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Pancreatic islet blood flow is selectively enhanced by captopril, irbesartan and pravastatin, and suppressed by palmitate ☆

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Abstract

Diabetic patients are often treated with a lipid lowering statin and an ACE inhibitor or angiotensin receptor antagonist against hypertension or albuminuria. These drugs may also improve glucose tolerance, but the mechanism for this remains elusive. We now studied whether these drugs and the fatty acid palmitate influence insulin secretion *in vivo* in rats through effects on islet blood perfusion. Whole pancreatic blood flow was markedly increased by captopril and irbesartan, and decreased by palmitate. Islet blood flow was significantly and preferentially enhanced by captopril, irbesartan, and pravastatin, and suppressed by palmitate. Both captopril and irbesartan raised serum insulin concentrations significantly. However, glycemia was not affected in any group. In conclusion, the present study suggests that a local pancreatic RAS and pravastatin may be selectively controlling pancreatic islet blood flow and thereby influencing insulin secretion. The antidiabetic actions of statins and RAS inhibitors might in part occur through the beneficial direct islet effects shown here. Conversely, free fatty acids that are elevated in type 2 diabetic patients may contribute to an impaired nutritive islet blood flow and thereby further aggravate the diabetic state by limiting the supply of insulin needed to curb hyperglycemia.

Keywords: Islet; Blood flow; Microcirculation; Renin-angiotensin system; Statin; ACE inhibitor; Angiotensin receptor antagonist; Insulin; Diabetes

The systemic renin-angiotensin system (RAS) plays a crucial role in the regulation of arterial blood pressure. In the past few years, it has become increasingly clear that local RAS also exist in various tissues, implying that high local levels of angiotensin II (Ang II) might exert paracrine influences on neighboring cells [1,4–7]. In the pancreas of several species, mRNA encoding angiotensinogen and renin, as well as substantial levels of angiotensin II, have been detected [1,4–7]. Ang II has been shown to adversely influence pancreatic and islet blood flow through vasoconstractive effects [8,9]. Also, high affinity binding sites for Ang II were recently localized specifically to islet β-cells by double immunostaining and Ang II was found to block glucose-stimulated insulin secretion, an event fully reversible by losartan [5]. It is thus conceivable that pancreatic Ang II, locally produced by intrinsic RAS, may adversely influence insulin secretion *in vivo*, either directly by suppressing β-cell insulin exocytosis or indirectly through inhibitory effects on islet blood perfusion [5]. This may be of particular importance in diabetic patients since hypertension is markedly overrepresented in these individuals [2,3], and angiotensinogen expression seems to be upregulated by hypertension [2,3]. Hence, many diabetic patients are treated with ACE inhibitors or angiotensin receptor antagonists against their hypertension or as part of a renal protection strategy. An additional hallmark of diabetic cardiovascular risk is hyperlipidemia and elevated serum levels of free fatty acids; consequently many diabetic patients use lipid lowering drugs, most notably statins. Interestingly, both ACE inhibitors or angiotensin receptor antagonists and certain statins have been reported to decrease the risk

☆ *Abbreviations:* ABF, adrenal blood flow; ACE, angiotensin-converting enzyme; Ang II, angiotensin II; ELISA, enzyme-linked immunosorbent assay; IBF, islet blood flow; KBF, kidney blood flow; NO, nitric oxide; PBF, pancreatic blood flow; RAS, renin-angiotensin system.

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of developing diabetes in large clinical trials [2]. However, the mechanisms behind these antidiabetic effects remain elusive. In this paper, we aimed at evaluating the influence of ACE inhibition, angiotensin receptor antagonism, pravastatin treatment, and palmitate administration on pancreatic and islet blood flow, as well as on blood glucose and insulin concentrations, in the rat. We show that these vasoactive drugs that are frequently given to diabetic patients may directly stimulate the insulin-secreting β-cell by preferentially increasing islet blood flow and that palmitate may exert opposite effects.

Materials and methods

Animals and drugs. Male Wistar rats (ScanBur, Sollentuna, Sweden), weighing 300–350 g, were used in all experiments. The animals had free access to pelleted food (Type R34; ScanBur, Sollentuna, Sweden) and tap water at all times. All experiments were approved by the local Animal Ethics Committee at Uppsala University. Captopril and pravastatin were graciously donated by Bristol-Myers Squibb Company (New York, NY). Irbesartan was generously given by Sanofi-Synthelabo (Paris, France), whereas sodium palmitate was bought from Sigma–Aldrich (St. Louis, MO). Palmitate was administered in a 10% ethanol solution.

