Upsala Journal of Medical Sciences. 2014; 119: 316–323

informa
healthcare

ORIGINAL ARTICLEDIABETES

Effects of cyclooxygenase inhibition on insulin release and pancreatic islet blood flow in rats

MONICA SANDBERG & LEIF JANSSON

Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden

Abstract

Objectives. To examine the effects of inhibition of cyclooxygenase (COX) on islet hormone secretion *in vitro* and on pancreatic islet blood flow *in vivo*.

Methods. Insulin release was measured in a static incubation system of islets isolated from Wistar-F rats after inhibition of COX-1 and COX-2 with SC 560 (COX-1), FR 122047 (COX-1), rofecoxib (COX-2), or indomethacin (both COX-1 and COX-2). In other rats organ blood flow values were measured with a microsphere technique during both normo- and hyperglycemia after administration of these enzyme inhibitors.

Results. Serum insulin values were lower after pretreatment with a COX-1 inhibitor or a non-selective COX inhibitor in both control and glucose-injected rats *in vivo,* whereas COX-2 inhibition had no such effects. However, inhibition of COX had only minor effects on insulin release *in vitro.* Inhibition of COX affected neither total pancreatic nor islet blood flow in normoglycemic rats. Hyperglycemia caused an increase in both these flow values and in the duodenum. The increase in total pancreatic and duodenal blood flow was prevented by inhibition of COX-2 or non-selective COX inhibition. However, no effects on islet blood flow were seen after COX inhibition.

Conclusion. Inhibition of COX affects insulin release and blood glucose concentrations *in vivo.* However, COX inhibition has only minor effects on pancreatic islet blood flow, but prevents the glucose-induced increase in total pancreatic blood flow.

Key words: *COX inhibition, insulin release, islet blood flow*

Introduction

Arachidonic acid can be modified by three major pathways, namely cyclooxygenase (COX), lipoxygenase, and cytochrome P450 into biologically active eicosanoids. These substances have many biological activities, e.g. influencing smooth muscle contraction, platelet aggregation, and inflammatory responses (1-3). The present study focuses on COX, which converts arachidonic acid into various prostaglandins (4). Non-steroid anti-inflammatory drugs (NSAIDs) inhibit the COX activity, but not the peroxidase activity of the enzyme (4).

COX is present in two isoforms of which COX-1 is constitutively expressed in nearly all cells at a constant level, whereas COX-2 is constitutively expressed in the brain and spinal cord. In most cells COX-2 expression is induced by pro-inflammatory cytokines and growth factors (1).

Since a chronic low-grade inflammation is associated with the peripheral insulin resistance in type 2 diabetes (T2D) possible mediators have been extensively studied (5-7), and a clear correlation with COX-mediated inflammation has been found (8). Furthermore, there is also a report on an association between a promoter variant of COX-2 gene with T2D in Pima Indians (9). Also the possibilities to modulate insulin resistance by COX inhibitors have been investigated, and most studies demonstrate beneficial effects of non-specific COX or selective COX-2 inhibition (5,10).

Correspondence: Dr Monica Sandberg, Department of Medical Cell Biology, Uppsala University, Box 571, SE-751 23 Uppsala, Sweden. Fax: +46 18 4714059. E-mail: Monica.Sandberg@mcb.uu.se

(Received 1 September 2014; accepted 8 September 2014)

ISSN 0300-9734 print/ISSN 2000-1967 online
DOI: 10.3109/03009734.2014.964381

Isolated pancreatic islets contain, depending on species, COX-1, COX-2, and 12-lipoxygenase, and their products have been shown to affect insulin secretion (11,12). COX-2 is constitutively expressed in pancreatic islets (12-14), and its expression increases glucose-dependently (15). COX products are unlikely to have major effects on islet endocrine function, but modulate insulin secretion (12,13,16). It has recently also been shown that prostaglandins have a regulatory role in crinophagy in pancreatic islet β-cells (14,17).

Prostaglandins are also versatile mediators in blood flow regulation, and the endothelium is the most prominent source of these substances in the peripheral circulation (2,18,19). They play an important role in gastric and duodenal blood flow regulation, where they are crucial for normal mucosal defense (20,21), and they also affect the pathogenesis of acute pancreatitis (22).

Thus, COX products affect β-cell function as well as the vasculature. In view of this we decided to study further how selective and combined inhibition of COX-1 and COX-2 affected islet insulin secretion *in vivo* and *in vitro* and how this correlated to the blood perfusion of the pancreatic islets.

Materials and methods

Animals

Male Wistar–Furth rats (Scanbur, Sollentuna, Sweden) weighing 320 ± 2 g ($n = 92$) with free access to pelleted food and tap water were used. All experiments were approved by the local animal ethics committee at Uppsala University.

