ELSEVIER

European Journal of Pharmacology 298 (1996) 287–292

ejp

A specific β_3-adrenoceptor agonist induces increased pancreatic islet blood flow and insulin secretion in rats

Nadia Atef [a], Max Lafontan [b], Alexandre Doublé [a,c], Christophe Hélary [a], Alain Ktorza [a], Luc Pénicaud [a,c,*]

[a] *Laboratory of Physiopathology of Nutrition, CNRS URA 307, University Paris VII, Paris, France*
[b] *Laboratory of Adrenergic Regulations and Metabolic Adaptations, INSERM U 317, Toulouse, France*
[c] *Laboratory of Neurobiology, Plasticity and Energy Metabolism, CNRS URA 1937, Paul Sabatier University, Toulouse, France*

Received 3 October 1995; revised 16 November 1995; accepted 21 November 1995

Abstract

In order to study the role of β_3-adrenoceptor stimulation on insulin secretion in rats, plasma insulin level and islet blood flow were measured during treatment with CL 316243 which is chemically named disodium (*R,R*)-5-[2-[[2,3-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate, a specific β_3-adrenoceptor agonist. CL 316243 induced a marked increase in both islet blood flow and plasma insulin concentration without changes in whole pancreatic blood flow. This increase was totally prevented when the rats were pretreated with bupranolol, a β_1,β_2,β_3-adrenoceptor antagonist, but not with nadolol, a β_1,β_2-adrenoceptor antagonist. We conclude that β_3-adrenoceptor stimulation provokes a marked vasodilatation of microvessels in the islets of Langerhans, which in turn could contribute to the increase in insulin secretion.

Keywords: Glucose; Insulin; Pancreatic islet, blood flow; Blood pressure; β-Adrenoceptor

1. Introduction

β_3-Adrenoceptor agonists have been reported to present an antidiabetic effect in rats and mice (Caroll et al., 1985; Cawthorne et al., 1984). Although the exact mechanism of this action is not well understood, it has been shown that these agents increase both insulin action and secretion (Cawthorne et al., 1984; Ferré et al., 1992; Sennitt et al., 1985; Smith et al., 1985). With regard to the latter parameter, enhanced insulin release has been demonstrated in vivo both in rats and mice (Sennitt et al., 1985). However, this stimulatory effect of a β_3-adrenoceptor agonist is no longer present when tested in vitro on pancreatic islets (Lacey et al., 1991; Yoshida, 1992). It should be emphasized that the presence of β_3-adrenoceptors has been described on different cell types but whether β_3-adrenoceptors are present or absent in pancreatic islets (or β cells) is unknown (Granneman et al., 1991; Krief et al., 1993). These results suggest that the β_3-adrenocpetor agonist-induced insulin secretion is not due to a direct effect of the drug on the pancreatic β cell but to indirect mechanisms.

Recent reports suggest that β_3-adrenoceptor agonists are potent stimulators of vasodilatation in specific territories like skin and white adipose tissue in dogs (Berlan et al., 1994; Shen et al., 1994). On the other hand, islet blood flow could be an important factor involved in the control of insulin secretion (Jansson, 1984; Jansson and Hellerström, 1983) and some data showed that islet blood flow is under the influence of the autonomic nervous system in rats (Atef et al., 1992; Jansson and Hellerström, 1986). Thus, we postulated that β_3-adrenoceptors could be involved in vasodilator processes specifically in microvessels in the islets of Langerhans. The present work was thus undertaken to determine whether a β3-adrenoceptor agonist could modify islet blood flow in rats. Experiments were performed with CL 316243 which is chemically named disodium (*R,R*)-5-[2-[[2,3-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate (American Cyanamid Company, Pearl River, NY,

* Corresponding author. Laboratoire de Neurobiologie, Plasticité Tissulaire et Métabolisme Energétique, CNRS URA 1937, Université Paul Sabatier, 1 Avenue Jean Poulhés, 31054 Toulouse Cédex, France. Tel.: (33) 62 17 08 91; fax: (33) 62 17 09 05.

