Cephalic-Phase Insulin and Glucagon Release in Normal Subjects and in Patients Receiving Pancreas Transplantation

Antonio Secchi, Rossana Caldara, Andrea Caumo, Lucilla D. Monti, Doretta Bonfatti, Valerio Di Carlo, and Guido Pozza

The aim of the study was to evaluate whether the cephalic phase of insulin release is still present in patients submitted to simultaneous kidney and pancreas transplantation. Subjects were five kidney-pancreas–transplanted patients (group P) and five control (group C). The experimental protocol lasted 30 minutes, and blood samples were collected at 1-minute intervals. After a 20-minute period of steady-state fasting (premeal period), subjects received a palatable standard meal (pizza). Samples were collected over the subsequent 10 minutes (meal period). No evidence of an increase in serum free insulin, serum C-peptide, and plasma glucagon during food ingestion was observed in group P whereas the test was effective in eliciting cephalic-phase insulin and glucagon release in group C. Gastric inhibitory polypeptide and somatostatin did not show any variation during the test in both groups. In conclusion, the absence of cephalic-phase insulin and glucagon release in group P could be explained by denervation of the grafted pancreas. This early alteration could contribute to the impairment in glucose tolerance frequently observed in successfully pancreas-transplanted patients.

THE ACTIVITY of β cells is influenced by several factors which can affect insulin release through different pathways: the bloodstream (circulating substrates), central nervous system (brain-islet axis), and gut hormones (enteroinsular axis). Circulating substrates, mainly carbohydrates and amino acids, can influence β-cell activity through a direct action on cell membrane receptors.[1] The brain-islet axis acts through different control mechanisms, as previously described by Helman et al.[2] Three types of nerve fibers innervating the pancreas have been described: parasympathetic fibers originating from the vagus nerves, sympathetic fibers originating from the splanchnic nerves, and afferent fibers arising from the pancreas. Central nervous structures including the ventromedial and lateral areas of the hypothalamus contribute to the regulation of pancreatic hormone secretion in both physiologic and pathological conditions.[2-4] The role of the enteroinsular axis (hormonal factors, produced by gastrointestinal mucosa, acting as a possible transmitter of signals from the gut to pancreatic islets)[5] became evident in recent years. The better-characterized insulinogenic hormone of gastrointestinal mucosa is gastric inhibitory polypeptide, which is responsible for a strictly glucose-dependent effect.[5] In fact, gastric inhibitory polypeptide is released by nutrients, especially carbohydrates, and stimulates insulin secretion only in the presence of elevated blood glucose levels.[5] Finally, paracrine stimuli are also operative within the islets.

These different humoral and nervous factors interact in the determination of insulin release. In particular, the cephalic phase is a nerve-mediated reflex triggered by sensory signals (olfactory, visual, and gustatory stimuli) and takes place in the preabsorptive phase.[6] Cephalic-phase insulin release has been demonstrated in several animal species and in humans.[7-12] In this context, Bellisle et al[13] described a peak of insulin release within a few minutes after a meal. Its amplitude was strictly related to the degree of nutrient palatability and was independent of nutrient absorption.

Pancreas transplantation is performed in insulin-dependent diabetic patients to provide a self-regulated source of insulin.[14,15] Although successful pancreas transplantation leads to insulin independence, some minor metabolic abnormalities such as impaired glucose tolerance and hyperinsulinemia are frequently observed.[16] Several factors explain these abnormalities, such as peripheral insulin secretion, reduced β-cell mass, or denervation.[17,18] Indeed, a grafted pancreas is denervated and therefore is not subjected to the influence of external innervation. This leads to the possibility of studying the mechanisms governing early cephalic-phase insulin secretion during food ingestion.

The aim of this study was to evaluate whether cephalic-phase insulin and glucagon release is still present during food ingestion in patients submitted to simultaneous segmental pancreas and kidney transplantation.

