) an injection of 1 ml Intralipid was given. Values are means \( \pm SE \) for 8 experiments. All values from 25 min and onward are higher (\( P > 0.05 \)) in the islet grafts as calculated with Student’s unpaired t-test. The value 100% represents 8.9 and 14.0 tissue perfusion units for renal cortical and islet graft blood flow, respectively.

Fig. 7. Changes in the diameter of islet arterioles isolated from normoglycemic Wistar-Furth rats after administration of buffer containing 10% (vol/vol) Intralipid and SR-59230A (10^{-6} M) and/or norepinephrine (10^{-5}). Values are given in percent of the diameter before administration of any of the test substances (original diameter \( \sim 35 \) \( \mu \)m) in 7 animals/group. All values from 5 min and onward after Intralipid administration are higher (\( P < 0.05 \)) in the preconstricted arterioles. SR-59230A has no effect on arteriolar diameters.

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fig_6

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fig_7

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pretreated with L-NAME, a nonspecific powerful inhibitor of NOS (49) we also performed studies in which the animals were vagotomized nontransplanted animals. In islet-transplanted rats, the increase in graft blood flow was ~50%. This suggests that the intrinsic pancreatic nervous system [mainly calcitonin gene-related peptide and substance P (29)] helps to maintain reactivity to increased blood lipids.

Intralipid administration caused an increase in graft blood flow also in the islet transplants, even though it was only 50%, i.e., similar to that seen in the endogenous pancreas when Intralipid was given alone. This can reflect a lipid-mediated increase in β-cell metabolism, and, in the endogenous pancreas, increased islet metabolism per se causes a vasodilation in the islets preferentially mediated by adenosine (12). The denervation is likely to help unmask the metabolic component of the IBF and PBF responses.

That Intralipid has a direct effect on islet vasculature, i.e., endothelial and vascular smooth muscle cells, independent of the nervous system was confirmed by our findings in isolated ex vivo perfused single islets. Intralipid induced a 15% dilation of the islet afferent arteriole when given to islets receiving no pretreatment. However, during the more physiologically relevant conditions when the vasculature had been preconstricted with norepinephrine, a 60% dilation was seen. Such dilation could, since the blood flow according to Poiseuille’s law is proportional to the fourth power of the radius, explain the very high blood flow increase. However, coadministration of SR-59230A did not affect arteriolar vasodilation at all in these experiments. Thus, arteriolar effects of Intralipid may be caused by a direct effect on the endothelium and/or vascular smooth muscle, even though the nature of this effect is unknown. The findings nevertheless suggest that β3-adrenoceptors of importance for the IBF are absent from islet arterioles.

Besides the islets, also the liver plays a crucial role in glucose metabolism. It is known that both blood lipid and glucose concentrations are monitored in the liver (36) and hypothalamus (41) and that this information is used to modify hormone release and blood perfusion of islets. Local hyperglycemia in either the liver or brain increases IBF and insulin secretion (9, 21). In the present study, we infused Intralipid in the portal vein to achieve a high intrahepatic concentration without affecting systemic blood lipids. This led to an increase in serum insulin concentrations but did not affect PBF or IBF.

The question is to what extent our findings are relevant for islet physiology during normal and diabetic conditions. We believe, as stated already 15 years ago by us (18) and later also by others (33, 43), that development of type 2 diabetes, at least in rodents, is associated with a dysfunction in islet endothelium. This is initially seen when IBF is increased to serve the augmented need for insulin production seen during the early stages of insulin resistance and overt type 2 diabetes. The increased blood perfusion is likely to adversely affect islet arteriolar and capillary endothelium, leading to impaired formation of local endothelium-derived factors and maybe also the vascular smooth muscle cells. This maintains IBF abnormalities, and the endothelial dysfunction may also lead to changes in replication rate of islet endocrine cells since endothelial cell metabolism, and, in the endogenous pancreas, increased islet metabolism per se causes a vasodilation in the islets preferentially mediated by adenosine (12). The denervation is likely to help unmask the metabolic component of the IBF and PBF responses.

That Intralipid has a direct effect on islet vasculature, i.e., endothelial and vascular smooth muscle cells, independent of the nervous system was confirmed by our findings in isolated ex vivo perfused single islets. Intralipid induced a 15% dilation of the islet afferent arteriole when given to islets receiving no pretreatment. However, during the more physiologically relevant conditions when the vasculature had been preconstricted with norepinephrine, a 60% dilation was seen. Such dilation could, since the blood flow according to Poiseuille’s law is proportional to the fourth power of the radius, explain the very high blood flow increase. However, coadministration of SR-59230A did not affect arteriolar vasodilation at all in these experiments. Thus, arteriolar effects of Intralipid may be caused by a direct effect on the endothelium and/or vascular smooth muscle, even though the nature of this effect is unknown. The findings nevertheless suggest that β3-adrenoceptors of importance for the IBF are absent from islet arterioles.

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During hyperglycemia and/or hyperlipidemia, a paradoxical increase in endothelial NOS expression occurs (13, 35). Because lack of cofactors, endothelial NOS becomes uncoupled and instead produces reactive oxygen species (ROS) (13, 35), some of which are known to stimulate IBF (24). Actually, the powerful ROS generator alloxan acutely increases IBF, which is very likely caused by the formed ROS (24). The present finding that vagotomy potentiates the blood flow effects does not fit well with this observation. Furthermore, total PBF, as opposed to that of the islets, is markedly decreased by ROS (24), and we actually saw a marked increase in the former in the present study. Thus, we deem it unlikely that ROS is of major importance for the observed blood flow effects.

In view of the profound sensitivity of islet vasculature to NO (49) we also performed studies in which the animals were pretreated with l-NAME, a nonspecific powerful inhibitor of NOS (49) that, as expected, markedly decreased all organ blood flow values, including IBF and PBF also after vagotomy + Intralipid. We interpret this to reflect, as previously suggested by us (48, 49), that the islet vasculature in particular is extremely dependent on local production of NO, which is permissive and necessary to ascertain the high basal blood perfusion of this organ.

To further ascertain the importance of nerves for the observed responses, we used two models of transplantation, viz. whole pancreas-duodenum and isolated islet grafts, at a time point when no exogenous innervation had occurred. The former animals possessed one normally innervated endogenous gland and one externally denervated transplanted gland that, however, contained nerves intrinsic to the pancreas (29). Isolated islet grafts are completely devoid of innervation during the first 3–4 mo postimplantation (27). This means that all of these animals lacked both sympathetic and parasympathetic innervation, the latter being similar to a chronic vagotomy.

In whole pancreas transplants, Intralipid acutely increased both IBF and PBF in the endogenous pancreas, whereas only IBF was stimulated in the graft. The latter response amounted to a threefold increase, i.e., considerably smaller than in acutely vagotomized nontransplanted animals. In islet-transplanted rats, the increase in graft blood flow was ~50%. This suggests that the intrinsic pancreatic nervous system [mainly calcitonin gene-related peptide and substance P (29)] helps to maintain reactivity to increased blood lipids.
hyperlipidemia. This suggests that the interactions between autonomic nerves in the regulation of IBF are more complex than previously expected. On speculation that emanates from the results is that parasympathetic nerves are mainly involved in the increase in IBF seen during hyperglycemia, whereas the sympathetic nerves are more important during hyperlipidemia.

GRANTS

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DISCLOSURES

There are no conflicts of interest for any of the authors.

AUTHOR CONTRIBUTIONS


REFERENCES


