Reciprocal Gastropancreatic Modulations for the Release of Somatostatin-like Immunoreactivity, Glucagon, and Insulin in the Rat

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SUMMARY

In order to assess the interrelationships between stomach and pancreas regarding the secretions of somatostatin-like immunoreactivity (SLI), glucagon (IRG), and insulin (IRI), concentrations of the three hormones were assayed in portal plasma and portal blood flow was measured in enterectomized rats before and after the selective removal of stomach or pancreas.

Portal plasma SLI, IRG, and IRI concentrations were significantly increased by i.v. arginine in control rats (pancreas + stomach present). After gastrectomy, SLI, IRG, and IRI concentrations were, respectively, 52 ± 13% (N = 15; P < 0.005), 234 ± 40% (P < 0.001), and 119 ± 15% (NS) of the pregastrectomy values. A decreased SLI secretion, an increased IRG release, and an unmodified basal IRI release were estimated by portal flow measurement. The A- and B-cell responses to arginine in the gastrectomized rats were significantly higher than in the control rats, while the D-cell response was no longer detectable. After pancreatectomy, by contrast, SLI concentrations were 360 ± 75% of the prepancreatectomy values (N = 12; P < 0.001). This reflected an actual increment of SLI release, taking into account the concomitant measurement of portal blood flow. The concentrations of IRG declined by 51 ± 5% (P < 0.001) and IRI was no longer measurable. A- and B-cell responses to arginine also were no longer detectable.

These results suggest that in these experimental conditions (1) the stomach restrained pancreatic A- and B-cell responses to arginine, perhaps through the SLI released from the stomach and (2) the pancreas restrained gastric SLI secretion, perhaps through insulin. DIABETES *32*:768–773, August 1983.

In the rat species, stomach and pancreas are two major sources of somatostatin-like immunoreactivity (SLI).[1-3] The amounts of SLI measured in gastric tissues are higher than those measured in pancreatic tissues.[1-5] In both organs, SLI predominantly consists of a 1.6 kilodalton molecular-weight peptide.[4,5] By contrast, glucagon immunoreactivity is mainly located within the rat pancreatic A-cells,[6,7] while insulin is not detectable in rat gastric extracts.[7] It has been reported that the pancreatic secretions of insulin and glucagon can be modified by anti-somatostatin immune sera using in vitro systems, and this suggested a paracrine inhibitory influence of somatostatin on A- and B-cells.[8,9] The injection of anti-somatostatin antiserum can also enhance insulin concentrations in response to a test meal in dogs,[10] probably by neutralizing the circulating amounts of SLI. Conversely, the extrapancreatic secretion of SLI may be inhibited by circulating insulin, as suggested by in vivo experiments in diabetic rats,[11,12] and in vitro studies using isolated perfused rat stomach.[13]

For these reasons, it was of interest to study whether the gastric and pancreatic releases of SLI, glucagon, and insulin might interact, at least in some experimental conditions. Comparative studies were set up in vivo using the catheterization of portal vein in rats, the stomach and pancreas being maintained, and after gastrectomy or pancreatectomy. An infusion of arginine was used as a pharmacologic stimulator of A-, B-, and D-cells. This experimental preparation permitted hormone measurements in portal blood, which may be more sensitive than in peripheral venous samples.[14,15]

MATERIAL AND METHODS

EXPERIMENTAL PROCEDURES

Male Wistar rats (250–300 g), fasted for 12 h, were anesthetized with thiopental (50 mg/kg i.p.). Subtotal enterectomy and catheterization of portal vein were performed as previously described.[6] The gastropancreatic block and the spleen were left intact in a first group of animals (control rats). In two further groups, total pancreatectomy or gastrectomy were selectively performed. Those animals are fur-

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Received for publication 23 June 1982 and in revised form 28 February 1983.