SUBJECTS AND METHODS

Subjects

Two groups of subjects were investigated: kidney-pancreas–transplanted patients (group P) and a control group (group C). Group P consisted of five normal-weight insulin-dependent diabetic uremic patients (aged 33 to 59 years) submitted to simultaneous kidney and segmental, duct-obstructed pancreas transplantation according to the technique reported by Dubernard et al.[19] Durations of diabetes, dialysis, and transplant were 25.8 ± 1.2 years, 16.4 ± 6.6 months, and 30.0 ± 6.0 months, respectively. Immunosuppression was accomplished via steroid (10 mg/d except in patient no. 2), azathioprine (60.0 ± 12.7 mg/d), and cyclosporin A (4.5 ± 0.3 mg/kg/d). All patients showed good pancreas and kidney function at the time of the test (follow-up study, 29.4 ± 5.5 months: hemoglobin A_{1c}, 4.9% ± 0.4%; plasma creatinine, 95.4 ± 5.3 mmol/L). All patients were on a freely selected diet from at least 12 months before the study. Group C consisted of five normal-weight subjects (aged 25 to 35 years). All had normal carbohydrate tolerance and no family history of diabetes or impaired glucose tolerance. The two groups had a comparable diet, with no weight loss in the 15 days before the test.

From the Department of Internal Medicine, San Raffaele Scientific Institute, Milan, Italy.

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Address reprint requests to Antonio Secchi, MD, San Raffaele Scientific Institute, Via Olgettina 60-20132 Milan-Italy.

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Experimental Procedure

Informed consent was provided by both groups before the study. Each subject had a standard breakfast at 7:30 AM. At 11:30 AM, a sampling 20-gauge cannula (Venisistems Abbocath-T; Abbot, Dublin, Ireland) was inserted anterogradely in a vein on the dorsum of the hand and kept patent with 0.9% saline. In group P, an arteriovenous fistula was used, and in group C, the hand was placed in a plexiglas box (Rohm & Haas, Philadelphia, PA) heated to 55°C to arterialize the blood. During the subsequent 75 minutes, the subject was encouraged to rest in a recumbent position in a comfortable room to prevent interference due to external stimuli or stressful conditions.

The test started at 12:45 AM. Blood samples for determination of blood glucose, serum free insulin, serum C-peptide, plasma glucagon, plasma somatostatin, and plasma gastric inhibitory polypeptide (evaluated in only seven of 10 subjects) were collected at 1-minute intervals over 30 minutes. At minute 20, subjects received an unexpected, palatable standard meal (pizza: 210 g, 570 kcal, 12 g protein, 11 g lipid, 111 g carbohydrate). Subjects ate the meal within 5 to 10 minutes. A cephalic phase of 10 minutes was thereafter considered, according to Teff et al[10] and others.[11-13] This short period was defined to avoid the insulin and C-peptide peaks related to food absorption and not to a true cephalic phase.

Assays

Plasma glucose level was measured by the glucose oxidase method (Beckman Glucose Analyzer II; Beckman Instruments, Palo Alto, CA). Serum samples for human insulin measurements were added at bedside to 1 mL polyethylene glycol (PEG). The supernatant was then separated by centrifugation at 4°C and assayed using a commercial radioimmunoassay kit. Serum without PEG precipitation was assayed similarly for comparison. Insulin values in sera processed with PEG demonstrated a recovery of 98.6% ± 1.9% (mean ± SEM). Samples for insulin and C-peptide measurements were assayed using commercial kits; intraassay and interassay coefficients of variation were 3.0% and 5.0% in both cases, respectively. Glucagon samples were collected in aprotinin/EDTA and immediately centrifuged and stored at −20°C until radioimmunoassay. Intraassay and interassay coefficients of variation were 3.0% and 10.0%, respectively. Plasma somatostatin samples were assayed according to the method reported by Arimura et al[20]: Plasma was extracted with cold, analytic-grade acetone. The clarified extract was further purified with ether and dried. The dried extract was reconstituted and assayed by radioimmunoassay. Using this procedure, recovery ranged from 80% to 108%. Plasma samples for determination of gastric inhibitory polypeptide were extracted using a Sep-Pak C18 column. (Amprep octadecyl C^{18}; Amersham International, Buckinghamshire, UK). The eluent was evaporated to dryness, and the residue was subsequently dissolved and assayed by radioimmunoassay. In our laboratory, recovery with this method was 94%.