Chemicals

Chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) unless stated otherwise. The specificity of the COX inhibitors is as follows: Indomethacin, non-specific COX inhibitor; SC 560 and FR 122047, COX-1 inhibitors; rofecoxib, COX-2 inhibitor. The rationale for the use of two COX-1 inhibitors is that some doubts have been raised on the specificity of SC 560 for COX-1 (23). As seen below, both alleged COX-1 inhibitors had similar effects.

Islet isolation

Pancreatic islets were isolated from rats by collagenase digestion (24) and cultured in groups of 150 islets for 3–4 days in 5 mL of culture medium consisting of RPMI 1640 supplemented with L-glutamine, benzylpenicillin (100 U/mL; Roche Diagnostics Scandinavia, Bromma, Sweden), streptomycin (0.1 mg/mL), and 10% (vol/vol) fetal calf serum. To some of the cultures we added SC 560 (3 μmol/L), FR 122047 (5 μmol/L), rofecoxib (10 μmol/L), or indomethacin (10 μmol/L), all of which were dissolved in dimethyl sulfoxide (DMSO) at a final concentration of 0.1% (vol/vol). Culture medium was changed every second day, and COX inhibitors were added during the final 1–2 days of culture.

Glucose-stimulated insulin release and islet insulin contents

Groups of 10 islets, control or pretreated islets, were transferred to vials containing Krebs–Ringer bicarbonate buffer supplemented with 10 mmol/L HEPES and 2 mg/mL bovine serum albumin (BSA; ICN Biomedicals Inc. Aurora, Ohio, USA; hereafter referred to as KRBH buffer). The KRBH buffer contained 1.67 mmol/L D-glucose during the first hour of incubation at 37°C (O_2/CO_2, 95:5). The medium was then removed and replaced by KRBH supplemented with 16.7 mmol/L glucose, and the islets were then incubated for a second hour. As mentioned above, some islets had been cultured with different COX inhibitors for the final 1–2 days of culture, and these substances were added also during the release experiments. That is, SC 560 (3 μmol/L), FR 122047 (5 μmol/L), rofecoxib (10 μmol/L), or indomethacin (10 μmol/l), all of which were dissolved in DMSO at a final concentration of 0.1% (vol/vol), was added to the release medium throughout the 2-h period. The islets were harvested, following retrieval of medium, and homogenized by sonication in 200 μL redistilled water. DNA and insulin contents were then measured as previously described (24).

Blood flow measurements

The rats were anesthetized with an intraperitoneal injection of thiobutabarbital sodium (120 mg/kg body weight; Inactin®; Research Biochemicals International, Natick, MA, USA). The animals were then placed on a heated operating table to maintain body temperature at approximately 37.5°C. Polyethylene catheters were inserted into the ascending aorta, via the right carotid artery, and into the left femoral artery and vein. The former catheter was connected to a pressure transducer (PDCR 75/1; Druck Ltd, Groby, UK), whereas the latter was used to infuse Ringer solution (6 mL/kg body weight/h) to substitute for fluid losses. When the blood pressure had remained stable for at least 20 min, vehicle (0.03 mg/mL of DMSO in saline; 1 mL/kg body weight), SC 560 (2.5 mg/kg body weight), FR 122047 (1.5 mg/kg body weight), rofecoxib (10 mg/kg body weight), or

Table I. Anesthetized rats were injected intravenously with 1 mL/kg of vehicle (0.03 mg/mL of DMSO in saline), SC 560 (2.5 mg/kg body weight), FR 122047 (1 mg/kg body weight), rofecoxib (10 mg/kg body weight), or indomethacin (5 mg/kg body weight) 10 min earlier. The animals were also injected intravenously with 1 mL saline or 30% (w/v) D-glucose 3 min before measurements.

Substance	Vehicle	SC 560	FR 122047	Rofecoxib	Indometh	Vehicle	SC 560	FR 122047	Rofecoxib	Indometh
Glucose	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes
No of animals	8	7	8	8	8	8	7	7	8	7
Plasma glucose concentration (mmol/L)	4.6 ± 0.1	4.3 ± 0.1	4.9 ± 0.1	4.3 ± 0.1	4.2 ± 0.1	13.9 ± 1.4[b]	9.8 ± 0.8[a,b]	14.1 ± 1.4[a]	17.0 ± 1.1[b]	8.4 ± 0.9[a,b]
Mean arterial blood pressure (mmHg)	129 ± 2	121 ± 4	122 ± 4	137 ± 4[c]	129 ± 3	125 ± 4	128 ± 3	115 ± 9	129 ± 1	122 ± 5
Duodenal blood flow	1.75 ± 0.20	2.17 ± 0.14	2.79 ± 0.67	2.24 ± 0.34	2.18 ± 0.17	3.82 ± 3.81[b]	2.84 ± 0.29	3.19 ± 0.22	2.11 ± 0.21[b]	2.61 ± 0.31
Colonic blood flow	1.04 ± 0.21	1.18 ± 0.17	0.96 ± 0.13	1.05 ± 0.12	1.50 ± 0.16	1.66 ± 0.38	1.29 ± 0.20	1.31 ± 0.22	1.16 ± 0.12	1.28 ± 0.22
Adrenal blood flow	3.79 ± 0.54	3.39 ± 0.47	2.81 ± 0.20	3.83 ± 0.54	3.53 ± 0.43	7.54 ± 0.53[b]	5.72 ± 0.40[b]	3.73 ± 0.38	3.69 ± 0.33	3.40 ± 0.36