Blood flow measurements. The experiments were performed according to a protocol previously described in detail [16]. The animals were anesthetized with an intraperitoneal injection of thiobutabarbital sodium (120 mg/kg body weight; Inactin™, Research Biochemicals International, Natick, MA) and placed on a heated operating table to maintain body temperature. Polyethylene catheters were inserted into the ascending aorta, via the right common carotid artery, and into the left femoral artery. The catheter in the aorta was connected to a pressure transducer (model PDCR 75/1, Druck Ltd., Groby, Leicestershire, UK) to allow constant monitoring of the mean arterial blood pressure. After the blood pressure was stable, the animals were injected intravenously with 1 ml of saline, 1 ml of pravastatin (0.5 mg/kg), 1 ml of irbesartan (3 mg/kg) or 1 ml of captopril (3 mg/kg). All these substances were dissolved in saline. Ten minutes later, $1.5–2.0 \times 10^5$ non-radioactive microspheres (IMT, Stason Labs, Irvine, CA), with a mean diameter of 10 μm, were injected during 10 s via the catheter with its tip located in the ascending aorta. An arterial blood sample was collected from the catheter in the femoral arterial 5 s before the microsphere injection, and this process continued for a total of 60 s.

In a separate set of experiments (Fig. 4a–c), the effects of sodium palmitate on blood flow, serum insulin levels, and glycemia were investigated. This was done in a separate series, since the fatty acid had to be dissolved in 10% ethanol, and thus controls were given this solvent only. To this end, 1 ml of palmitate (60 mg/kg BW) or solvent was injected i.v. exactly as described for the other drugs above.

The exact withdrawal rate in each experiment was determined by weighing the sample. Additional arterial blood samples were obtained and later analyzed for hematocrit, blood glucose, and serum insulin concentrations (see below). After the animals were killed by cervical dislocation, the whole pancreas and both adrenal glands, as well as a 100-mg slice of the left kidney (including both cortex and medulla), were collected. The microsphere contents in these organs were determined separately. The organs were treated with a freeze-thawing technique [17], which enabled the visualization and localization of the microspheres from either the endocrine or the exocrine parenchyma of the pancreas. This was achieved by applying a microscope (Zeiss MB6; Leica AB, Stockholm, Sweden) equipped with both bright and dark field illumination. The former type of illumination allowed us to count the microspheres, whereas the latter enabled localization of the microspheres from either the endocrine or exocrine parenchyma [17]. The number of microspheres in the islets and exocrine tissue was counted as previously described in detail [17]. The microsphere contents of the adrenal glands were used as a control to confirm an even distribution of the microspheres in the arterial circulation. The microsphere content of each of the arterial reference samples was determined by transferring the samples to glass microfiber filters and counting the microspheres in a stereomicroscope.

The blood flow rates were calculated according to the formula $Q_{org} = Q_{ref} \times N_{org}/N_{ref}$, where Q_{org} denotes organ blood flow (mL/min), Q_{ref} denotes withdrawal rate of the reference sample (mL/min), N_{org} denotes the number of microspheres in the organ, and N_{ref} denotes the number of microspheres in the reference sample.

Measurement of glucose and insulin concentrations. Blood glucose concentrations were measured with test reagent strips (Medisense, Solna, Sweden) and serum insulin concentrations with ELISA kit (Rat Insulin ELISA, Mercodia, Uppsala, Sweden).

Statistical analysis. All values are given as means ± SEM. Statistical comparisons were made with two-way analysis of variance (ANOVA) (SigmaStat; SSPD, Erfart, Germany). A value of $p < 0.05$ was deemed statistically significant.

Results

Effects of captopril, irbesartan, and pravastatin on blood flow

Intravenous injection of captopril (3 mg/kg BW) and irbesartan (3 mg/kg BW) significantly enhanced PBF, whereas pravastatin (0.5 mg/kg BW) had no such effects (Fig. 1a). IBF was significantly (Fig. 1b) and preferentially (Fig. 1c) augmented by all three substances.

Renal blood flow was markedly increased after administration of irbesartan and captopril, whereas pravastatin had no effects (Fig. 2a).

Only captopril augmented adrenal blood flow significantly, whereas irbesartan and pravastatin failed to influence adrenal blood perfusion (Fig. 2b).

Blood glucose concentrations, serum insulin levels, and mean arterial blood pressure

Captopril and irbesartan increased serum insulin levels, whereas pravastatin failed to do so (Fig. 3a). There were no discernable differences in blood glucose concentrations between any of the treatment groups (Fig. 3b). No effects on mean arterial blood pressure (averaging 110 mmHg) were detected by any of the treatments given (data not shown).

Effects of palmitate on blood flow

As shown in Fig. 4a, i.v. injection of palmitate (60 mg/kg BW) significantly decreased PBF. As are evident from Fig. 4b and c, IBF was significantly (Fig. 4b) and preferentially (Fig. 4c) suppressed by palmitate. The fatty acid also decreased KBF, but did not significantly influence ABF (not shown). Palmitate affected neither mean arterial blood pressure, blood glucose nor serum insulin concentrations (data not shown).