Data Analysis

Data are expressed as the mean ± SEM. Basal levels of serum free insulin, serum C-peptide, plasma glucagon, and plasma somatostatin were calculated as mean values during the premeal period (0 to 20 minutes) and compared between groups (P *v* C) using a nonpaired, two-tailed Student's *t* test.

To ascertain the presence of cephalic-phase insulin release, the area under the curve (AUC) of serum free-insulin concentrations during the 10 minutes of the meal period (meal-AUC) was compared with the AUC during the last 10 minutes of the premeal period (pre-AUC). The areas were calculated by the trapezoidal rule. Statistical difference between pre-AUC and meal-AUC within each group was tested using a paired, two-tailed Student's *t* test. To rule out the possibility that the increasing portion of a basal cyclic oscillation could be misinterpreted as a cephalic phase, we also compared the sequence of 10 insulin values measured during the meal period (21 to 30 minutes) with two sequences of basal insulin values measured in the premeal period (0 to 10 and 11 to 20 minutes, respectively) using a nonpaired, two-tailed Student's *t* test. When the meal sequence was significantly higher than both basal sequences, the role of a cyclic plasma insulin oscillation was excluded and a cephalic phase of insulin release demonstrated. Since results of this analysis confirmed conclusions of the pre-AUC versus meal-AUC comparison, they were not reported in the results.

The above-described procedures were also used to evaluate cephalic-phase C-peptide and glucagon release.

RESULTS

Figure 1 shows the average profiles of blood glucose, serum free insulin, and serum C-peptide in groups P and C. Time courses of plasma glucagon and plasma somatostatin in the two groups are shown in Fig 2.

Premeal Period (0 to 20 minutes)

All subjects were studied in euglycemic conditions. Mean blood glucose levels were 4.6 ± 0.4 and 4.3 ± 0.2 mmol/L in groups P and C, respectively. Serum free-insulin levels were four times higher in group P than in group C (110.9 ± 19.6 *v* 27.6 ± 5.0 pmol/L, $P < .01$). Serum C-peptide levels were 2.5 times higher in group P than in group C (0.79 ± 0.1 *v* 0.30 ± 0.05 nmol/L, $P < .01$). Plasma glucagon levels tended to be higher, although not significantly, in group P than in group C (88.0 ± 8.1 *v* 75.5 ± 2.6 ng/L, P = NS). Similar plasma somatostatin levels were observed in groups P and C (12.1 ± 2.9 *v* 11.0 ± 1.2 pmol/L).

Meal Period (20 to 30 minutes)

Blood glucose remained at basal levels during the meal period in both groups. Pre-AUC and meal-AUC were 46.0 ± 3.9 and 47.2 ± 4.4 mmol/L · min (P = NS) in group P and 43.5 ± 2.2 and 44.2 ± 2.6 (P = NS) in group C.

Table 1 lists individual values of pre- and meal-AUC for serum free insulin, serum C-peptide, and plasma glucagon in each group. The data suggest the presence of a cephalic phase for serum free insulin, serum C-peptide, and plasma glucagon in group C but not in group P.

Plasma somatostatin remained at basal levels during the meal period in both groups. Pre-AUC and meal-AUC were 118.6 ± 25.9 and 126.2 ± 17.3 mmol/L · min (P = NS) in group P and 111.4 ± 12.2 and 110.1 ± 11.3 (P = NS) in group C.

Plasma gastric inhibitory polypeptide levels were monitored at 1-minute intervals in two C subjects only. In these cases, we did not observe any variation during the meal as compared with basal values.