Values are means ± SEM. All blood flow values are given as mL/min × g organ weight.
[a] $P < 0.05$ against the corresponding normoglycemic group.
[b] $P < 0.05$ compared with the hyperglycemic vehicle-treated rats.

indomethacin (5 mg/kg body weight) was injected intravenously. Ten minutes later blood flow values were measured as outlined below. In separate animals an additional intravenous injection of 1 mL D-glucose (300 mg/mL) was given 3 min before the blood flow measurements. A total of 2.5×10^5 black non-radioactive microspheres (EZ-Trac™; Triton Microspheres, San Diego, CA, USA), with a diameter of 10 μm were injected via the catheter with its tip in the ascending aorta during 10 s and subsequently processed as previously described in detail (25).

The animals were then killed, and the pancreas and adrenal glands were removed *in toto*, blotted, and weighed. Samples (approximately 100 mg) from the mid-regions of the duodenum, descending colon, and left kidney were also removed, blotted, and weighed. The number of microspheres in the samples referred to above, including the pancreatic islets, was estimated as previously described, and organ blood flows were calculated (25). With regard to islet blood perfusion it was expressed both per gram wet weight of the whole pancreas, and the estimated wet weight of the islets.

Statistical calculations

All values are given as means ± SEM. Probabilities (P) of chance differences were calculated with Student's unpaired t test, or one-way repeated measurement ANOVA with Tukey's correction (SigmaStat™; SSPD, Erfart, Germany). A value of $P < 0.05$ was considered to be statistically significant.

Results

There were no changes in mean arterial blood pressure in any of the groups (Table I). Both SC 560 and indomethacin induced a decrease in hematocrit during hyperglycemia when compared with the corresponding normoglycemic control rats, whereas no effects were seen in the other groups (Table I).

Insulin release and insulin content

Basal insulin release at 1.67 mmol/L glucose was similar in all groups, besides islets pretreated with indomethacin, where a lower value was seen. The degree of stimulation of insulin release by high glucose concentrations was approximately three times in the control islets when challenged with the inhibitors only in the release medium (data not shown) or after 1–2 days of culture with the inhibitors (Figure 1A). Glucose increased insulin release in all groups when compared with basal values, but this response was potentiated by inhibition of COX-1 by either SC