SSDI 0014-2999(95)00802-0

USA). CL 316243 is a highly selective agent for rat β_3-adrenoceptors compared with previously used compounds which are known to exhibit some β_1,β_2 activity when used at higher concentrations although having similar potency at β_3-adrenoceptors (Bloom et al., 1992; Dolan et al., 1994; Himms-Hagen et al., 1994).

2. Materials and methods

2.1. Animals

Wistar female rats (220–240 g), 11–12 weeks old, were used. They were housed in cages in animal quarters in which the temperature was maintained at 22 ± 1°C with light on from 7 a.m. to 7 p.m. They had free access to water and laboratory chow pellets (UAR, Villemoisson, France, 53% carbohydrates, 5% lipids, 22% proteins).

2.2. Surgery

After a 4-h fast, the rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and heparinized with an intravenous injection of 200 IU of heparin (Roche, Neuilly, France). Polyethylene catheters were placed into the left ventricle of the heart, via the right carotid artery for blood sampling and, in some cases, into the lower abdominal aorta to measure arterial blood pressure. Body temperature was recorded with a rectal thermistor probe. The mean arterial blood pressure was monitored with a pressure transducer connected to the arterial catheter. Preliminary dose-response studies on insulin secretion and plasma glucose concentration were undertaken first to settle the suitable dose of CL 316243 and to determine the effects of bupranolol and nadolol alone. Compounds were infused via a butterfly needle placed into the left saphenous vein. Blood samples were taken before and 5, 10 and 15 min after the beginning of the infusion, then centrifuged and frozen. Plasma glucose and insulin concentrations were determined using a glucose analyzer (Glucose analyzer 2, Beckman, Fullerton, CA) and a radioimmunoassay kit (INSIK 1, CEA, Saclay, France), respectively.

2.3. Blood flow measurements

Blood flow measurements were performed as described previously according to the method of Jansson et al. (Atef et al., 1992; Jansson, 1984; Jansson and Hellerström, 1981, 1983, 1986). Briefly, $1-1.5 \times 10^5$ non-radioactive microspheres (New England Nuclear Corp., Boston, MA) with a diameter of 10 μm were injected via the intracardiac catheter. Simultaneously, an arterial blood sample was withdrawn from the catheter in the abdominal aorta with a peristaltic pump adjusted to a rate of 0.6 ml/min for 90 s. This reference sample was used to calculate the organ blood flow as described below. Then, 500 μl of blood was quickly sampled, centrifuged and the plasma was frozen until subsequent determinations of plasma glucose and insulin concentrations as described above.

The rats were killed by cervical dislocation and the pancreas and both adrenal glands were removed, blotted and weighed. The organs and the reference sample were further processed and examined for microsphere content as previously described. Briefly the pancreas and the adrenal glands were treated according to a freeze-thawing technique which fragilizes the exocrine tissue and allows vizualization and counting of the microspheres in the islets and the exocrine parenchyma separately (Atef et al., 1992; Jansson, 1984; Jansson and Hellerström, 1983, 1986). The number of microspheres in the reference samples was determined by transferring the sample to glass microfiber filters and counting them in transmitted light.

The blood flow was calculated according to the following formula:

$$Q_{org} = \frac{N_{org} \times Q_{ref}}{N_{ref}}$$

where Q_{org} = organ blood flow (ml/min), Q_{ref} = withdrawal rate of the reference sample (ml/min), N_{ref} = number of microspheres in the reference sample, N_{org} = number of microspheres in the organ.

The microsphere content of the adrenal gland was used as a measure of the mixing of the microspheres with the blood. A difference of more than 10% between the two adrenal glands excluded the animal from the study. Likewise, blood pressure and body temperature were continuously monitored and variations in blood pressure or in body temperature exceeding 10% and 0.5°C, respectively, also led to exclusion of the animal.