Discussion

Type 2 diabetes is increasing in the Western world and is seen in ever-younger age groups [10]. We can expect this to

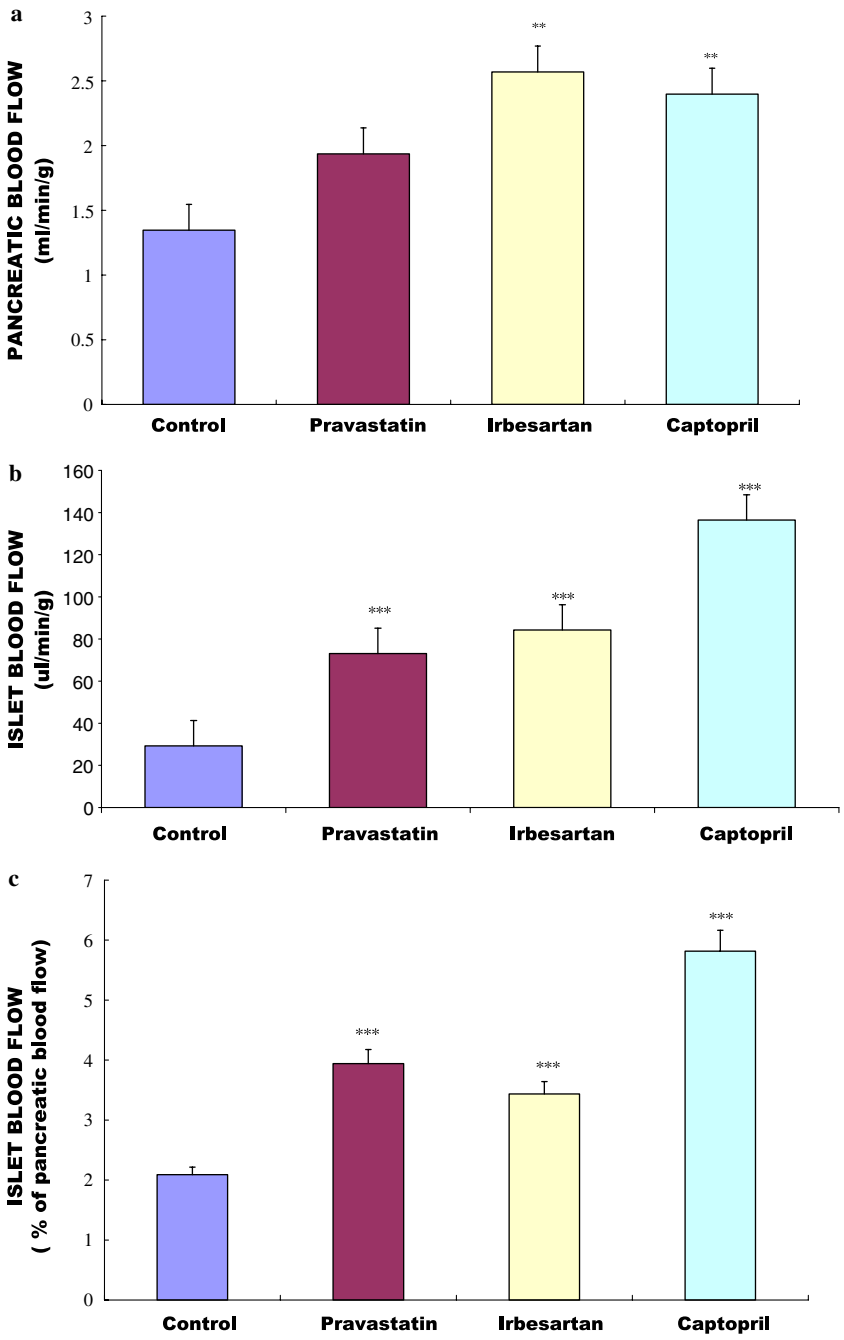

Fig. 1. Enhancement of pancreatic blood flow by captopril, irbesartan, and pravastatin. Following i.v. injection of captopril (3 mg/kg BW), irbesartan (3 mg/kg BW), or pravastatin (0.5 mg/kg BW) into normal rats, rates of blood perfusion in the whole pancreas (a), pancreatic islets (b), and the fraction of total pancreatic blood flow contributed by islets (c) were measured using a microsphere technique. Bars represent means ± SEM for eight independent experiments. ** and *** denote $p < 0.01$ and $p < 0.001$, respectively, for chance differences vs controls using ANOVA.