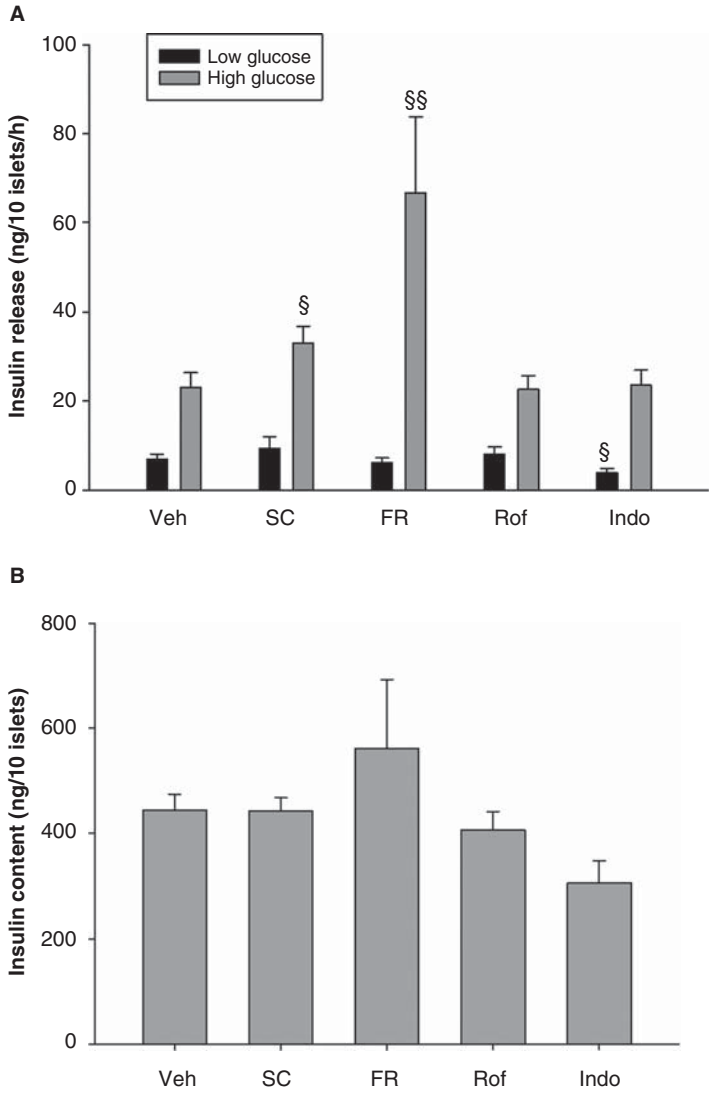

Figure 1. A: Insulin release from isolated rat islets pre-cultured for 2–3 days with SC 560 (3 μmol/L), FR 122047 (FR; 5 μmol/L), rofecoxib (10 μmol/L), or indomethacin (10 μmol/L), all of which were dissolved in DMSO at a final concentration of 0.1% (vol/vol). During the release experiments the islets were incubated in KRBH during 2 consecutive h at 1.7 and 16.7 mM glucose, respectively. Values are means ± SEM for 7–8 observations. *denotes $P < 0.001$ when compared with the corresponding low glucose value, §denotes $P < 0.05$, and $^{\S\S}P < 0.01$ when compared with the corresponding vehicle-treated group. B: Insulin content of isolated rat islets cultured for 2–3 days with SC 560 (3 μmol/L), FR 122047 (FR; 5 μmol/L), rofecoxib (10 μmol/L), or indomethacin (10 μmol/L), all of which were dissolved in DMSO at a final concentration of 0.1% (vol/vol). Values are means ± SEM for 7–8 observations.

560 or FR 122047. Insulin content was similar in all groups (~40 ng/islet) (Figure 1B).

Blood glucose and serum insulin

None of the COX inhibitors affected plasma glucose concentrations in control rats not injected with glucose (Table I). There was a lower blood glucose in glucose-injected animals pretreated with SC 560, FR 122047, or indomethacin, but not rofecoxib (Table I). Serum insulin values 10 min after pretreatment with SC 560, FR 122047, or indomethacin were markedly lower in both control and glucose-injected rats, whereas rofecoxib had no such effects (Figure 2).

Blood flow values

Inhibition of COX did not affect total pancreatic blood flow in normoglycemic rats, except for an increase caused by FR 122047 (Figure 3A), whereas none of the pretreatments affected islet blood flow (Figure 3B). Hyperglycemia per se caused an increase of both total pancreatic and islet blood flow

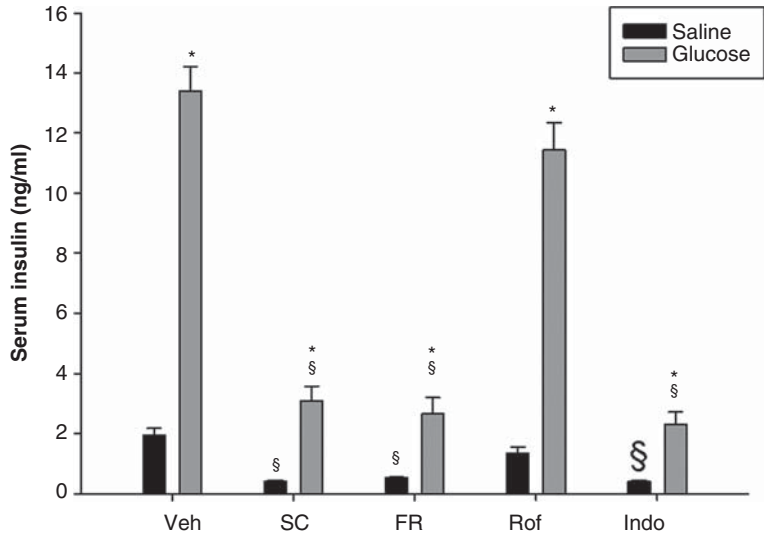

Figure 2. Serum insulin concentrations in anesthetized rats injected intravenously with 1 mL/kg of vehicle (Veh; 0.03 mg/mL of DMSO in saline), SC 560 (SC; 2.5 mg/kg body weight), FR 122047 (FR; 1.5 mg/kg body weight), rofecoxib (Rof; 1 mg/kg body weight), or indomethacin (Indo; 5 mg/kg body weight) 10 min earlier. The animals were also injected intravenously with 1 mL saline or 30% (w/v) D-glucose 3 min before measurements. Values are means ± SEM for 7–8 experiments. *denotes $P < 0.01$ when compared with the corresponding saline-injected group, and §denotes $P < 0.05$ when compared with the corresponding vehicle-treated group.

(Figure 3A and B). The increase in total pancreatic blood flow was prevented by administration of rofecoxib or indomethacin (Figure 3A), whereas no effects on islet blood flow was observed after any of the pretreatments given, even though there was a trend ($P = 0.07$) for an increase after administration of FR 122047 (Figure 3B).

