Pancreatic Islet Blood Flow in the Rat After Administration of Islet Amyloid Polypeptide or Calcitonin Gene-Related Peptide

ANNIKA M. SVENSSON, STELLAN SANDLER, AND LEIF JANSSON

Anesthetized male Sprague-Dawley rats (350–400 g) were injected intravenously with either 0.1, 1, 15, or 25 nmol rat islet amyloid polypeptide (IAPP), 65 or 650 pmol rat calcitonin gene-related peptide (CGRP), or saline alone. IAPP at the two highest doses decreased the mean arterial blood pressure (BP), increased blood glucose concentrations, and decreased serum insulin concentrations. CGRP at both doses decreased the BP but did not affect the blood glucose concentrations. The blood flow to the whole pancreas, pancreatic islets, adrenal glands, colon, duodenum, liver, and kidney was measured with a microsphere technique 30 min after administration of IAPP and 3 min after injection of CGRP. The two higher doses of IAPP (15 and 25 nmol) markedly reduced the whole pancreatic blood flow, whereas the islet blood flow remained unaffected. This resulted in an increase in the fraction of whole pancreatic blood flow diverted through the islets from ~10 to 17%. No blood flow changes in the pancreas or the islets were observed when 0.1 or 1 nmol IAPP was injected. CGRP at both doses caused a decrease in both whole pancreatic and islet blood flow. No changes in fractional islet blood flow were observed, despite similar effects on mean arterial BP as observed after IAPP injections. Neither adrenal, duodenal, colonic, hepatic, skeletal muscle, nor renal blood flow were significantly affected by any of the concentrations of IAPP used, whereas 650 pmol CGRP decreased both duodenal and colonic blood flow. We conclude that IAPP and CGRP have different effects on pancreatic islet blood flow and that IAPP may be of importance for islet blood flow regulation. *Diabetes* 43:454–58, 1994

From the Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden.

Address correspondence and reprint requests to Dr. Annika M. Svensson, Department of Medical Cell Biology, Biomedical Center, P.O. Box 571, S-751 23, Uppsala, Sweden.

Received for publication 30 March 1993 and accepted in revised form 7 October 1993.

IAPP, islet amyloid polypeptide; CGRP, calcitonin gene-related peptide; BP, blood pressure.

Islet amyloid polypeptide (IAPP) or amylin is a 37-amino acid peptide that forms the major constituent of the amyloid deposits found in islets of most type II diabetic patients (1–3). IAPP is synthesized in the β-cells (2), stored within insulin secretory granules (4), and subsequently released, essentially in concert with insulin (5–8). The physiological effects of IAPP have been suggested to include a receptor-mediated glycogen degradation and lactate release from skeletal muscle and associated effects on hepatic fuel metabolism, which could counteract hypoglycemic effects induced by insulin (9,10). The possible endocrine and paracrine effects of IAPP on islet hormone secretion remain controversial (11,12). However, it has been suggested that IAPP may act on the endocrine pancreas by directly stimulating the islet blood perfusion (13). The rationale for this suggestion was that IAPP may cause a vasodilation (14,15) analogous to that seen after administration of the potent vasodilator calcitonin gene-related peptide (CGRP) (16–18), a neuropeptide that shares an ~50% homology with IAPP (1). Because of these putative effects of IAPP on blood perfusion, the aim of this study was to evaluate, with a microsphere technique, whether IAPP affected the blood flow within the pancreas and particularly in the islets. In addition, the specific effect of CGRP on the pancreatic islets was investigated.

RESEARCH DESIGN AND METHODS

Male Sprague-Dawley rats, weighing 350–400 g, were obtained from a local breeding colony (Biomedical Center, Uppsala, Sweden) and used in all experiments. The rats had free access to pelleted food (Type R36; AB AnalyCen, Lidköping, Sweden) and tap water throughout the experiments.