lead to momentous public health problems, especially in the form of premature cardiovascular morbidity. In terms of quantity, the most important complications of type 2 diabetes are macroangiopathies, i.e., myocardial infarction and stroke, which cause some 70% of the deaths related to type 2 diabetes [10,11]. In contrast to microangiopathies (e.g., nephropathy and retinopathy), where the causal relation to hyperglycemia is well supported, the link between hyperglycemia and macroangiopathy is uncertain, at least in terms of the possibility of reducing macrovascular morbidity solely by reducing hyperglycemia [11]. To improve prognosis of diabetic patients, several other risk factors [e.g., hypertension, albuminuria (a biomarker of generalized endothelial dysfunction), dyslipidemia, etc.] need to be treated as well [11]. The disease is characterized not only by hyperglycemia, but also insulin resistance with attendant dyslipidemia and increased levels of circulating free fatty acids. Diabetic patients whose risk factor profile is well controlled are thus being treated with one or more antidiabetic drugs, a lipid lowering statin, and an ACE

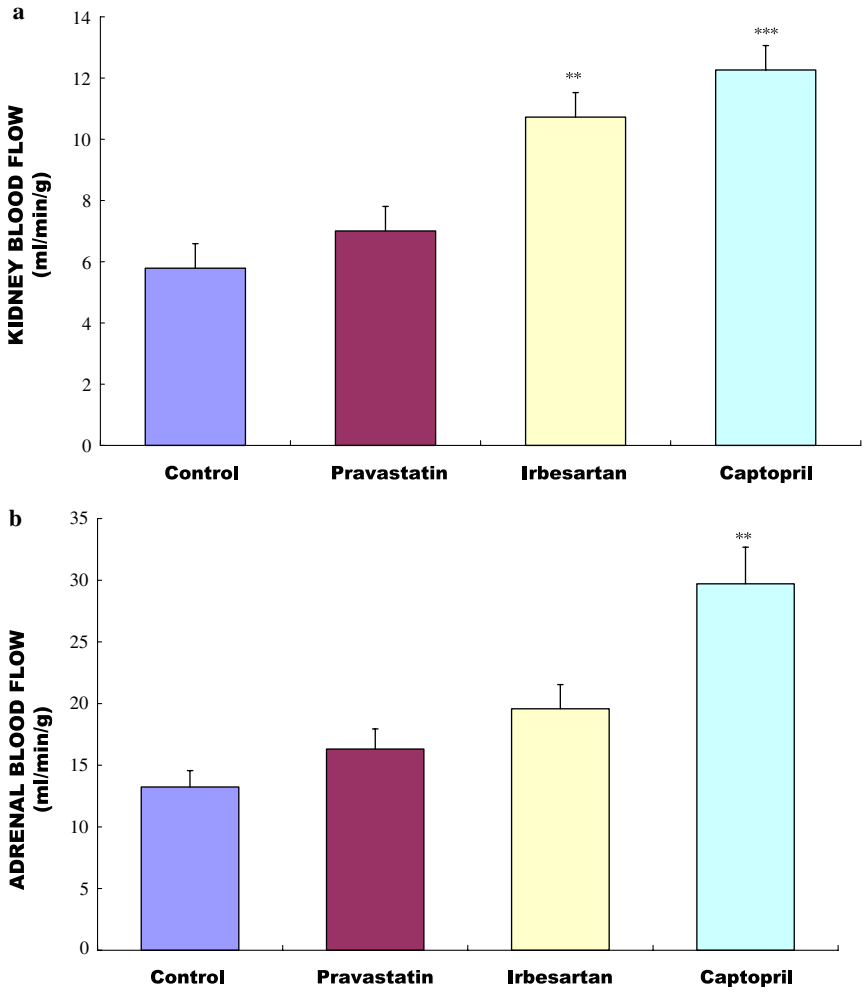

Fig. 2. Enhancement of renal blood flow and adrenal blood flow by captopril, irbesartan, and pravastatin. Following i.v. injection of captopril (3 mg/kg BW), irbesartan (3 mg/kg BW), or pravastatin (0.5 mg/kg BW) into normal rats, rates of blood perfusion in the kidneys (a) and adrenals (b) were measured using a microsphere technique. Bars represent means ± SEM for eight independent experiments. ** and *** denote $p < 0.01$ and $p < 0.001$, respectively, for chance differences vs controls using ANOVA.

inhibitor or angiotensin receptor antagonist against hypertension and albuminuria. These drugs are also exerting beneficial metabolic effects, causing an improved glucose tolerance in patients, but the precise nature of the mechanisms by which this is achieved remains elusive [2]. We have now studied whether these drugs influence islet blood perfusion, glycemia, and insulin levels *in vivo*.