Duodenal blood flow changed in concert with that of the whole pancreas in the different experimental groups, whereas colonic blood flow was unaffected (Table I). Rofecoxib administration decreased renal blood flow in normoglycemic rats (Figure 3C). Induced hyperglycemia increased renal blood flow, in vehicle-treated control rats, and such an increase was also seen after rofecoxib administration (Figure 3C).

Discussion

Local production of prostaglandins in blood vessel walls constitutes an important system for modulation of local blood perfusion, even though the importance varies considerably between different regional circulations (18,19,26). It is well known that an imbalance between vasoconstrictor and vasodilator prostanoids is present in arteries from diabetic animals, which, at least partially, causes the endothelial dysfunction characteristic of this condition (27,28). However, in the present study all examined inhibitors of COX failed to affect islet blood flow. This confirms the finding in a previous study where the non-selective COX inhibitor indomethacin also failed to affect islet blood perfusion (29). In the present study, glucose administration increased the need for islet insulin release, and, as previously shown (30,31), islet blood flow was also markedly increased. However, there was no change in this glucose-stimulation of islet blood flow after administration of any of the COX inhibitors, once again emphasizing that prostaglandins are of minor importance for islet blood flow regulation.

When viewing total pancreatic blood flow, on the other hand, a different picture emerges. There was no change during basal conditions, which is in line with other studies suggesting that prostaglandins per se have only minor effects on pancreatic circulation during basal conditions (32). However, both rofecoxib and indomethacin prevented glucose-induced increase in total pancreatic blood flow when compared with control rats, whereas COX-1 inhibition had no such effects. This suggests that prostaglandins derived from the actions of COX-2 are at least partially involved in this blood flow response, which is limited to the exocrine pancreas. It has been shown in other contexts that when increased demands are put upon the exocrine pancreas, such as during the development of acute pancreatitis, prostaglandins can affect pancreatic blood perfusion (22). Thus, the present findings extend these observations and suggest that also the normal physiologic blood flow response to hyperglycemia depends on COX-1-derived products.

Also the duodenal blood flow response was similar to that of the whole pancreas, with no effects seen during basal conditions, but a COX-2-dependent