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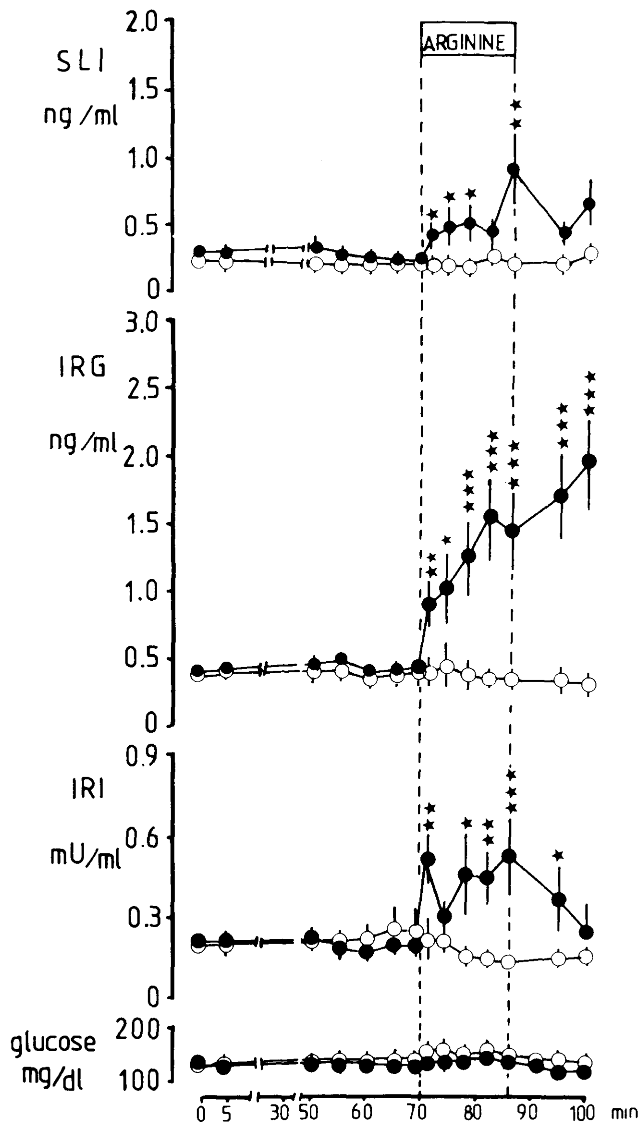

FIGURE 1. Somatostatin-like immunoreactivity (SLI), glucagon (IRG), insulin (IRI), and glucose concentrations in portal plasma from enterectomized rats, with pancreas and stomach present. The open circles (○) symbolize rats not infused with arginine (N = 8); solid circles (●) symbolize the arginine-infused rats (N = 9). Results are presented as mean values ± SEM. Stars denote significant differences between arginine-infused rats and those not infused with arginine: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Time zero is counted 20 min after the end of enterectomy + portal catheterization. The time corresponding to arginine infusion is marked by the dotted lines and the white rectangle at top of figure.

ther denominated pancreatectomized and gastrectomized rats. All rats were kept euthermic and breathed a mixture of O_2 and CO_2 (93%:7%). Careful hemostasis was performed. Blood subtractions were quantitatively replaced with fresh blood drawn from fasted donor rats.

Arginine HCl (Vitrum, Stockholm) was infused into a jugular vein with a priming dose of 25 μmol, then a constant flow rate of 5 μmol/min for 16 min, using a Braun infusion pump (Melsungen, West Germany). The total volume of fluid infused did not exceed 2.0 ml in each animal. Blood samples (1.0 ml each) were collected from the portal catheter at predetermined intervals. Experiments were also performed in rats similarly operated on, but not subjected to arginine i.v.

TABLE 1
Splanchnic regional blood flows

	Splanchnic regional blood flow (ml/min/rat)	
	Microsphere measurements	Direct flow reading
Control (enterectomized) rats	2.02 ± 0.22 (6)	1.76 ± 0.11 (15)
Gastrectomized rats	1.80 ± 0.35 (6)	1.41 ± 0.11 (6)
Pancreatectomized rats	0.72 ± 0.17 (6)	0.78 ± 0.09 (5)

Blood flows were measured by the microsphere technique and by direct volumetric measurement of the flow through the portal catheter in rats maintained normovolemic (see text for details). Numbers of animals appear in parentheses.

infusion. Blood samples were collected in chilled test tubes on aprotinin (Iniprol, Choay, Paris), 20,000 antiprotease U/ml and EDTA 1.2 mg/ml, then centrifuged at +4°C. Plasma samples were frozen at −20°C until the glucagon and insulin assays. Samples intended for SLI determinations were lyophilized for shipment to Cape Town, where they were resuspended in an appropriate amount of water before SLI assay.