Our study shows a preferential increase in pancreatic islet blood flow by pravastatin treatment, but no significant changes in total pancreatic, renal or adrenal blood flow. Neither is serum insulin nor blood glucose concentrations affected. The antithrombotic and anti-inflammatory effects by the statin may play a role in enhancing endothelium-dependent vasodilation [12]. Dyslipidemia—a salient feature in type 2 diabetes—is known to impair endothelium-mediated vasodilatation [18] and impaired endothelial function has been shown to result in diminished capillary recruitment [19]. Pravastatin has beneficial effect on endothelial function [20–22]; therefore, pravastatin may significantly influence selective tissue perfusion by restoring endothelial function. Beyond simply lowering cholesterol, it also has beneficial antithrombotic effect by inhibiting platelet aggregation and promoting local nitric oxide (NO) synthesis [23–25]. Since islet blood circulation is extremely sensitive to NO, a local increase in NO production would be expected to preferentially increase islet blood flow, rather than total pancreatic blood perfusion [25]. As this is exactly what happened in response to pravastatin, it is possible—albeit not proven—that local NO formation might be involved in the salutary effects of pravastatin noted in the current study. There appear to be important differences between the statins in this regard, as pravastatin is in a class of its own in terms of preventing diabetes [2,3,13]. Pravastatin is not metabolized by hepatic CYP-450 enzymes, shows very little binding to proteins, and is markedly hydrophilic. Whether these characteristics or other attributes, such as anti-inflammatory actions, underlie pravastatin's anti-diabetogenic effect remains to be shown. Other mechanisms are conceivable, for instance direct effects on the endocrine pancreas. *In vitro* studies have shown that lipophilic statins (simvastatin) inhibit glucose-stimulated insulin secretion by blocking voltage-gated L-type Ca^{2+} channels in insulin-secreting

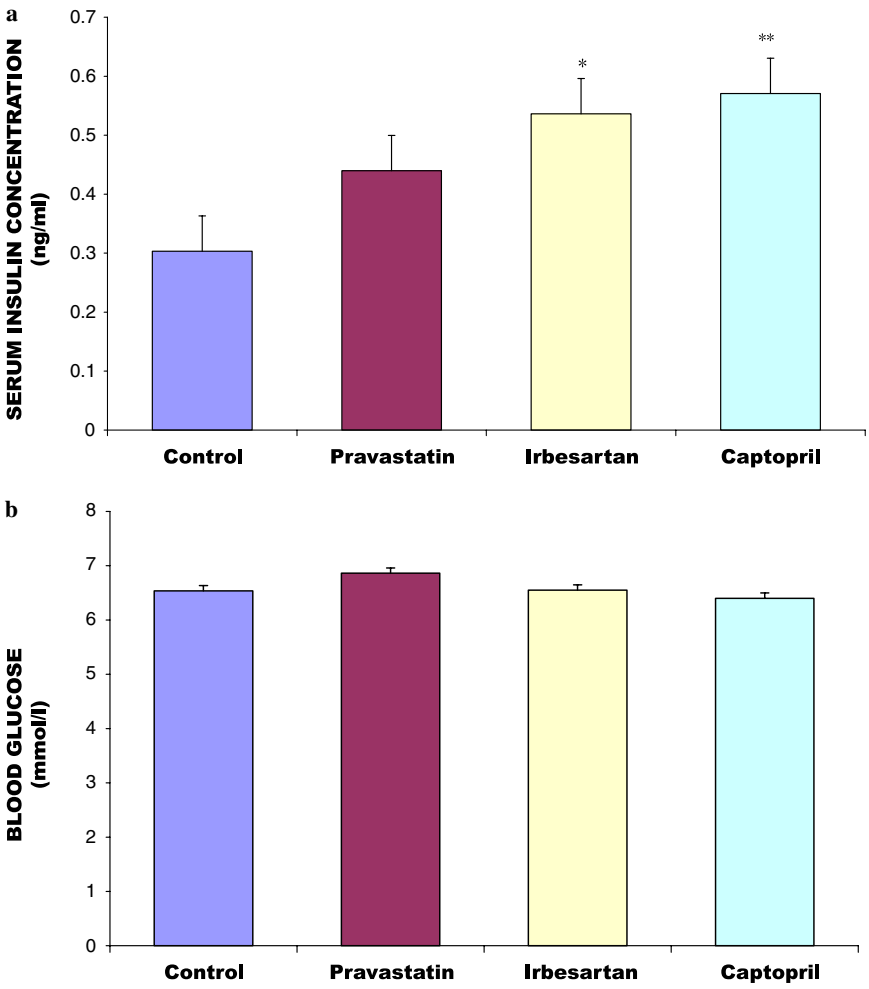

Fig. 3. Effects of captopril, irbesartan, and pravastatin on serum insulin concentrations and blood glucose levels. Following i.v. injection of captopril (3 mg/kg BW), irbesartan (3 mg/kg BW), or pravastatin (0.5 mg/kg BW) into normal rats, serum insulin concentrations (a) were measured with ELISA and blood glucose levels (b) with test reagent strips. Bars represent means ± SEM for eight independent experiments. * and ** denote $p < 0.05$ and $p < 0.001$, respectively, for chance differences vs controls using ANOVA.

β-cells, whereas pravastatin has no such adverse effect [14]. Furthermore, pravastatin can prevent inflammation and rejection of transplanted islets of Langerhans [15].