The rats were infused with CL 316243 (0.4 nmol/kg/min) or with the vehicle (isotonic saline) via the left saphenous vein for 5 min. β-Adrenergic effects were antagonized with two kinds of β-adrenoceptor antagonists. First, bupranolol a non-selective (e.g. β_1,β_2,β_3-) adrenoceptor was used. There is, to our knowledge, no report in the litterature demonstrating that this drug exhibits β-adrenoceptor subtype selectivity. Second, we used nadolol, a compound which presents with β_1,β_2-adrenoceptor selectivity at doses which have been shown to block metabolic and cardiovascular effects (Berlan et al., 1994; Ford et al., 1992). Differences between the two sets of results could account for the existence of β_3-adrenergic effects. Thus, a group of rats was injected, 10 min before the infusion of CL 316243, with the β_1,β_2,β_3-adrenoceptor antagonist, bupranolol, at the dose of 5 mg/kg body weight, via the right saphenous vein. Another group of rats was injected, 10 min before the infusion of CL 316243, with the β_1,β_2-adrenoceptor antagonist, nadolol, at the dose of 1 mg/kg body weight, via the right saphenous vein.

Table 1
Time course of bupranolol and nadolol effect on plasma glucose and insulin concentrations

Time (min)	0		5		10		15	
Plasma	Glucose (mM)	Insulin (pmol/l)	Glucose (mM)	Insulin (pmol/l)	Glucose (mM)	Insulin (pmol/l)	Glucose (mM)	Insulin (pmol/l)
Bupranolol 5 mg/kg	5.92 ± 0.17	189 ± 24	5.76 ± 0.10	186 ± 18	5.88 ± 0.09	243 ± 42	6.09 ± 0.13	267 ± 45
Nadolol 1 mg/kg	6.06 ± 0.21	157 ± 17	6.05 ± 0.16	123 ± 15	5.87 ± 0.09	165 ± 31	5.93 ± 0.13	149 ± 13

The results are expressed as means ± S.E.M. The statistical significance of differences between means was evaluated using the Mann-Whitney U-test.

3. Results

3.1. Preliminary studies

3.1.1. Effect of bupranolol and nadolol (Table 1)

Bupranolol at the dose of 5 mg/kg induced no change in plasma glucose concentrations whereas the insulin level increased slightly but not significantly at times 10 and 15 min after the injection. Nadolol (1 mg/kg) provoked no alterations either in glycemia or insulinemia.

3.1.2. Time course of the effect of CL 316243 on plasma glucose and insulin concentrations and arterial blood pressure (Table 2)

Whatever the dose used, plasma glucose decreased slowly, this fall being significant 10 min after the beginning of the infusion. This decrease corresponded to an increase in plasma insulin concentration as soon as 5 min after the beginning of the infusion. In view of the responses we decided to use the dose of 0.4 nmol/kg/min for further experiments. Indeed, insulin secretion was more marked and lasted longer at this dose than at 0.2 nmol/kg/min.

The infusion of CL 316 243 at the dose of 0.4 nmol/kg/min induced a significant fall of the arterial blood pressure 10 min after the beginning of the infusion (99 ± 5–83 ± 5 mm Hg, $P < 0.05$). To avoid any effect of either arterial blood pressure or plasma glucose concentration on islet blood flow, we decided to perform all the measurements in subsequent experiments 5 min after the beginning of the infusion of CL 316 243, at which time neither arterial blood pressure nor plasma glucose were significantly altered.

3.2. Effect of the infusion of CL 316243 on islet blood flow and insulin concentration

3.2.1. Alone

The infusion of CL 316243 did not change the plasma glucose concentration but produced a significant increase in plasma insulin level over baseline (Fig. 1). Concomitantly, whereas neither arterial blood pressure nor pancreatic blood flow were altered, islet blood flow was significantly enhanced (Table 3 and Fig. 1).