DETERMINATIONS

Immunoreactive insulin (IRI) and glucagon (IRG) were measured as previously published.[16,17] SLI was determined by radioimmunoassay on unextracted plasma as previously described.[18] The antiserum used showed no crossreaction with a variety of peptide hormones and neurotransmitters, and its locus of binding was suggested to be related to amino acids 6–8 of the tetradecapeptide.[2] Assay sensitivity was 35 pg/ml and inter- and intra-assay variations were 15% and 13%, respectively. It was verified with plasma processed as described above from Paris to Cape Town that degradation of tracer was no greater than in assay buffer, as assessed by nonabsorption to charcoal after a 20-h incubation. The recovery of synthetic somatostatin added to plasma samples was 87 ± 8% (N = 6). Very similar results were obtained when fresh plasma samples were assayed in Paris, using a similar assay system. Serial dilutions of plasma SLI showed parallelism with decreasing amounts of synthetic somatostatin; 85–90% of SLI measured in rat portal plasma collected during the experiments described thereafter coeluted with the synthetic tetradecapeptide on Sephadex G-25 gel chromatography columns.[18] Plasma glucose was assayed by the glucose-oxidase method[19] using a Beckman analyzer (Beckman Instruments, Fullerton, California).

Regional splanchnic blood flows were measured by the labeled microsphere technique.[20,21] A silastic catheter (Dow-Corning, Midland, Michigan) was introduced in the right carotid artery down to the left ventricular cavity and a polyethylene catheter into the left femoral artery. Calibrated dextran microspheres, ^{113}Sn labeled, diameter 15 μm, were suspended in 10% dextran and 0.1% Tween-80 to prevent aggregation of beads (NEN Chemicals, Deieich, West Germany) and injected intracardially in a volume of 200 μl, containing on average 6 μCi and 5200 beads/rat. Simultaneously, 0.6 ml femoral arterial blood was withdrawn (ref-

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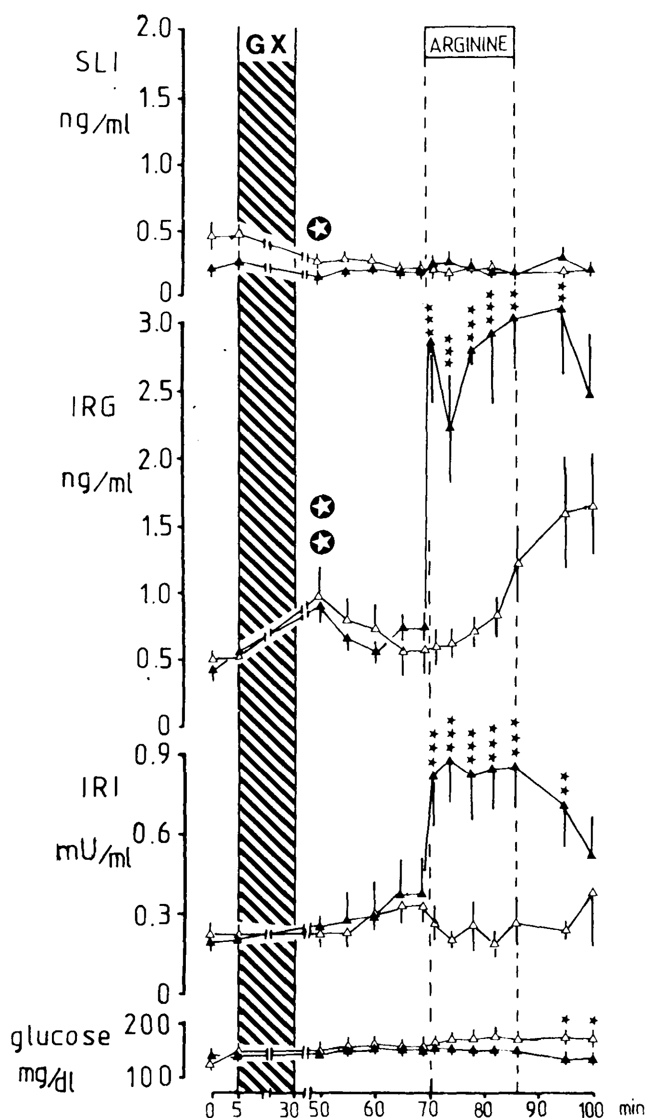