Serum levels of free fatty acids are usually elevated in type 2 diabetic patients, secondary to insulin resistance and increased lipolysis [2,10,11,13]. It is generally believed that free fatty acids are involved in endothelial dysfunction and vascular damage in type 2 diabetes [2,10,11,13]. They may also contribute to β-cell dysfunction and demise through steatosis and apoptosis (collectively termed lipotoxicity [28–31]). Our present findings add another means by which free fatty acids may negatively impact β-cell function in diabetes, i.e., by impeding nutritive islet blood flow and thereby further aggravating the diabetic state by limiting the supply of insulin needed to curb hyperglycemia. Alternatively, the preferential impairment of islet blood flow evoked by palmitate could represent a protective mechanism by which islet exposure to free fatty acid toxicity can be limited.

The RAS is a circulating hormonal system which is primarily related to the regulation of blood pressure, fluid, and electrolyte homeostasis. Among its several components, Ang II plays a pivotal pathophysiological role [26]. Irbesartan is an Ang II receptor antagonist, characterized by high selectivity and insurmountable blockade of the type 1 Ang II receptor. In our study, intravenous injection of irbesartan or the ACE inhibitor captopril induced a robust increase in blood flow not only in the pancreas and pancreatic islets, but also (as expected) in the kidney. Pancreatic blood flow was preferentially diverted to the endocrine part, i.e., islets, which coincided with a significantly increased serum insulin concentration. This can be explained by a local or tissue RAS operative in such diverse targets as kidney, pancreas, pituitary, brain, adrenal, gonads, and fat [27]. Such a system enables local production of Ang II, yielding Ang II concentrations much higher than those encountered in peripheral blood. Some publications showed that islet blood flow seems to be suppressed by locally produced Ang II [5,11], lending support to our present findings. Additionally, Ang II appears to play an important role in regulating islet insulin secretion. Recent evidence also suggests that irbesartan has the capacity to