3.2.2. Plus bupranolol

When rats were pretreated with bupranolol, a potent β-adrenoceptor antagonist (β_1,β_2,β_3), the effect of CL 316243 was abolished. The plasma glucose concentration was slightly increased without modification of the plasma insulin level (Fig. 1). The combination of CL 316243 plus bupranolol induced a small but significant increase of islet blood flow which was probably due to the increase of pancreatic blood flow (Table 3). Indeed, when islet blood flow was expressed as a percent of total pancreatic blood flow, the difference was not significant (Fig. 1).

3.2.3. Plus nadolol

In the presence of nadolol, a specific β_1,β_2-adrenoceptor antagonist, CL 316243 was as potent as when infused alone (Table 3 and Fig. 1). Indeed, whereas plasma glu-

Table 2
Time course of the effect of different doses of CL 316243 infusion on plasma glucose and insulin concentrations

Time (min)	0		5		10		15	
Plasma	Glucose (mM)	Insulin (pmol/l)	Glucose (mM)	Insulin (pmol/l)	Glucose (mM)	Insulin (pmol/l)	Glucose (mM)	Insulin (pmol/l)
CL 316243 (nmol/kg)								
0.2	6.12 ± 0.34	198 ± 24	5.70 ± 0.18	321 ± 21 [b]	5.41 ± 0.13 [a]	279 ± 27 [a]	5.40 ± 0.13 [a]	244 ± 18
0.4	6.55 ± 0.17	171 ± 17	6.33 ± 0.17	322 ± 35 [b]	6.05 ± 0.17	350 ± 12 [b]	5.77 ± 0.17 [b]	329 ± 34 [b]
0.8	6.83 ± 0.34	162 ± 21	6.30 ± 0.13	495 ± 45 [a]	5.89 ± 0.16 [a]	431 ± 70 [c]	5.53 ± 0.16 [b]	360 ± 39 [c]

$n = 4$–6; [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$, significantly different from time 0.

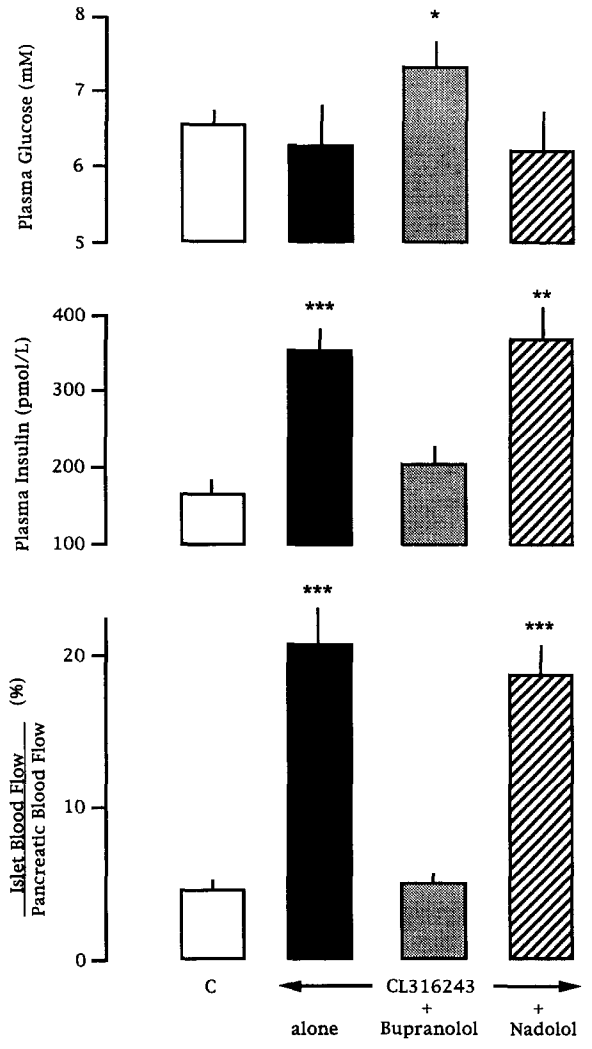

Fig. 1. Plasma glucose and insulin concentrations, and islet blood flow, a percentage of pancreatic blood flow, in rats under basal conditions (open columns), after perfusion of CL 316243 alone (closed columns) or in combination with an injection of bupranolol (grey columns) or nadolol (shaded columns). Data are means ± S.E.M. of four to seven determinations. Statistically significant difference between control and treated rats, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