FIGURE 2. Somatostatin-like immunoreactivity (SLI), glucagon (IRG), insulin (IRI), and glucose concentrations in portal plasma from enterectomized rats. The time of gastrectomy (GX) is symbolized by the hatched bars. Open triangles (△) denote the rats not infused with arginine (N = 6) and solid triangles (▲) the arginine-infused animals (N = 9). Time of arginine infusion is represented as in Figure 1. Stars denote a significant variation between pre- and postgastrectomy values (paired *t* test): ○ P < 0.005; ○○ P < 0.001. Stars denote differences between arginine-infused rats and those not infused with arginine at same sampling times: *P < 0.05, **P < 0.01; ***P < 0.001.

erence sample). The rat was killed with ether. Intra-abdominal viscera were dissected and weighed, and radioactivity was measured with a gamma-counter (Kontron MF 252, Roche Bioelectronique, Montigny, France). The arterial flow for each organ was calculated by dividing its radioactivity by that of the reference sample. Experiments were considered valid when left and right kidney flows were different by less than 20%.[22] Portal blood flow was calculated as the sum of the pancreatic, gastroduodenal, and splenic flows. Hepatic blood flow was calculated as the sum of portal plus hepatic arterial flows.

Portal blood flow also was assessed by direct measurement of the blood flow through the portal catheter after occluding the portal vein below the surface of the liver: flow was measured for 1 min, the rats being maintained normovolemic by concomitant compensation of blood subtraction. It was verified that both pressure and resistance through the catheter were similar to those in the portal vein. The direct flow measurements were performed in control, pancreatectomized, and gastrectomized rats, and were compared with the results obtained by the microsphere technique.

PRESENTATION OF RESULTS AND STATISTICAL ANALYSIS

Results are presented as mean values ± SEM for the corresponding sampling times. The variations in hormone releases after gastrectomy or pancreatectomy were estimated by measuring hormone concentrations and blood flows in the same rats before and after corresponding surgery. The magnitude of A-, B-, and D-cell responses to arginine was expressed as the difference between the hormone concentrations measured immediately before and at the end of arginine infusion. Statistical analysis was performed using the Student *t* test for paired and nonpaired values.[23]

RESULTS

Control rats (Figure 1). In basal samples, collected 20 min after portal catheterization (time zero in Figure 1), portal plasma SLI concentration was 0.21 ± 0.02 ng/ml; IRG, 0.35 ± 0.07 ng/ml; IRI, 0.22 ± 0.04 mU/ml; and glucose, 135 ± 10 mg/dl. These concentrations did not vary significantly for the following 100 min of observation in the absence of arginine infusion (N = 8). Portal blood flow was 1.76 ± 0.11 ml/min in rats weighing 300 g (N = 15). This value, obtained by direct flow reading, was similar to that obtained by the microsphere technique (Table 1).

In rats subjected to arginine infusion, portal SLI concentration increased from 0.26 ± 0.04 ng/ml to 0.88 ± 0.25 ng/ml (N = 9; P < 0.05). It returned toward basal levels at the end of arginine infusion. Portal IRG concentration rose from 0.42 ± 0.14 ng/ml to 1.58 ± 0.27 ng/ml (P < 0.001). A biphasic IRI increase was observed from 0.22 ± 0.05 mU/ml up to 0.52 ± 0.08 mU/ml (P < 0.01). Portal plasma glucose rose from 130 ± 9 mg/dl to 150 ± 8 mg/dl during arginine, then declined to 125 ± 9 mg/dl at 100 min. Portal blood flow was not significantly modified during arginine infusion: 2.10 ± 0.24 ml/min, i.e., 121 ± 5% of the preinfusion values (N = 4; NS).