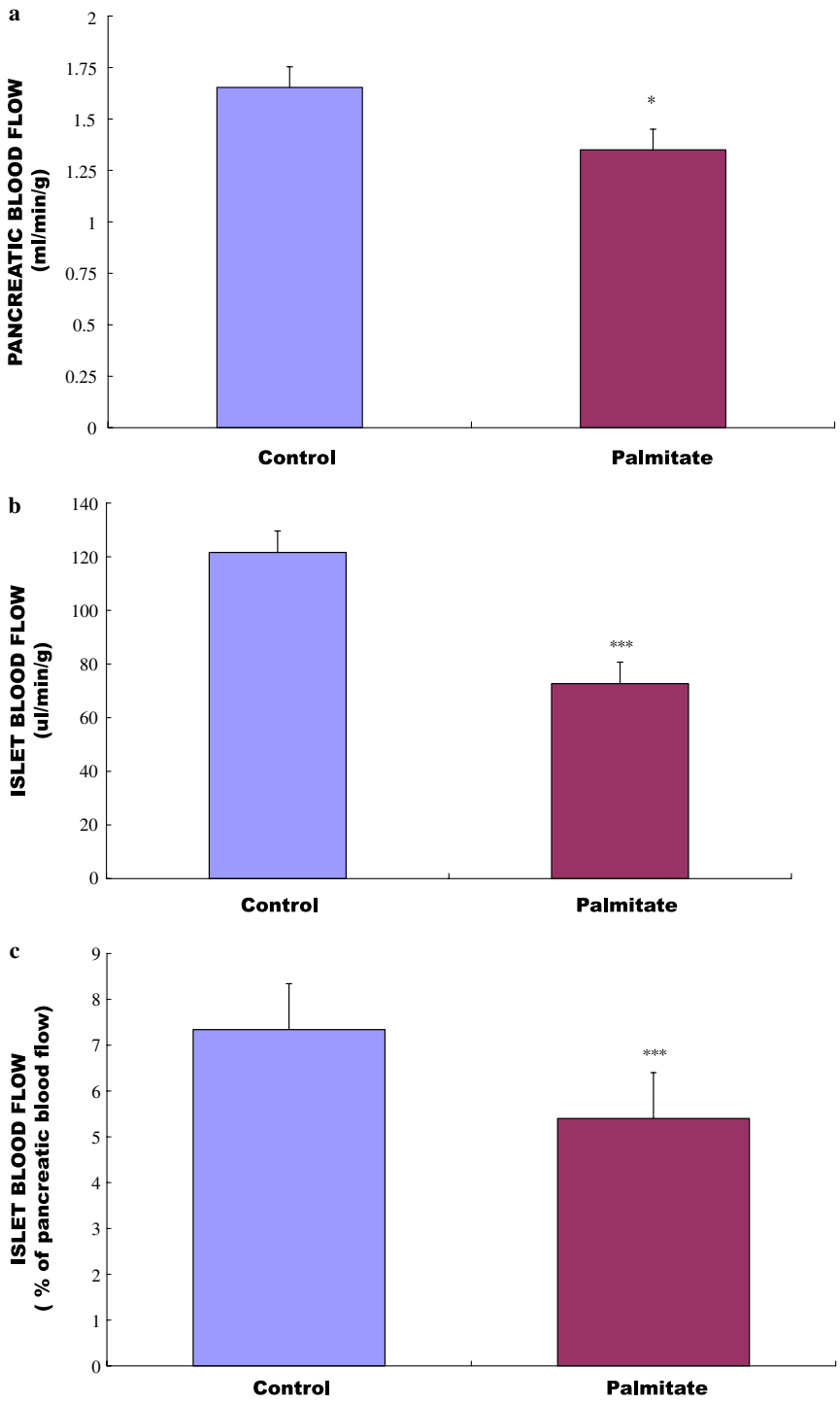

Fig. 4. Suppression of pancreatic blood flow by palmitate. Following i.v. injection of palmitate (60 mg/kg BW) or solvent into normal rats, rates of blood flow in the whole pancreas (a), pancreatic islets (b), and the fraction of total pancreatic blood flow contributed by islets (c) were measured using a microsphere technique. Bars represent means ± SEM for eight independent experiments. * and *** denote $p < 0.05$ and $p < 0.001$, respectively, for chance differences vs controls using ANOVA.

enhance vascular vasodilatation [5,11], which might be another mechanism contributing to our current findings.

In conclusion, we have shown that vasoactive drugs that are frequently given to diabetic patients and improve their glucose tolerance may rapidly stimulate the insulin-secreting β-cell by preferentially increasing islet blood flow and increasing serum insulin levels. Conversely, free fatty acids that are elevated in type 2 diabetic patients may contribute to an impaired nutritive islet blood flow and thereby further aggravate the diabetic state by limiting the supply of insulin needed to curb hyperglycemia. The results may prove useful in tailoring treatment strategies that improve the function of native and transplanted islets, contributing to an improved glucose tolerance in diabetic patients.

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References

[1] C. Tikellis, P.J. Wookey, R. Candido, S. Andrikopoulos, M.C. Thomas, M.E. Cooper, Improved islet morphology after blockade of the renin-angiotensin system in the ZDF rat, Diabetes 53 (4) (2004) 989–997.

[2] Å. Sjöholm, T. Nyström, Inflammation and the etiology of type 2 diabetes, Diabetes Metab. Res. Rev. 22 (2006) 4–10.

[3] Å. Sjöholm, T. Nyström, Endothelial inflammation in insulin resistance, Lancet 365 (9459) (2005) 610–612 (Review).

[4] P.O. Carlsson, The renin-angiotensin system in the endocrine pancreas, JOP 2 (1) (2001) 26–32.

[5] T. Lau, P.O. Carlsson, P.S. Leung, Evidence for a local angiotensin-generating system and dose-dependent inhibition of glucose-stimulated insulin release by angiotensin II in isolated pancreatic islets, Diabetologia 47 (2) (2004) 240–248.

[6] P.S. Leung, P.O. Carlsson, Tissue renin-angiotensin system: its expression, localization, regulation and potential role in the pancreas, J. Mol. Endocrinol. 26 (3) (2001) 155–164.

[7] M. Tahmasebi, J.R. Puddefoot, E.R. Inwang, G.P. Vinson, The tissue renin-angiotensin system in human pancreas, J. Endocrinol. 161 (2) (1999) 317–322.

[8] R. Olsson, L. Jansson, A. Andersson, P.O. Carlsson, Local blood flow regulation in transplanted rat pancreatic islets: influence of adenosine, angiotensin II, and nitric oxide inhibition, Transplantation 70 (2) (2000) 280–287.

[9] P.O. Carlsson, C. Berne, L. Jansson, Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats, Diabetologia 41 (2) (1998) 127–133.

[10] P. Zimmet, K.G. Alberti, J. Shaw, Global and societal implications of the diabetes epidemic, Nature 414 (6865) (2001) 782–787 (Review).

[11] P. Gaede, P. Vedel, N. Larsen, G.V. Jensen, H.H. Parving, O. Pedersen, Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes, N. Engl. J. Med. 348 (5) (2003) 383–393.

[12] J. Auer, R. Berent, T. Weber, B. Eber, Clinical significance of pleiotropic effects of statins: lipid reduction and beyond, Curr. Med. Chem. 9 (20) (2002) 1831–1850 (Review).

[13] D.J. Freeman, J. Norrie, N. Sattar, R.D. Neely, S.M. Cobbe, I. Ford, C. Isles, A.R. Lorimer, P.W. Macfarlane, J.H. McKillop, C.J. Packard, J. Shepherd, A. Gaw, Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study, Circulation 103 (3) (2001) 357–362.