DISCUSSION

Cephalic-phase insulin release plays an important role in the dynamics of insulin release, since hyperglycemia is anticipated by an early insulin secretion.[2] This phenomenon seems to be neuromediated rather than due to

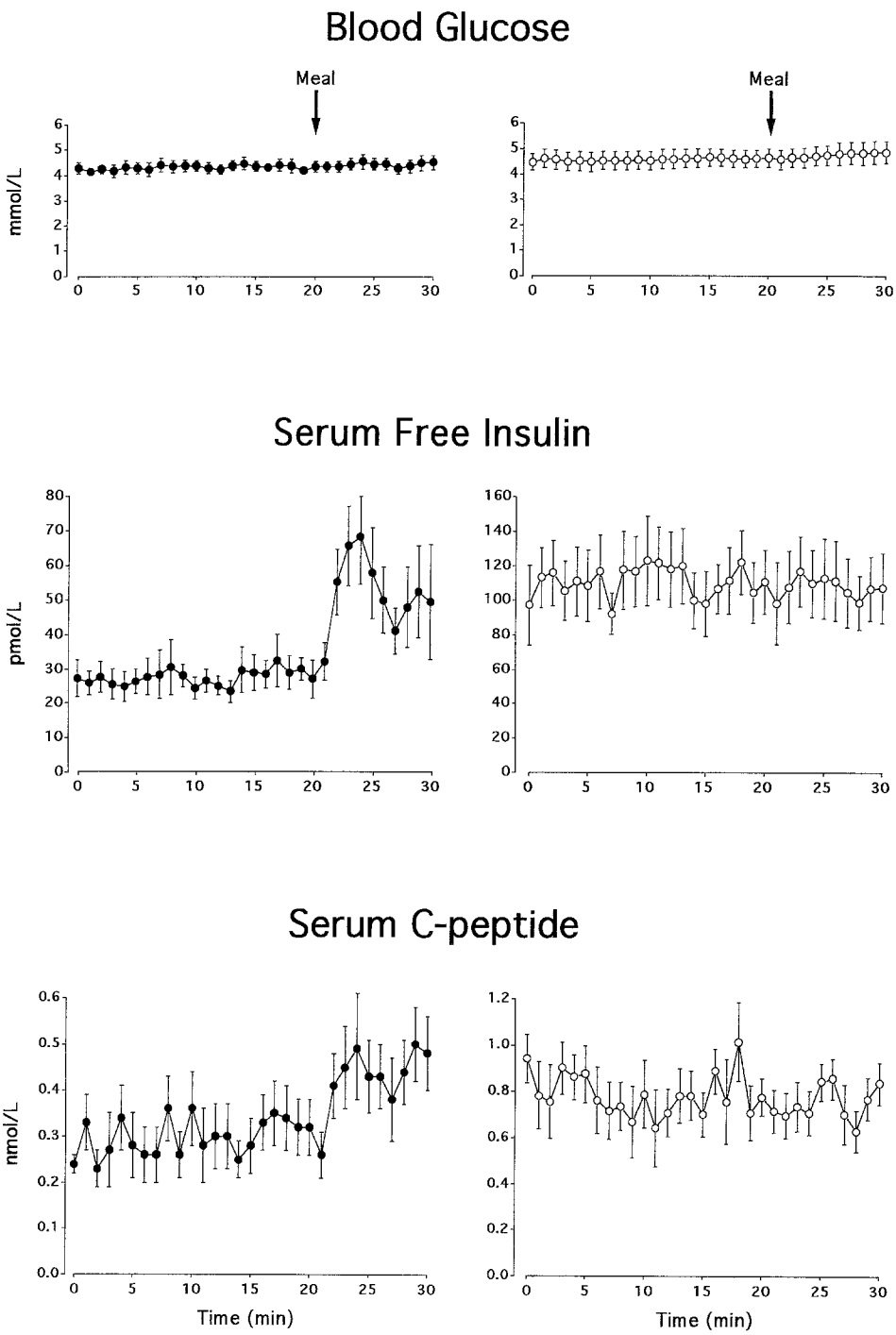

Fig 1. Blood glucose, serum free-insulin, and serum C-peptide levels before (0 to 20 minutes) and during (21 to 30 minutes) the meal in group C (●) and group P (○).

enterohormones, since the only insulinogenic enterohormone, gastric inhibitory polypeptide, requires an increase of blood glucose levels to develop its insulinogenic action.[5]

The presence of cephalic-phase insulin release in humans has been clearly demonstrated by several investigators.[7-12] Among them, Bellisle et al[13] performed an elegant study in which they compared meal-associated insulin responses with premeal spontaneous insulin fluctuations. Furthermore, they showed the important role of meal palatability in conditioning insulin release. An insufficient meal palatability could contribute to explaining why some investigators were unable to elicit cephalic-phase insulin release in normal subjects.[21] To overcome this problem, we selected a particularly palatable meal for our population (pizza).