TABLE 2
Variations of hormone outputs induced by gastrectomy or pancreatectomy

	Percent of control values		
	SLI	IRG	IRI
Gastrectomized rats (15)	45 ± 10***	203 ± 9**	99 ± 13
Pancreatectomized rats (12)	184 ± 32*	24 ± 2***	<5***

In each case, output was calculated by multiplying plasma hormone concentrations by the concomitant plasma flow. Results in gastrectomized and pancreatectomized rats are presented as percent of the corresponding values in same rats, before gastrectomy or pancreatectomy (control values).
Numbers of animals appear in parentheses.
Asterisks denote significant differences from control values: *P < 0.05; **P < 0.02; ***P < 0.001.

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TABLE 3
Magnitude of the hormone responses to arginine in the three groups of rats

	Control rats (9)	Gastrectomized rats (9)	Pancreatectomized rats (6)
Increase in SLI concentration (ng/ml)	0.61 ± 0.24	0.02 ± 0.04*	1.05 ± 0.24
Increase in IRG concentration (ng/ml)	0.94 ± 0.25	2.39 ± 0.39**	0.06 ± 0.01**
Increase in IRI concentration (mU/ml)	0.19 ± 0.04	0.60 ± 0.13**	0.01 ± 0.01***

For each hormone, hormone response to arginine is presented as the difference between preinfusion values and the values measured at end of arginine infusion.
Numbers of animals appear in parentheses.
Results are presented as mean values ± SEM.
Asterisks denote a significant difference between control rats and the gastrectomized or pancreatectomized rats: *$P < 0.05$; **$P < 0.01$; ***$P < 0.005$.

Gastrectomized rats (Figure 2). Gastrectomy modified significantly the portal SLI and IRG basal concentrations. The concentration of SLI declined from 0.36 ± 0.03 ng/ml to 0.18 ± 0.02 ng/ml 20 min after gastrectomy, i.e., 52 ± 13% of values measured before gastrectomy in the same rats (N = 15; $P < 0.005$). The concentration of IRG rose from 0.44 ± 0.05 ng/ml up to 0.96 ± 0.10 ng/ml at 50 min, i.e., 234 ± 40% of the pregastrectomy values in the same rats (N = 15; $P < 0.001$). Insulin concentration was not significantly modified: 0.23 ± 0.06 mU/ml versus 0.21 ± 0.08 mU/ml, i.e., 119 ± 15% of the pregastrectomy values (N = 15; NS). Glucose was not significantly altered: 138 ± 10 mg/dl versus 132 ± 5 mg/dl (N = 15; NS).

For the next 50 min, when these gastrectomized rats were not infused with arginine, the SLI concentration remained low and did not vary significantly (0.16 ± 0.01 ng/ml). By contrast, the IRG concentration rose progressively, reaching 1.65 ± 0.41 ng/ml at 100 min (N = 6; $P < 0.05$ versus initial postgastrectomy values). The IRI concentration did not vary: 0.37 ± 0.20 mU/ml at 100 min (N = 6; NS). The glucose level did not change.

After gastrectomy, portal blood flow was 1.41 ± 0.11 ml/min, i.e., 83 ± 5% of the initial values in the same rats (N = 6; NS). An estimation of hormone output variations derived from this data suggested that gastrectomy was followed by a decline in SLI output, an increase in IRG release, without modification of IRI release (Table 2).

When the gastrectomized rats were infused with arginine, the SLI concentration did not change, the maximal value during infusion being 0.25 ± 0.10 ng/ml (N = 9; NS versus initial value in same rats; NS versus noninfused rats). A biphasic rise in IRG concentration occurred, with an early peak at first min of infusion, then a decline and a progressive reascension up to 2.87 ± 0.43 ng/ml (N = 9; $P < 0.001$ versus initial postgastrectomy value and versus noninfused rats at same time). A final trend toward decline of IRG concentrations was detectable after the end of arginine infusion. Insulin concentration was increased during arginine infusion up to 0.87 ± 0.16 mU/ml (N = 9; $P < 0.05$ versus initial value; $P < 0.001$ versus rats not infused with arginine). Glucose level was, at the end, significantly lower than in gastrectomized rats not infused with arginine ($P < 0.05$). The magnitude of A- and B-cell responses to arginine was significantly higher than in controls, while the D-cell response was suppressed (Table 3). As in control rats, arginine induced a slight increase in portal blood flow: 121 ± 8% of preinfusion values (N = 4; NS).