Surgical preparation. Rats were anesthetized with an intraperitoneal injection of pentobarbital (50 mg/kg body

wt; Mebumal Vet, Nordvacc AB, Solna, Sweden), heparinized (500 IU intravenously), and placed on a heated operating table. Polyethylene catheters were inserted into the ascending aorta via the right carotid artery and into the left femoral artery. The former catheter was connected to a pressure transducer (PDCR 75/1i, Druck, Groby, U.K.), and the mean arterial blood pressure (BP) was monitored on a recorder throughout the experiments. The right femoral vein was dissected free, and the BP of the rats was allowed to stabilize until it had remained constant (<5% variation) for 15 min. Then 0.1, 1, 15, or 25 nmol rat IAPP (Peninsula, Belmont, CA) dissolved in 0.6 ml saline or saline alone was injected into the femoral vein of some of the rats during 15–20 s. Other rats were injected with 65 or 650 pmol CGRP (Sigma, St. Louis, MO) dissolved in 0.2 ml saline or with saline alone.

Blood flow measurements. The arterial blood perfusion of the whole pancreas, pancreatic islets, duodenum, colon, liver, adrenal glands, iliopsoas muscle, and kidneys (the two latter structures only in IAPP-injected animals) was determined with a microsphere technique, described in detail previously (19), 3 min after injection of CGRP and 30 min after injection of IAPP. The time points were chosen according to results published previously (17,20), so that the peptide-induced circulatory effects after the bolus injection should be maximal at the time of measurement. Briefly, 1.5–2 × 10^5 nonradioactive microspheres (NEN-Trac, Du Pont, Wilmington, DE) with a diameter of 11 μm were injected during 10 s through the catheter with its tip in the ascending aorta. Starting 5 s before the microsphere injection and continuing for a total of 60 s, an arterial blood reference sample was collected by free flow (~0.50 ml/min) from the catheter placed in the femoral artery. The exact withdrawal rate in each separate experiment was controlled by weighing the sample.

The rats were then killed, and the whole pancreas and adrenal glands were removed, blotted, and weighed. Approximately 150 mg each of the duodenum, colon, liver (median lobe), iliopsoas muscle, and right kidney also were removed and weighed. The kidney was sampled as a slice, through the midportion of the organ, containing both cortical and medullary tissue. All organs were treated with a freeze-thawing technique to visualize the microspheres when viewed in an inverted light microscope (21). This technique also allows one to distinguish between microspheres in the endocrine and exocrine parts of the pancreas by examining the preparations using a dark field condenser. Within the organ samples referred to above, all microspheres were counted. In particular, the entire pancreas, including all islets, was examined. The content of microspheres was evaluated by one examiner, unaware of the previous experimental treatment of the sample. Blood flow values were calculated according to the formula $Q_{org} = Q_{ref} \times N_{org}/N_{ref}$, where Q_{org} is organ blood flow (ml/min), Q_{ref} is withdrawal rate of the reference sample (ml/min), N_{org} is the number of microspheres in the organ, and N_{ref} is the number of microspheres in the reference sample. The blood flow to each of the adrenal glands was calculated for each experimental animal. A difference in adrenal blood flow <10% between the two glands was defined as confirming an adequate mixture of the microspheres with the circulation. Two rats were excluded from the study because they did not fulfill this criterion.

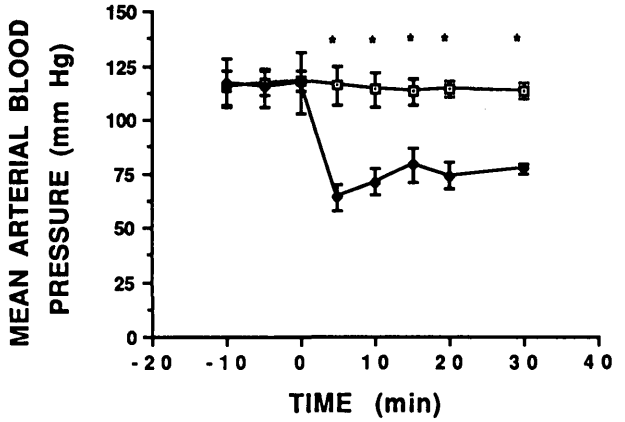

FIG. 1. Mean arterial BP at different times before and after administration at time 0 of saline (□; n = 11) or 25 nmol IAPP (■; n = 9). Data are means ± SE. *P < 0.001.