The experimental approach used in the present study was effective in eliciting a cephalic-phase response of the β cell. In fact, all group C subjects showed a significant increase in both insulin and C-peptide levels during food ingestion in the absence of changes in levels of glucose and gastric

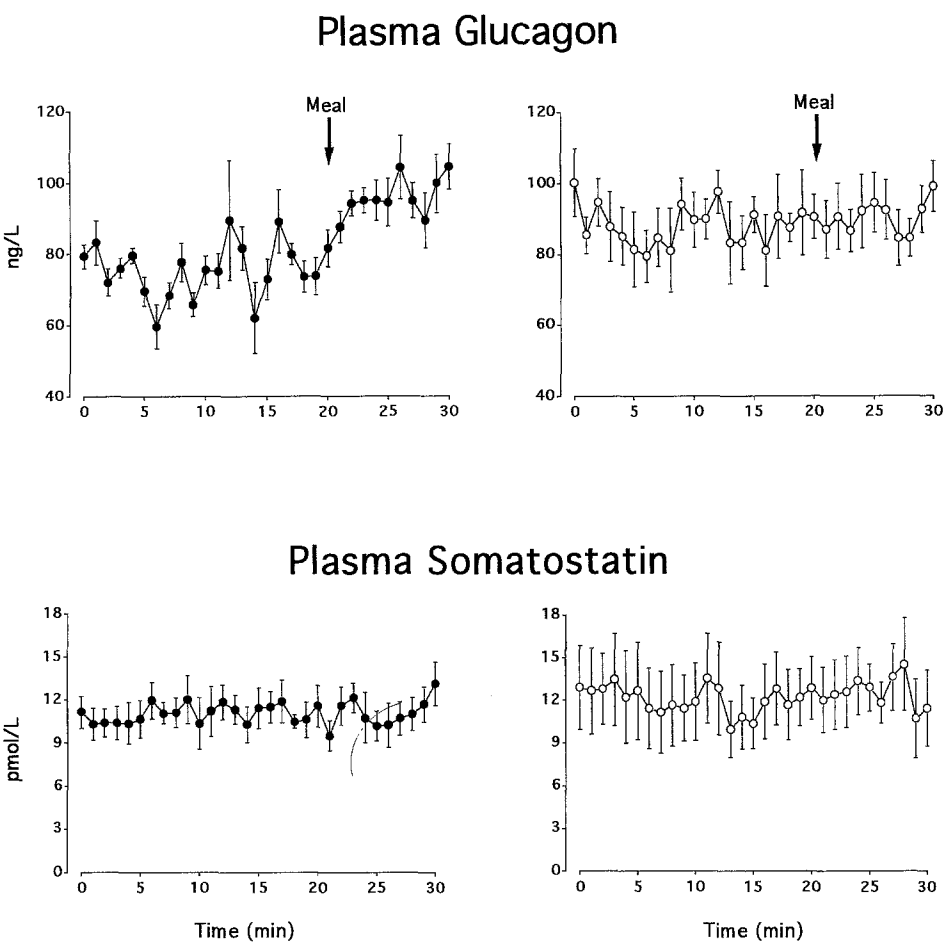

Fig 2. Plasma glucagon and somatostatin levels before (0 to 20 minutes) and during (21 to 30 minutes) the meal in group C (●) and group P (○).

inhibitory polypeptide, with the latter monitoring the influence of enterohormones on pancreatic response. Of note is that the increase in C-peptide levels, although statistically significant, in keeping with the results of the study reported by Teff et al,[22] was less pronounced than the increase in insulin levels, as previously reported by Bruce et al.[7] This is evident from insulin and C-peptide AUC data listed in Table 1 and can be further appreciated by looking at the

Table 1. AUCs for Serum Free Insulin, Serum C-Peptide, and Plasma Glucagon Before (pre-AUC) and During (meal-AUC) the Meal in Group B, C and P