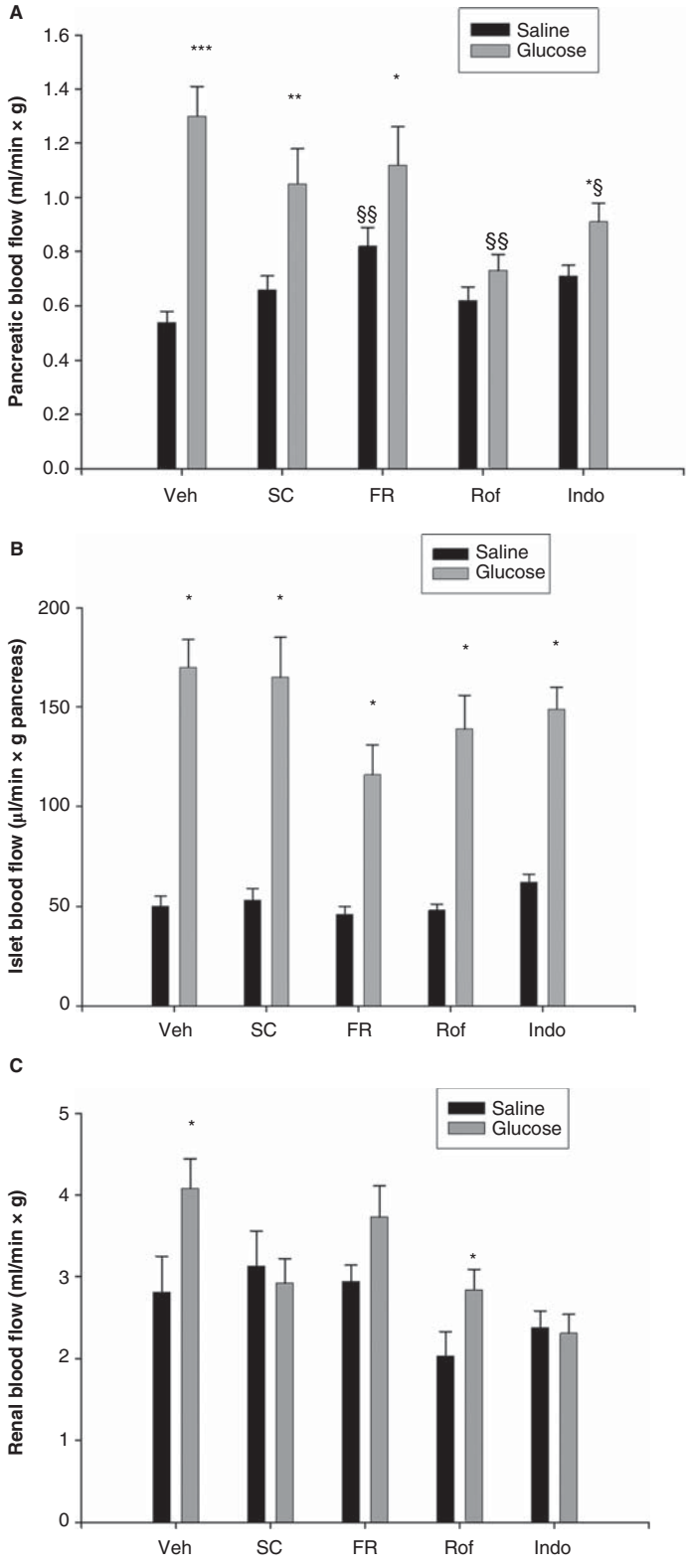

Figure 3. A: Total pancreatic blood flow in anesthetized rats injected intravenously with 1 mL/kg of vehicle (Veh; 0.03 mg/mL of DMSO in saline), SC 560 (SC; 2.5 mg/kg body weight), FR 122047 (FR; 1.5 mg/kg body weight), rofecoxib (Rof; 1 mg/kg body weight), or indomethacin

inhibition of glucose-induced stimulation. This suggests that the response may be limited to the superior mesenteric artery which provides all of the blood perfusion to the duodenum and approximately two-thirds of that to the pancreas (33). Arguing against this is, however, the findings that renal blood flow reacted similarly. Thus, it may be glucose per se that affects phospholipase A_2 (PLA_2), which catalyzes the cleavage of arachidonic acid from cellular membranes in different organs, which then is differently processed by COX or lipoxygenase in tissues. There was no systemic vascular effect by any of the COX inhibitors, as evidenced by the unchanged mean arterial blood pressure in all groups. The functional importance of this response in the pancreatic and duodenal circulation is at present unknown.

Arachidonic acid, presumably released through the actions of cytosolic PLA_2, is critical for normal islet beta-cell function. Thus, if PLA_2 is inhibited, normal glucose-stimulated insulin release is decreased from human islets (12). Arachidonic acid facilitates hormone release through activation of several ionic channels (34,35). Undoubtedly it exerts some of its effects by itself, whereas a major part is mediated by its metabolism through COX, lipoxygenase, or cytochrome P450 (36). Initial reports on the role of prostaglandins formed by COX in insulin release suggested that mainly PGE_2 was involved and inhibited insulin release (13,37), primarily through the EP3 receptor (38). However, more recent experiments in human islets have failed to confirm this (12). It was recently suggested that arachidonic acid in beta-cells is metabolized by both COX-1 and COX-2 and their products exert either stimulatory (those derived from COX-1) or inhibitory (those from COX-2) effects on insulin release (36). Our present results on serum glucose and blood insulin concentrations *in vivo* are well in accordance with the latter view. When examining the effects of the different COX inhibitors *in vitro* the picture is more complex. If the inhibitors were added to the medium only during the 2-h duration of the experiments, there were no effects on insulin release (data not shown). Also, when the islets had been pre-cultured for 2 days with the inhibitors present, we observed only minor effects on insulin release and no effects at all on islet insulin content. There was, however, a slight increase in basal insulin secretion when indomethacin was added and a slight increase of glucose-stimulated insulin secretion in the presence of SC 560 and FR 122047, i.e. when COX-2 activity was maintained. It should be noted that the studies by Keane and Newsholme (36) were performed on different cell lines, and this may explain some of the differences.

Of more interest is that our *in-vitro* findings are opposite to the effects on insulin secretion seen *in vivo*. The reasons for these differences are unknown, but COX exists in most tissues, and a general, systemic inhibition of one or both isoforms in the whole body is naturally associated with many local changes, which then may affect the pancreas and its insulin release. However, the exact nature of these signals is unknown, but is certainly worthy of further studies.

The present study demonstrated that inhibition of COX affects insulin secretion and blood glucose concentrations *in vivo*, whereas the effects observed *in vitro* were more modest. Furthermore, COX inhibition has only minor effects on pancreatic islet blood flow, but prevents glucose-induced increase in total pancreatic blood flow.

Acknowledgements

The skilled technical assistance of Birgitta Bodin and Astrid Nordin is gratefully acknowledged.