Statistical analysis. All values are given as means ± SE. All statistical comparisons were made with a two-tailed, unpaired Student's t test.

RESULTS

Administration of 25 nmol IAPP resulted in a decrease in mean arterial BP, which was most pronounced 5 min after administration, but remained throughout the 30-min observation period (Fig. 1). With a dose of 15 nmol IAPP, a similar change in BP was observed, whereas 0.1 and 1.0 nmol IAPP did not affect the BP (data not shown). At 30 min after injection of 15 or 25 nmol IAPP, the blood glucose concentrations were elevated, and the serum insulin levels were decreased (Table 1). When 0.1 or 1 nmol IAPP was administered, no effects on either blood glucose or serum insulin concentrations were found (Table 1). A marked reduction in whole pancreatic blood flow was seen after administration of 15 or 25 nmol of IAPP, whereas the islet blood flow remained unchanged (Table 1). As a result, the fraction of whole pancreatic blood flow diverted through the islets increased markedly after administration of the two higher doses of IAPP (Table 1). Injection of 0.1 or 1 nmol IAPP had no effect on either pancreatic or islet blood flow (Table 1). No significant effects on duodenal, colonic, arterial hepatic, renal, skeletal muscle, or adrenal blood flow could be discerned after administration of any of the doses of IAPP (Table 2).

In another series of experiments, both 65 and 650 pmol CGRP produced a decrease in mean arterial BP, whereas the blood glucose concentrations remained unaffected (Table 3). Also, the whole pancreatic blood flow and the islet blood flow were reduced by both concentrations of CGRP (Table 3). However, these blood flows decreased in concert, so that the fractional islet blood flow remained constant (Table 3). The duodenal and colonic blood flows were significantly decreased by

TABLE 1
Blood glucose and serum insulin concentrations and whole pancreatic and islet blood flow values in anesthetized rats 30 min after an intravenous injection of either saline or IAPP

		IAPP (nmol)			
	Saline	0.1	1.0	15	25
Rats (*n*)	11	5	5	7	9
Blood glucose (mM)	4.9 ± 0.3	4.4 ± 0.1	4.2 ± 0.2	9.0 ± 0.6*	7.0 ± 0.5*
Serum insulin concentration (pM)	240 ± 40	480 ± 150	270 ± 130	110 ± 30†	120 ± 20†
Pancreatic blood flow (ml/min × g)	0.44 ± 0.05	0.48 ± 0.08	0.42 ± 0.06	0.22 ± 0.03‡	0.18 ± 0.03*
Islet blood flow (μl/min × g)	46 ± 8	40 ± 8	40 ± 9	38 ± 8	30 ± 6
Islet blood flow (% pancreatic blood flow)	10.1 ± 1.1	8.3 ± 1.0	9.4 ± 1.0	16.8 ± 1.8‡	16.7 ± 1.7‡

Data are means ± SE.
*$P < 0.001$ compared with saline-injected animals.
†$P < 0.05$ compared with saline-injected animals.
‡$P < 0.01$ compared with saline-injected animals.

the highest dose of CGRP, whereas arterial hepatic blood flow remained unchanged (Table 3).

DISCUSSION

Blood flow of the pancreas is normally regulated by a complex interaction between local, hormonal, and neural factors. Mechanisms that can be envisaged behind the effects of IAPP on the pancreas, other than direct effects of the peptide on vascular smooth muscle, include induction of release of neuropeptides or influence on the local production of prostaglandins or endothelial-derived vasoactive substances.