cose, arterial blood pressure and pancreatic blood flow were not affected by the treatment, insulin levels and islet blood flow were markedly increased.

4. Discussion

The major finding of the present study was that, in vivo in rats, β_3-adrenoceptor activation induced a clear cut increase in both plasma insulin concentration and islet blood flow. This effect seems to be quite specific for β_3-adrenoceptors since (1) CL 316243 is, up to now, the most potent stimulator of β_3-adrenoceptors in rats (Bloom et al., 1992; Dolan et al., 1994; Himms-Hagen et al., 1994). (2) Although no potent and selective β_3-adrenoceptor antagonist is available, studies have shown that high concentrations of non-selective β_3-adrenoceptor antagonists are able to antagonize the effect of β_3-adrenoceptor stimulation (Galitzky et al., 1993a; Galitzky et al., 1993b). Bupranolol, one of the most potent of these drugs, reversed the enhanced insulin secretion and increase in islet blood flow induced by CL 316243. (3) Nadolol, a β_1,β_2- but not β_3-adrenoceptor antagonist did not prevent the effect of CL 316243 on islet blood flow and insulin secretion. Although not tested directly, in view of the absence of effects of both bupranolol and nadolol on plasma glucose and insulin, it is unlikely that these two compounds themselves have effects on islet blood flow.

The vasodilator effect induced by β_3-adrenoceptor stimulation has already been described in other tissues. In dogs, sustained peripheral vasodilatation has been reported in fat and skin (Berlan et al., 1994; Shen et al., 1994). Furthermore, in anesthetized rats, β_3-adrenoceptor agonists increase markedly the blood flow to brown adipose tissue (Takahashi et al., 1992) and there is considerable evidence indicating the presence of β_3-adrenoceptors in both brown and white adipose tissue (Granneman et al., 1991; Krief et al., 1993; Galitzky et al., 1993b; Langin et al., 1991). Although no direct measurements have been done on the skin and pancreas, the data cited above as well as the present results suggest the presence of β_3-adrenoceptors in microvessels in these tissues. Together, these data indicate that β_3-adrenoceptors are present in the microvasculature of some specific territories and confirm that the distribution of receptor subtypes varies according to the localisation of the vessels (McGrath et al., 1989).

An influence of the autonomic nervous system on islet blood flow has been demonstrated. Thus, the glucose-induced increase in islet blood flow is totally blunted by

Table 3
Effect of CL 316243 (0.4 nmol/kg) alone or associated with bupranolol or nadolol on arterial blood pressure and pancreatic and islet blood flow

	Control	CL 316243	CL 316243 + bupranolol	CL 316243 + nadolol
Arterial blood pressure (mm Hg)	99 ± 5	89 ± 5	87 ± 5	92 ± 2
Pancreatic blood flow (ml/min/g)	1.09 ± 0.08	1.06 ± 0.17	1.48 ± 0.07 [a]	1.06 ± 0.08
Islet blood flow (μl/min/g)	49.8 ± 6.3	206.0 ± 17.4 [c]	74.0 ± 6.9 [a]	194.2 ± 1.8 [c]

n = 4–7 rats; [a] $P < 0.05$, [c] $P < 0.001$, significantly different from control rats.