[14] T. Yada, M. Nakata, T. Shiraishi, M. Kakei, Inhibition by simvastatin, but not pravastatin, of glucose-induced cytosolic Ca^{2+} signalling and insulin secretion due to blockade of L-type Ca^{2+} channels in rat islet beta-cells, Br. J. Pharmacol. 126 (5) (1999) 1205–1213.

[15] S. Arita, T. Nagai, M. Ochiai, Y. Sakamoto, L.A. Shevlin, C.V. Smith, Y. Mullen, Prevention of primary nonfunction of canine islet autografts by treatment with pravastatin, Transplantation 73 (1) (2002) 7–12.

[16] L. Jansson, C. Hellerström, Stimulation by glucose of the blood flow to the pancreatic islets of the rat, Diabetologia 25 (1) (1983) 45–50.

[17] L. Jansson, C. Hellerstrom, A rapid method of visualizing the pancreatic islets for studies of islet capillary blood flow using non-radioactive microspheres, Acta Physiol. Scand. 113 (3) (1981) 371–374.

[18] W.H. Leung, C.P. Lau, C.K. Wong, Beneficial effect of cholesterol lowering therapy on coronary endothelium-dependent relaxation in hypercholesterolemic patients, Lancet 341 (1993) 1496–1500.

[19] E.H. Serne, C.D.A. Stehouwer, J.C. ter Maaten, et al., Microvascular function relates to insulin sensitivity and blood pressure in normal subjects, Circulation 99 (1999) 896–902.

[20] K. Egashira, Y. Hirooka, H. Kai, et al., Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia, Circulation 89 (1994) 2519–2524.

[21] J. Muramatsu, A. Kobayashi, N. Hasegawa, et al., Hemodynamic changes associated with reduction in total cholesterol by treatment with the HMG-CoA reductase inhibitor pravastatin, Atherosclerosis 130 (1997) 179–182.

[22] J.K. Williams, G.K. Sukhova, D.M. Herrington, et al., Pravastatin has cholesterol-lowering independent effects on the artery wall of atherosclerotic monkeys, J. Am. Coll. Cardiol. 31 (1998) 684–691.

[23] C.G. Sotiriou, J.W. Cheng, Beneficial effects of statins in coronary artery disease—beyond lowering cholesterol, Ann. Pharmacother. 34 (12) (2000) 1432–1439 (Review).

[24] Y. Tsuda, K. Satoh, M. Kitadai, T. Takahashi, Y. Izumi, N. Hasomi, et al., Effects of pravastatin sodium and simvastatin on plasma fibrinogen level and blood rheology in type II hyperlipoproteinemia, Atherosclerosis 122 (1996) 225–233.

[25] A.M. Svensson, C.-G. Östenson, S. Sandler, S. Efendic, L. Jansson, Inhibition of nitric oxide synthase by N^G-nitro-L-arginine causes a preferential decrease in pancreatic islet blood flow in normal rats and spontaneously GK rats, Endocrinology 135 (3) (1994) 849–853.

[26] P.S. Leung, M.C. Chappell, A local pancreatic renin-angiotensin system: endocrine and exocrine roles, Int. J. Biochem. Cell Biol. 35 (6) (2003) 838–846 (Review).

[27] M.I. Phillips, E.A. Speakman, B. Kimura, Levels of angiotensin and molecular biology of the tissue renin-angiotensin system, Regul. Pept. 43 (1993) 1–20.

[28] R.A. DeFronzo, Dysfunctional fat cells, lipotoxicity and type 2 diabetes, Int. J. Clin. Pract. Suppl. (143) (2004) 9–21.

[29] K. Maedler, G.A. Spinas, D. Dyntar, W. Moritz, N. Kaiser, M.Y. Donath, Distinct effects of saturated and monounsaturated fatty aids on beta-cell turnover and function, Diabetes 50 (1) (2001) 69–76.

[30] R. Lupi, F. Dotta, L. Marselli, S. Del Guerra, M. Masini, C. Santangelo, G. Patane, U. Boggi, S. Piro, M. Anello, E. Bergamini, F. Mosca, U. Di Mario, S. Del Prato, P. Marchetti, Prolonged exposure to free fatty acids has cytostatic and pro-apoptotic effects on human pancreatic islets: evidence that beta-cell death is caspase mediated, partially dependent on ceramide pathway, and Bcl-2 regulated, Diabetes 51 (5) (2002) 1437–1442.

[31] I. Kharroubi, I. Ladriere, A.K. Cardozo, Z. Dogusan, M. Cnop, D.L. Eizirik, Free fatty acids and cytokines induce pancreatic beta-cell apoptosis by different mechanisms: role of nuclear factor-kappaB and endoplasmic reticulum stress, Endocrinology 145 (11) (2004) 5087–5096, Epub 2004 Aug 5.