Administration of IAPP resulted in elevated blood glucose concentrations when 15 or 25 nmol doses of the drug were given, but not at lower doses. This is of particular interest, because an increased blood glucose concentration can selectively increase islet blood flow (19). The degree of hyperglycemia must be, however, at least 25–30% higher than that observed in this study (22). The underlying mechanism causing the increased blood glucose levels could be assumed to consist of an IAPP-induced insulin resistance in skeletal muscles (10,23). An additional explanation would be that increased catecholamine secretion induced by the decreased BP contributes to the blood glucose changes. The reduced serum insulin levels observed after injection of the higher doses of IAPP agree with previous studies showing decreased insulin secretion after administration of IAPP (11,24). However, other authors have reported divergent results, with no effect of IAPP on insulin secretion (25–27), albeit using different concentrations and/or different preparations of IAPP.

The observed decrease in mean arterial BP caused by administration of 15 or 25 nmol IAPP and 65 or 650 pmol CGRP confirms previous findings (14,17,20). The vasodilator effect of IAPP has been suggested to be a result of the structural similarity with CGRP (1,28) and to be mediated by cross-talk at CGRP vascular receptors. The decline in BP caused by 15 and 25 nmol IAPP or by 65 pmol CGRP was ~20%, whereas the highest dose of CGRP caused an even more pronounced decline (~35%) in mean arterial BP. A 20% decrease in BP is not enough to cause any marked changes in the blood flow to splanchnic organs (29). This is corroborated by the unchanged blood flow to the intestines and liver after administration of 65 pmol CGRP and 15 and 25 nmol IAPP found in this study. It remains difficult to ascertain whether the currently observed reduction in whole pancreatic blood flow represents an unspecific response to the reduced BP or a specific effect of CGRP and IAPP, even though the data are more consistent with the latter action. However, the effects on whole pancreatic blood flow of the highest dose of CGRP, which further diminished the BP an additional 10–15%, may be caused by

TABLE 2
Duodenal, colonic, arterial hepatic, renal, skeletal muscle, and adrenal blood flow values in anesthetized rats 30 min after an intravenous injection of either saline or IAPP

		IAPP (nmol)			
	Saline	0.1	1.0	15	25
Rats (*n*)	11	5	5	7	9
Blood flow					
Duodenal	0.70 ± 0.11	0.80 ± 0.11	0.77 ± 0.09	0.56 ± 0.08	0.61 ± 0.11
Colonic	0.26 ± 0.05	0.44 ± 0.12	0.43 ± 0.12	0.25 ± 0.03	0.25 ± 0.05
Arterial hepatic	0.09 ± 0.02	0.15 ± 0.06	0.13 ± 0.05	0.09 ± 0.04	0.10 ± 0.03
Renal	2.36 ± 0.31	2.68 ± 0.17	3.18 ± 0.49	2.32 ± 0.31	1.90 ± 0.25
Adrenal	2.32 ± 0.38	3.15 ± 0.35	2.50 ± 0.23	1.86 ± 0.24	1.79 ± 0.29
Skeletal muscle	0.008 ± 0.002	0.008 ± 0.002	0.008 ± 0.002	0.013 ± 0.004	0.013 ± 0.04

Data are means ± SE. Blood flow values are ml/min × g organ wt.