vagotomy or atropine (Jansson and Hellerström, 1986). In obese Zucker rats, the enhanced islet blood flow is brought back to the values for lean rats by both vagotomy and clonidine (α_2-adrenoceptor agonist) (Atef et al., 1992). Furthermore, norepinephrine infusion has been reported to inhibit islet microcirculation (Rappaport et al., 1971; Rooth et al., 1985; Rooth and Täljedal, 1987) although this result has been debated (Meyer et al., 1982). This effect of norepinephrine has been shown to be blocked by phentolamine, suggesting mediation by α-adrenoceptors (Rooth et al., 1985). Concerning the role of β-adrenoceptors in islet blood flow, our results are in agreement with those of two other studies. First, stimulation of islet blood flow has been demonstrated after administration of the non-specific β-adrenoceptor agonist, isoproterenol (Meyer et al., 1982). Second, the administration of terbultaline, a β_2-adrenoceptor agonist, leads to a decreased islet blood flow (Jansson et al., 1989). Furthermore, there is evidence that β_3-adrenoceptors are under the influence of noradrenergic innervation (Taneja and Clarke, 1992). Thus islet blood flow could be under the influence of the sympathetic nervous system via both α- and β_3-adrenoceptors. The two types of receptors would have opposite effects on the regulation of blood flow, as already reported for insulin secretion. The exact role of each of these receptors remains to be determined.

Several lines of evidence suggest that changes in pancreatic islet blood flow modulate the transport of secretagogues (nutrients and hormones) as well as the clearance of insulin in the whole body vasculature. Thus, such changes could be involved at least in part in the regulation of insulin release. There is an abundance of data showing good parallelism or a correlation between islet blood flow and plasma insulin levels (Atef et al., 1992, 1994; Jansson and Hellerström, 1983, 1986). The increased islet blood flow could be due to a direct effect of insulin itself. Thus, some data demonstrate such an effect of insulin (Sparrow and Beckingham, 1989; Vetterlein et al., 1985), although other data showed the inverse effect, i.e. an inhibiting effect of insulin on islet blood flow (Jansson and Berne, 1993). Due to the differences in the effect of β_3-adrenoceptor agonists on insulin secretion according to whether it was studied in vivo or in vitro, we believe that the present data suggest that the increased islet blood flow induced by β_3-adrenoceptor stimulation could be one of the mechanisms involved in the increased insulin secretion described in animals treated with β_3-adrenoceptor agonists (this work, Caroll et al., 1985; Cawthorne et al., 1984; Sennitt et al., 1985; Yoshida, 1992).

In conclusion the present study demonstrated that β_3-adrenoceptor stimulation induces a significant increase in both insulin secretion and pancreatic islet blood flow, in vivo. These data may provide insights into the mechanism of the antidiabetic and insulinotropic effect of β_3-adrenoceptor agonists.

References

Atef, N., A. Ktorza, L. Picon and L. Pénicaud, 1992, Increased islet blood flow in obese rats: role of the autonomic nervous system, Am. J. Physiol. 262, E736.

Atef, N., B. Portha and L. Pénicaud, 1994 Changes in islet blood flow in rats with NIDDM, Diabetologia 37, 677.

Berlan, M., J. Galitzky, A. Bousquet-Melou, M. Lafontan and J.L. Montastruc 1994, Beta-3 adrenoceptor-mediated increase in cutaneous blood flow in the dog, J. Pharmacol. Exp. Ther. 268, 1444.

Bloom, J.D., M.D. Dutia, B.D. Johnson, A. Wissner, M.G. Burns, E.E. Largis, J.A. Dolan and T.H. Claus, 1992 Disodium (*R,R*)-5-[2[[2(3 chlorophenyl)-2-hydroxyethyl]-amino] propyl]-1,3-benzodioxole-2,2-dicarboxylate (CL 316243). A potent beta-adrenergic agonist virtually specific for beta3 receptors. A promising antidiabetic and antiobesity agent, J. Med. Chem. 35, 3081.