Declaration of interest: Financial support was received from the Swedish Research Council (72X-109), an EFSD/Novo Nordisk grant, an EXODIAB grant, the Swedish Diabetes Association and the Family Ernfors Fund. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

(Indo; 5 mg/kg body weight) 10 min earlier. The animals were also injected intravenously with 1 mL saline or 30% (w/v) D-glucose 3 min before measurements. Values are means ± SEM for 7–8 experiments. *denotes $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ when compared with the corresponding saline-injected group. §denotes $P < 0.05$, and §§ $P < 0.01$ when compared with the corresponding vehicle-treated group. B: Islet blood flow in anesthetized rats injected intravenously with 1 mL/kg of vehicle (Veh; 0.03 mg/mL of DMSO in saline), SC 560 (SC; 2.5 mg/kg body weight), FR 122047 (FR; 1.5 mg/kg body weight), rofecoxib (Rof; 1 mg/kg body weight), or indomethacin (Indo; 5 mg/kg body weight) 10 min earlier. The animals were also injected intravenously with 1 mL saline or 30% (w/v) D-glucose 3 min before measurements. Values are means ± SEM for 7–8 experiments. *denotes $P < 0.001$ when compared with the corresponding saline-injected group, and § denotes $P < 0.05$ when compared with the corresponding vehicle-treated group. C: Renal blood flow in anesthetized rats injected intravenously with 1 mL/kg of vehicle (Veh; 0.03 mg/mL of DMSO in saline), SC 560 (SC; 2.5 mg/kg body weight), FR 122047 (FR; 1.5 mg/kg body weight), rofecoxib (Rof; 1 mg/kg body weight), or indomethacin (Indo; 5 mg/kg body weight) 10 min earlier. The animals were also injected intravenously with 1 mL saline or 30% (w/v) D-glucose 3 min before measurements. Values are means ± SEM for 7–8 experiments. *denotes $P < 0.01$ when compared with the corresponding saline-injected group.