TABLE 3
Blood glucose concentration, mean arterial BP, and values for arterial blood flow to different organs 3 min after an intravenous injection of either saline alone or saline containing CGRP

		Calcitonin gene-related peptide (pmol)	
	Saline	65	650
Rats (*n*)	6	7	7
Blood glucose concentration (mM)	4.9 ± 0.5	5.0 ± 0.2	5.3 ± 0.3
Mean arterial BP (mmHg)	108 ± 6	79 ± 6*	68 ± 4†
Blood flow			
Pancreatic	0.55 ± 0.03	0.31 ± 0.07*	0.11 ± 0.02†
Islet (μl/min × g pancreas)	49 ± 6	28 ± 7‡	10 ± 2†
Islet (% pancreatic blood flow)	8.9 ± 0.8	8.9 ± 1.1	10.0 ± 1.1
Duodenal	1.06 ± 0.20	0.56 ± 0.15	0.41 ± 0.08*
Colonic	0.39 ± 0.08	0.31 ± 0.09	0.08 ± 0.02*
Arterial hepatic	0.12 ± 0.04	0.12 ± 0.04	0.03 ± 0.02

Data are means ± SE. Blood flow values are ml/min × g wet wt unless otherwise noted.
*$P < 0.01$ when compared with saline-injected animals.
†$P < 0.001$ when compared with saline-injected animals.
‡$P < 0.05$ when compared with saline-injected animals.

decreased BP. Note in this context that decreased arterial BP (~25%), induced by mechanical compression of the pancreatic arteries, causes a simultaneous and similar decrease in both whole pancreatic and islet blood flow (30). The present finding that islet blood flow, but not total pancreatic blood flow, is maintained after IAPP administration is therefore unlikely to be explained only by a decreased mean arterial BP.

Previous studies have shown that administration of pharmacological doses of CGRP or IAPP to normal rats increased splanchnic vascular resistance, whereas lower doses of CGRP decreased the resistance within the mesenteric blood vessels (14,20). However, when pharmacological doses of CGRP were given to spontaneously hypertensive rats, they induced a specific decline in whole pancreatic blood flow with only minor effects on the other splanchnic organs (18). This finding is similar to the findings in this study after an injection of 65 pmol CGRP, albeit the present experiments were performed on normal rats.

Administration of 15 or 25 nmol of IAPP caused a 50% reduction in whole pancreatic blood flow, whereas the absolute islet blood flow remained unaffected. However, a tendency toward a decrease could be seen with the highest dose (25 nmol) of IAPP. As a consequence, an increased fraction of whole pancreatic blood flow was diverted through the islets. This is consistent with previous findings demonstrating that the endocrine and exocrine parts of the pancreas have different blood flow regulatory mechanisms (31,32). Note that CGRP in this study decreased both whole pancreatic blood flow and islet blood flow to the same extent. The functional implications of the relative maintenance of islet blood flow caused by IAPP are intriguing. This effect was observed only after administration of the two highest doses of IAPP, i.e., at pharmacological concentrations. Nevertheless, it seems reasonable to assume that the extracellular concentration of IAPP within the islets may reach nanomolar concentrations, compare insulin (33). Because IAPP is released simultaneously with insulin (see above), we can speculate that an intrapancreatic function of IAPP might be to maintain islet blood flow, thereby facilitating the uptake of insulin and IAPP in the circulation (compare 13). This might have special implications during an increased functional load on the endocrine pancreas. Previously, animals that have been subjected to neonatal streptozocin treatments have shown a relative hypersecretion of amylin (34). Indeed, other conditions with an increased functional demand on pancreatic islets, e.g., partial pancreatectomy (35) and continuous glucose infusions (36), are associated with augmented islet blood flow. Thus, as suggested from this study, a physiological role of IAPP may be to maintain islet blood flow when there is an increased need for insulin disposal.

ACKNOWLEDGMENTS

This study was supported by grants from the Swedish Medical Research Council (12X-109, 12X-8273, 12P-9287, and 12P-10739), the Juvenile Diabetes Foundation International, the Swedish Diabetes Association, the Nordic Insulin Fund, the Procordia Research Foundation, the Family Ernfors Fund, and the Swedish Society of Medicine.