Caroll, M.J., C.A. Lister, M.V. Sennitt, V. Stewart-Long and M.A. Cawthorne, 1985, Improved glyacemic control in C57B1/KsJ(db/db) mice after treatment with the thermogenic β-adrenoceptor agonist BRL 26830A, Diabetes 24, 1198.

Cawthorne, M.A., M.J. Caroll and A.L. Levy, 1984, Effect of novel β-adrenoceptor agonists on carbohydrate metabolism: relevance for the treatment of non-insulin-dependent diabetes, Int. J. Obes. 8 (Suppl. 1), 93.

Dolan, J.A., H.A. Muenkel, M.G. Burns, S.M. Pellegrino, C.M. Fraser, F. Pietri, A.D. Strosberg, E.E. Largis, M.D. Dutia, J.D. Bloom, A.S. Bass, T.K. Tanikella, A.G. Cobuzzi, F.M. Lai and T.H. Claus, 1994, Beta-3-adrenoceptor selectivity of the dioxolane dicarboxylate phenethanolamines, J. Pharmacol. Exp. Ther. 269, 1000.

Ferré, P., L. Pénicaud, Y. Hitier, Meier, M. and J. Girard, 1992, Hypoglycemic effects of a β-agonist, RO 16-8714, in streptozotocin-diabetic rats: decreased hepatic glucose production and increased glucose utilization in oxidative muscles, Metabolism 41, 180.

Ford, A.P.D.W., D.T. Taneja and D.E. Clarke, 1992, Atipycal β-adrenoceptor-mediated relaxation and cyclic-AMP formation in tunica muscularis mucosae (TMM) of the rat oesophagus, Br. J. Pharmacol. 105 (Suppl.), 235P.

Galitzky, J., M. Reverte, C. Carpene, M. Lafontan and M. Berlan, 1993a, β3-Adrenoceptors in dog adipose tissue: studies on their involvment in the lipomobilizing effect of catecholamines, J. Pharmacol. Exp. Ther. 266, 358.

Galitzky, J., M. Reverte, M. Portillo, C. Carpene, M. Lafontan and M. Berlan, 1993b, Coexistence of β1, β2 and β3-adrenoceptors in dog fat cells and their differential activation by catecholamines, Am. J. Physiol. 264, E403.

Granneman, J.G., K.N. Lahners and A. Chaudhry, 1991, Molecular cloning and expression of the rat β3-adrenergic receptor, Mol. Pharmacol. 40, 895.

Himms-Hagen, J., J. Cui, E. Danforth, D.J. Taatjes, S.S. Lang, B.L. Waters and T.H. Claus, 1994, Effect of CL 316243, a thermogenic beta3-agonist, on energy balance and brown and white adipose tissues in rats, Am. J. Physiol. 35, R1371.

Jansson, L., 1984, The blood flow to the pancreas and islet of Langerhans during an intraperitoneal glucose load in the rat, Diabetes Res. Clin. Pratice 1, 111.

Jansson, L. and C. Berne, 1993, Hypoglycemia and pancreatic islet blood flow in the rat: evidence for a decreased islet blood perfusion mediated by the central nervous system, Acta Endocrinol. 128 (Suppl. 1), 10.

Jansson, L. and C. Hellerström, 1981, A rapid method of visualizing the pancreatic islets of studies of islet capillary blood flow using non radioactive microspheres, Acta Physiol. Scand. 113, 371.

Jansson, L. and C. Hellerström, 1983, Stimulation by glucose of the blood flow to the pancreatic islets of the rats, Diabetologia 25, 45.

Jansson, L. and C. Hellerström, 1986, Glucose induced changes in

pancreatic islet blood flow mediated by central nervous system, Am. J. Physiol. 251, E644.

Jansson, L., D.L. Eizirik and S. Sandler, 1989, Terbutaline decreases the blood flow of the pancreatic islets but does not reduce the diabetogenic action of streptozotocin in the rat, Eur. J. Pharmacol. 161, 79.