References

1. Simmons DL, Botting RM, Hla T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. Pharmacol Rev. 2004;56:387–437.
2. Praticò D, Dogné JM. Vascular biology of eicosanoids and atherogenesis. Expert Rev Cardiovasc Ther. 2009;7:1079–89.
3. Narumiya S. Prostanoids and inflammation: a new concept arising from receptor knockout mice. J Mol Med. 2009;87: 1015–22.
4. Narumiya S, Sugimoto Y, Ushikubi F. Prostanoid receptors: structures, properties, and functions. Physiol Rev. 1999;79: 1193–226.
5. Sjöholm A, Nyström T. Inflammation and the etiology of type 2 diabetes. Diabetes Metab Res Rev. 2006;22:4–10.
6. Bloomgarden ZT. Inflammation and insulin resistance. Diabetes Care. 2003;26:1619–23.
7. Donath MY, Boni-Schnetzler M, Ellingsgaard H, Ehses JA. Islet inflammation impairs the pancreatic beta-cell in type 2 diabetes. Physiology (Bethesda). 2009;24:325–31.
8. Helmersson J, Vessby B, Larsson A, Basu S. Association of type 2 diabetes with cyclooxygenase-mediated inflammation and oxidative stress in an elderly population. Circulation. 2004;109:1729–34.
9. Konheim YL, Wolford JK. Association of a promoter variant in the inducible cyclooxygenase-2 gene (PTGS2) with type 2 diabetes mellitus in Pima Indians. Hum Genet. 2003;113:377–81.
10. Hsieh PS, Tsai HC, Kuo CH, Chan JY, Shyu JF, Cheng WT, et al. Selective COX2 inhibition improves whole body and muscular insulin resistance in fructose-fed rats. Eur J Clin Invest. 2008;38:812–19.
11. Turk J, Wolf BA, McDaniel ML. The role of phospholipid-derived mediators including arachidonic acid, its metabolites, and inositoltrisphosphate and of intracellular Ca2+ in glucose-induced insulin secretion by pancreatic islets. Prog Lipid Res. 1987;26:125–81.
12. Persaud SJ, Muller D, Belin VD, Kitsou-Mylona I, Asare-Anane H, Papadimitriou A, et al. The role of arachidonic acid and its metabolites in insulin secretion from human islets of langerhans. Diabetes. 2007;56:197–203.
13. Robertson RP. Dominance of cyclooxygenase-2 in the regulation of pancreatic islet prostaglandin synthesis. Diabetes. 1998;47:1379–83.
14. Sandberg M, Borg LA. Intracellular degradation of insulin and crinophagy are maintained by nitric oxide and cyclooxygenase 2 activity in isolated pancreatic islets. Biol Cell. 2006;98:307–15.
15. Shanmugam N, Todorov IT, Nair I, Omori K, Reddy MA, Natarajan R. Increased expression of cyclooxygenase-2 in human pancreatic islets treated with high glucose or ligands of the advanced glycation endproduct-specific receptor (AGER), and in islets from diabetic mice. Diabetologia. 2006;49:100–7.
16. Persaud SJ, Muller D, Belin VD, Papadimitriou A, Huang GC, Amiel SA, et al. Expression and function of cyclooxygenase and lipoxygenase enzymes in human islets of Langerhans. Arch Physiol Biochem. 2007;113:104–9.
17. Sandberg M, Borg LA. Steroid effects on intracellular degradation of insulin and crinophagy in isolated pancreatic islets. Mol Cell Endocrinol. 2007;277:35–41.
18. Boushel R, Langberg H, Risum N, Kjaer M. Regulation of blood flow by prostaglandins. Curr Vasc Pharmacol. 2004;2:191–7.
19. Egan K, FitzGerald GA. Eicosanoids and the vascular endothelium. Handb Exp Pharmacol. 2006:189–211.
20. Holm L, Perry MA. Role of blood flow in gastric acid secretion. Am J Physiol. 1988;254:G281–93.
21. Ham M, Kaunitz JD. Gastroduodenal defense. Curr Opin Gastroenterol. 2007;23:607–16.
22. Formela LJ, Galloway SW, Kingsnorth AN. Inflammatory mediators in acute pancreatitis. Br J Surg. 1995;82:6–13.
23. Brenneis C, Maier TJ, Schmidt R, Hofacker A, Zulauf L, Jakobsson PJ, et al. Inhibition of prostaglandin E2 synthesis by SC-560 is independent of cyclooxygenase 1 inhibition. FASEB J. 2006;20:1352–60.
24. Sandler S, Andersson A, Hellerström C. Inhibitory effects of interleukin 1 on insulin secretion, insulin biosynthesis, and oxidative metabolism of isolated rat pancreatic islets. Endocrinology. 1987;121:1424–31.
25. Carlsson PO, Källskog Ö, Bodin B, Andersson A, Jansson L. Multiple injections of coloured microspheres for islet blood flow measurements in anaesthetised rats: influence of microsphere size. Ups J Med Sci. 2002;107:111–20.
26. Phillis JW, Horrocks LA, Farooqui AA. Cyclooxygenases, lipoxygenases, and epoxygenases in CNS: their role and involvement in neurological disorders. Brain Res Rev. 2006;52:201–43.
27. Matsumoto T, Kakami M, Noguchi E, Kobayashi T, Kamata K. Imbalance between endothelium-derived relaxing and contracting factors in mesenteric arteries from aged OLETF rats, a model of Type 2 diabetes. Am J Physiol Heart Circ Physiol. 2007;293:H1480–90.
28. Shi Y, Vanhoutte PM. Oxidative stress and COX cause hyperresponsiveness in vascular smooth muscle of the femoral artery from diabetic rats. Br J Pharmacol. 2008;154:639–51.
29. Jansson L, Sandler S. Alloxan-induced diabetes in the mouse: time course of pancreatic B-cell destruction as reflected in an increased islet vascular permeability. Virchows Arch A Pathol Anat Histopathol. 1986;410:17–21.
30. Jansson L, Grapengiesser E, Hellman B. Purinergic signalling in pancreatic islet endothelial cells. In Gerasimovskaya E, Kaczmarek E, editors. Extracellular ATP and adenosine as regulators of endothelial cell function. Berlin: Springer Verlag; 2010. p 215–31.
31. Jansson L. Glucose stimulation of pancreatic islet blood flow by redistribution of the blood flow within the whole pancreatic gland. Pancreas. 1988;3:409–12.
32. Jansson L, Sandler S. Alloxan, but not streptozotocin, increases blood perfusion of pancreatic islets in rats. Am J Physiol. 1992;263:E57–63.
33. Jansson L, Hellerström C. The blood flow to the islets of Langerhans in different regions of the rat pancreas. Proc Soc Exp Biol Med. 1987;185:474–7.
34. Woolcott OO, Gustafsson AJ, Dzabic M, Pierro C, Tedeschi P, Sandgren J, et al. Arachidonic acid is a physiological activator of the ryanodine receptor in pancreatic beta-cells. Cell Calcium. 2006;39:529–37.
35. Sharoyko VV, Zaitseva II, Leibiger B, Efendic S, Berggren PO, Zaitsev SV. Arachidonic acid signaling is involved in the mechanism of imidazoline-induced KATP channel-independent stimulation of insulin secretion. Cell Mol Life Sci. 2007;64:2985–93.
36. Keane D, Newsholme P. Saturated and unsaturated (including arachidonic acid) non-esterified fatty acid modulation of insulin secretion from pancreatic beta-cells. Biochem Soc Trans. 2008;36:955–8.
37. Seaquist ER, Walseth TF, Nelson DM, Robertson RP. Pertussis toxin-sensitive G protein mediation of PGE2 inhibition of cAMP metabolism and phasic glucose-induced insulin secretion in HIT cells. Diabetes. 1989;38:1439–45.
38. Tran PO, Gleason CE, Robertson RP. Inhibition of interleukin-1beta-induced COX-2 and EP3 gene expression by sodium salicylate enhances pancreatic islet beta-cell function. Diabetes. 2002;51:1772–8.