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

REFERENCES

1. Westermark P, Wernstedt C, Wilander E, Sletten K: A novel peptide in the calcitonin gene-related peptide family as an amyloid fibril protein in the endocrine pancreas. *Biochem Biophys Res Commun* 140:827–31, 1986
2. Westermark P, Wernstedt C, Wilander E, Hayden DW, O'Brien TD, Johnson KH: Amyloid fibrils in human insulinoma and islets of Langerhans of the diabetic cat are derived from a neuropeptide-like protein also present in normal islet cells. *Proc Natl Acad Sci USA* 84:3881–85, 1987
3. Cooper GJ, Willis AC, Clark A, Turner RC, Sim RB, Reid KB: Purification and characterization of a peptide from amyloid-rich pancreases of type II diabetic patients. *Proc Natl Acad Sci USA* 84:8628–32, 1987
4. Lukinius A, Wilander E, Westermark GT, Engström U, Westermark P: Colocalization of islet amyloid polypeptide and insulin in the β-cell secretory granules of the human pancreatic islets. *Diabetologia* 32:240–44, 1989
5. Kanatsuka A, Makino H, Ohsawa H, Tokuyama Y, Yamaguchi T, Yoshida S, Adachi M: Secretion of islet amyloid polypeptide in response to glucose. *FEBS Lett* 259:199–201, 1989