Pancreatectomized rats (Figure 3). Total pancreatectomy was followed by profound changes in portal hormone concentrations. Twenty minutes after pancreatectomy, the SLI concentration rose to 1.17 ± 0.10 ng/ml, versus 0.31 ± 0.04 ng/ml before pancreatectomy, i.e., 360 ± 74% of the initial values (N = 12; $P < 0.001$). The IRG concentration declined by 51 ± 5%, from 0.38 ± 0.04 ng/ml to 0.22 ± 0.02 ng/ml ($P < 0.001$). Insulin was undetectable. Glucose concentration at that time (50 min) was not significantly increased. Later on, SLI concentration went on rising: 1.88 ± 0.60 ng/ml at 100 min. The IRG concentration remained steady: 0.23 ± 0.03 ng/ml at 100 min (N = 6). The insulin remained undetectable and the blood glucose was not different from the control rats at the same sampling time: 156 ± 15 mg/dl.

Portal blood flow was reduced by pancreatectomy: 0.78 ± 0.09 ml/min, i.e., 46 ± 7% of the initial values in the same rats (N = 5; $P < 0.001$). The estimation of hormonal outputs suggested that SLI release was actually increased after pancreatectomy, while IRG output was significantly reduced: 24 ± 2% of initial values (Table 2).

When similar rats were infused with arginine (Figure 3), their SLI concentration rose higher than in their pancreatectomized noninfused counterparts: 1.92 ± 0.19 ng/ml (N = 6; $P < 0.02$ versus initial value and $P < 0.05$ versus noninfused pancreatectomized rats). Portal IRG concentration was not significantly modified by arginine: 0.34 ± 0.02 ng/ml versus a preinfusion value of 0.24 ± 0.09 ng/ml (N = 6; NS). Insulin remained undetectable. Blood glucose was unchanged. The magnitude of SLI response to arginine was not significantly higher than in the control rats, while IRG and IRI responses were unsignificant (Table 3). Portal blood flow was not modified by arginine infusion: 118 ± 15% of the preinfusion values (N = 4; NS).

DISCUSSION

These results emphasize the reciprocal modulations, by stomach and pancreas, of the SLI, IRG, and IRI releases in the rat. Pancreatectomy was not followed by a decline but, surprisingly, a rise in portal SLI concentration. On the other hand, gastrectomy reduced the portal SLI level, while glu-

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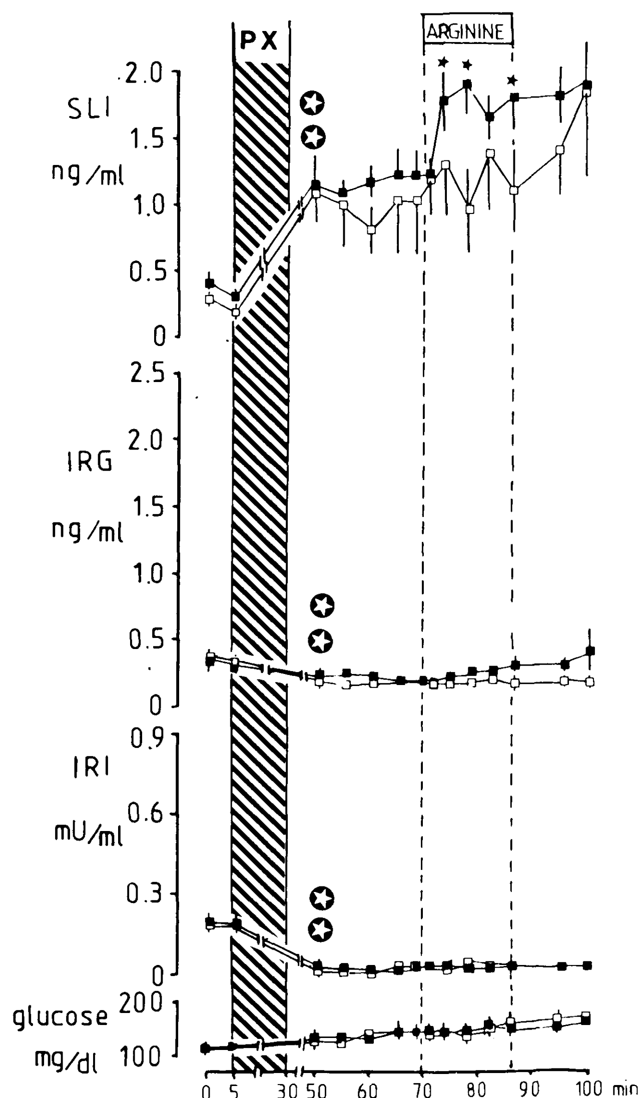