Krief, S., F. Lönnqvist, S. Raimbault, B. Baude, A. Van Spronsen, P. Arner, A.D. Strosberg, D. Ricquier and L.J. Emorine, 1993, Tissue distribution of β3-adrenergic receptor mRNA in man, J. Clin. Invest. 91, 344.

Lacey, R.J., N.S. Berrow, J.H. Scarpello and N.G. Morgan, 1991, Selective stimulation of glucagon secretion by beta-2-adrenoceptors in isolated islets of Langerhans of the rat, Br. J. Pharmacol. 103, 1824.

Langin, D., M.P. Portillo, J.S. Saulnier-Blache and M. Lafontan, 1991, Coexistence of three β-adrenoceptor subtypes in white fat cells of various mammalian species, Eur. J. Pharmacol. 199, 291.

McGrath, J.C., C.M. Brown and V.G. Wison, 1989, Alpha-adrenoceptors: a critical review, Med. Res. Rev. 9, 408.

Meyer, H.H., F. Vetterlein, G. Schmidt and A. Hasselblatt, 1982, Measurement of blood flow in pancreatic islets of the rat: effect of isoproterenol and norepinephrine, Am. J. Physiol. 242, E298.

Rappaport, A.M., T. Kawamura, J.K. Davidson, B.J. Lin, S. Ohira, M. Zeigler, J.A. Goddling, J. Henderson and R.E. Haist, 1971, Effects of hormones and of blood flow on insulin output of isolated pancreas in situ, Am. J. Physiol. 221, 343.

Rooth, P. and I.B. Täljedal, 1987, Vital microscopy of islet blood flow: Catecholamine effects in normal an ob/ob mice, Am. J. Physiol. 252, E130.

Rooth, P., K. Grankvist and I.B. Täljedal, 1985, In vivo fluorescence microscopy of blood flow in mouse pancreatic islets: adrenergic effect in lean an obese hyperglycemic mice, Microvasc. Res. 30, 176.

Sennitt, M.V., J.R.S. Arch, A.L. Levy, D.L. Simson, S.A. Smith and M.A. Cawthorne, 1985, Anti-hyperglycaemic action of BRL 26830, a novel β-adrenoceptor agonist, in mice and rats, Biochem. Pharmacol. 34, 1279.

Shen, Y.T., H. Zhang and S.F. Vatner 1994, Peripheral vascular effects of beta-3 adrenergic receptor stimulation in conscious dogs, J. Pharmacol. Exp. Ther. 268, 466.

Smith, S.A., A.L. Levy, M.V. Sennitt, D.L. Simson and M.A. Cawthorne, 1985, Effect of BRL 26830, a novel β-adrenoceptor agonist, on glucose tolerance, insulin sensitivity and glucose turnover in Zucker (fa/a) rats, Biochem. Pharmacol. 34, 2425.

Sparrow, R.A. and I.J. Beckingham, 1989, Islet blood flow following insulin administration, J. Anat. 163, 75.

Takahashi, H., T. Yoshida, M. Nishimura, T. Nakanishi, M. Kondo and M. Yoshimura, 1992, Beta-3 adrenergic agonist, BRL 26830A, and alpha/beta blocker, arotinolol, markedly increase regional blood flow in brown adipose tissue in anesthetized rats, Jpn. Circ. J. 56, 936.

Taneja, D.T. and D.E. Clarke, 1992, Evidence for a noradrenergic innervation to atypical beta adrenoceptors (or putative beta 3 adrenoceptors) in the illeum of guinea pig, J. Pharmacol. Ther. 260, 192.

Vetterlein, F., D. Senske, C. Bornkessel and G. Scmidt, 1985, Effect of tolbutamide on blood flow in islets and exocrine tissue of the rat pancreas, Eur. J. Pharmacol. 113, 395.

Yoshida, T., 1992, The antidiabetic β3-adrenoceptor agonist BRL 26830 works by release of endogenous insulin, Am. J. Clin. Nutr. 55, 237S.