6. Kahn SE, D'Alessio DA, Schwartz MW, Fujimoto WY, Ensick JW, Taborsky GT Jr, Porte D Jr: Evidence of secretion of islet amyloid polypeptide and insulin by β-cells. *Diabetes* 39:634–38, 1990
7. Inoue K, Hisatomi A, Umeda F, Nawata H: Release of amylin from perfused rat pancreas in response to glucose, arginine, β-hydroxybutyrate, and gliclazide. *Diabetes* 40:1005–1009, 1991
8. Stridsberg M, Sandler S, Wilander E: Cosecretion of islet amyloid polypeptide (IAPP) and insulin from isolated rat pancreatic islets following stimulation or inhibition of β-cell function. *Regul Pept* 45:363–70, 1993
9. Deems RO, Cardinaux F, Deacon RW, Young DA: Amylin or CGRP (8–37) fragments reverse amylin-induced inhibition of ^{14}C-glycogen accumulation. *Biochem Biophys Res Commun* 181:116–20, 1991
10. Young AA, Mott DM, Stone K, Cooper GJS: Amylin activates glycogen phosphorylase in the isolated soleus muscle of the rat. *FEBS Lett* 281:149–51, 1991
11. Ohsawa H, Kanatsuka A, Yamaguchi T, Makino H, Yoshida S: Islet amyloid polypeptide inhibits glucose-stimulated insulin secretion from isolated rat pancreatic islets. *Biochem Biophys Res Commun* 160:961–67, 1989
12. Bretherton-Watt D, Gilbey SG, Ghate MA, Beacham J, Bloom SR: Failure to establish islet amyloid polypeptide (amylin) as a circulating β-cell inhibiting hormone in man. *Diabetologia* 33:115–17, 1990
13. Steiner DF, Ohagi S, Nagamatsu S, Bell GI, Nishi M: Is islet amyloid polypeptide a significant factor in pathogenesis or pathophysiology of diabetes? *Diabetes* 40:305–309, 1991
14. Gardiner SM, Compton AM, Kemp PA, Bennett T, Bose C, Foulkes R, Hughes B: Antagonistic effect of human α-calcitonin gene-related peptide (8–37) on regional hemodynamic actions of rat islet amyloid polypeptide in conscious Long-Evans rats. *Diabetes* 40:948–51, 1991
15. Brain SD, Wimalawansa S, MacIntyre I, Williams TJ: The demonstration of vasodilator activity of pancreatic amylin amide in the rabbit. *Am J Pathol* 136:487–90, 1990
16. Brain SD, Williams TJ, Tippins JR, Morris HR, MacIntyre I: Calcitonin gene-related peptide is a potent vasodilator. *Nature* 313:54–56, 1985
17. DiPette DJ, Schwarzenberger K, Kerr N, Holland OB: Dose-dependent systemic and regional hemodynamic effects of calcitonin gene-related peptide. *Am J Med Sci* 297:65–70, 1989
18. Ando K, Pegram BL, Frohlich ED: Hemodynamic effects of calcitonin gene-related peptide in spontaneously hypertensive rats. *Am J Physiol* 258:R425–29, 1990
19. Jansson L, Hellerström C: Stimulation by glucose of the blood flow to the pancreatic islets of the rat. *Diabetologia* 25:45–50, 1983
20. Gardiner SM, Compton AM, Bennett T: Regional hemodynamic effects of calcitonin gene-related peptide. *Am J Physiol* 256:R332–38, 1989
21. Jansson L, Hellerström C: A rapid method of visualizing the pancreatic islets for studies of islet blood flow using non-radioactive microspheres. *Acta Physiol Scand* 113:371–74, 1981
22. Jansson L: Glucose stimulation of pancreatic islet blood flow by redistribution of the blood flow within the whole gland. *Pancreas* 3:409–12, 1988
23. Leighton B, Cooper GJS: Pancreatic amylin and calcitonin gene-related peptide cause resistance to insulin in skeletal muscle in vitro. *Nature* 335:632–35, 1988
24. Kogire M, Ishizuka J, Thompson JC, Greely GH Jr: Inhibitory action of islet amyloid polypeptide and calcitonin gene-related peptide on release of insulin from the isolated perfused rat pancreas. *Pancreas* 6:459–63, 1991
25. Pettersson S, Ahrén B: Failure of islet amyloid polypeptide to inhibit basal and glucose-stimulated insulin secretion in model experiments in mice and rats. *Acta Physiol Scand* 138:389–94, 1990
26. Ghatei MA, Datta HK, Zaidi M, Bretherton-Watt D, Wimalawansa SJ, MacIntyre I, Bloom SR: Amylin and amylin-amide lack an effect on blood glucose and insulin. *J Endocrinol* 124:R9–11, 1990
27. O'Brien TD, Westermark P, Johnson KH: Islet amyloid polypeptide and insulin secretion from isolated perfused pancreas of fed, fasted, glucose-treated, and dexamethasone-treated rats. *Diabetes* 40: 1701–707, 1991
28. Brain SD, MacIntyre I, Wimalawansa S, Williams TJ: Amylin amide, which is structurally similar to calcitonin gene-related peptides (CGRP), stimulates increased blood flow in vivo (Abstract). *Eur J Pharmacol* 183:2221, 1990
29. Kvietys PR, McLendon JM, Bulkley GB, Perry MA, Granger DN: Pancreatic circulation: intrinsic regulation. *Am J Physiol* 242:G596–602, 1982
30. Jansson L: Evidence of an active regulation of pancreatic islet blood flow in rats: studies in induced hypotension. *Horm Metab Res* 25:651–52, 1993
31. Jansson L, Sandler S: Pancreatic islet circulation in relation to the diabetogenic action of streptozotocin in the rat. *Endocrinology* 116:896–900, 1985
32. Jansson L: Dissociation between pancreatic islet blood flow and insulin release in the rat. *Acta Physiol Scand* 124:223–28, 1985
33. Bendayan M: Pathway of insulin in pancreatic tissue on its release by the β-cell. *Am J Physiol* 264:G187–94, 1993
34. Inoue K, Hisatomi A, Umeda F, Nawata H: Relative hypersecretion of amylin to insulin from rat pancreas after neonatal STZ treatment. *Diabetes* 41:723–27, 1992
35. Jansson L, Sandler S: Pancreatic and islet blood flow in the regenerating pancreas after a partial pancreatectomy in adult rats. *Surgery* 106:861–66, 1989
36. Styrud J, Eriksson UJ, Jansson L: A continuous 48-hour glucose infusion in rats causes both an acute and a persistent redistribution of the blood flow within the pancreas. *Endocrinology* 130:1692–96, 1992