FIGURE 3. Somatostatin-like immunoreactivity (SLI), glucagon (IRG), insulin (IRI), and glucose concentrations in portal plasma from pancreatectomized rats. The time of pancreatectomy (PX) is figured by the hatched bars. Open square (□) symbolizes the rats not infused with arginine (N = 6) and the solid square (■) the arginine-infused rats (N = 6). Same presentation of results as in Figure 2.

cagon level and A-cell response to arginine were increased. The B-cell response to arginine was also increased. These data suggest that the pancreas can influence gastric SLI release, and that some factor of gastric origin can modulate the pancreatic A- and B-cell responses to arginine in the rat.

This preparation was shown to be stable for hemodynamics and for hormone concentrations.[15] Subtotal enterectomy suppressed immunoreactive IRG and SLI materials of enteric origin.[4,5] Vascular and neural connections of stomach and pancreas were maintained,[6,15] and arginine infusion allowed simultaneous pharmacologic testing of A-, B-, and D-cells.[24,25] The influence of intraluminal factors, on the gastric D-cells,[26] was minimized by the 12-h fasting.

One major observation is the surge in SLI concentration and D-cell response to arginine after pancreatectomy. This cannot be explained by hyperglycemia, a D-cell stimulator,[18,25,27] since blood glucose was similar in both pancreatectomized and other rats. If one removes the pancreas, the stomach is the only organ left in the enterectomized rat to contribute to portal SLI. Insulin deficiency was present in the pancreatectomized rats, and this may account for the increase of portal vein SLI in these animals. Insulin deficiency enhances SLI secretion from the stomach in vitro.[27,28] In vivo, elevated concentrations of SLI have been observed in diabetic rats[11,12,29] and dogs.[30] Pancreatic but not gastric SLI venous concentrations have been found elevated in alloxan-diabetic dogs,[31] but the respective contributions of pancreas and stomach to this peripheral hypersomatostatinemia are still unclear, either in dogs[31] or in rats.[11,12] The present data support the concept that, in vivo, the rat gastric D-cells are stimulated by an abrupt decline of circulating insulin concentrations, in spite of a near-normal blood glucose value. It may also be possible that portal SLI increased after pancreatectomy because an organ with a high somatostatin uptake has been removed.[32,33] However, this explanation seems unlikely; in the absence of exogenous somatostatin infusion, the pancreas secretes more somatostatin than it extracts.[32,33]

In the gastrectomized rats, the increase in A- and B-cell functions is another unexpected observation. It cannot be explained by shock or vagotomy, which should have reduced insulin secretion.[15,34] It suggests that gastrectomy suppressed some inhibitory factor of gastric origin, able to restrain A- and B-cell secretions. This may be the gastric SLI. There is some evidence from in vitro studies that endogenous somatostatin may inhibit A- and B-cell functions.[8,9] However, this was related to the somatostatin released from the islets in these preparations. If due to the suppression of gastric SLI, the preferential deinhibition of pancreatic A-cells after gastrectomy might be consistent with previous in vitro studies, which suggested that A-cells are more sensitive than B-cells to exogenous somatostatin.[35]

ACKNOWLEDGMENTS

We wish to express our gratitude to the following persons: J. Boillot for expert technical assistance, and B. Déruti Windsor and B. Treiber for editorial help.

This work was supported by a research grant from UER Xavier Bichat-Paris.

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