Subject No.	Serum Free Insulin (pmol/L · min)		Serum C-Peptide (nmol/L · min)		Plasma Glucagon (ng/L · min)	
	Pre-AUC	Meal-AUC	Pre-AUC	Meal-AUC	Pre-AUC	Meal-AUC
Group C						
1	233.10	355.50	2.13	2.64	720.63	931.70
2	452.40	904.01	4.82	5.85	863.07	1,026.81
3	187.20	338.10	1.50	2.07	655.30	803.10
4	225.60	337.20	2.79	3.39	828.00	918.45
5	304.80	616.80	2.76	5.03	814.00	1,052.80
Mean ± SEM	280.62 ± 46.96	510.32 ± 111.79	2.80 ± 0.56	3.80 ± 0.71*	776.20 ± 38.32	946.57 ± 44.34†
Group P						
1	1,668.30	1,509.30	8.87	8.64	1,072.55	981.55
2	1,144.20	1,507.50	6.17	5.78	595.30	615.65
3	1,398.30	1,240.80	6.99	7.01	848.70	986.25
4	817.20	641.70	3.72	4.47	967.30	911.95
5	566.10	475.50	9.42	7.88	938.70	990.95
Mean ± SEM	1,118.82 ± 197.12	1,074.96 ± 217.98	7.03 ± 1.02	6.75 ± 0.74	884.51 ± 80.65	897.27 ± 71.88

NOTE. A significant increase of serum free insulin serum C-peptide, and plasma glucagon was observed in group C, but no increase was observed in group P.

*$P < .05$ *v* pre-meal AUC.

†$P < .01$ *v* pre-meal AUC.

dynamics of insulin and C-peptide responses during the meal shown in Fig 1. The most likely explanation for this finding is related to the slower kinetic of C-peptide as compared with insulin.[23] In fact, the relatively long half-life of C-peptide (~30 minutes) produces a dampening effect on the time course of C-peptide concentration during the meal. As a consequence, cephalic-phase C-peptide is less evident than that of insulin.

At variance with normal subjects, group P showed no evidence of insulin and C-peptide increases during the meal, implying that they did not have cephalic-phase insulin release. Inspection of Table 1 shows that in patient no. 2 of group P, meal-AUC was higher than pre-AUC measured during the 10-minute interval of the fasting period immediately before food ingestion (1,507.5 *v* 1,144.2 pmol/L · min). This difference is probably due to spontaneous oscillations of insulin levels rather than to the presence of a true cephalic phase. In fact, if meal-AUC is compared with pre-AUC measured during the first 10 minutes of the fasting state, the difference vanishes (1,507.5 *v* 1,441.5 pmol/L · min). Thus, it is plausible that the increase in AUC observed in this patient simply reflects an increasing segment of the spontaneous basal oscillation of insulin, an occurrence already documented by Bellisle et al.[13] The notion that this patient had no cephalic-phase β-cell release is corroborated by the absence of any increase in C-peptide level after food ingestion (Table 1).

The absence of cephalic-phase insulin release in pancreas-transplanted patients might be the first sign of a disruption of neuromediated secretion of insulin, as previously suggested.[24] This early alteration in insulin release could contribute to the impairment in glucose tolerance frequently observed in successfully pancreas-transplanted patients.[16] Impaired glucose tolerance was hypothesized to be a consequence of the reduced β-cell mass (segmental technique), although it was also observed in patients receiving a whole-pancreas graft.[25] Denervation of the pancreas was stated as a possible cause of impaired insulin release in these patients, but studies reported in the literature were not clear on this point, since the influence of various factors such as reduced β-cell mass, peripheral insulin release, and insulin resistance was not ruled out.[18,26-38]

The hypothesis that this abnormality could be the consequence of the diabetogenic action of cyclosporin or steroid must be considered. Previous observations showed that cyclosporin does not exert a negative influence on intravenous glucose disappearance rates or phasic insulin secretion[39] in nondiabetic patients affected by multiple sclerosis. Moreover, cyclosporine did not change the kinetics of insulin release after oral glucose in nondiabetic kidney-transplant recipients[40] or simultaneous kidney- and pancreas-transplanted patients.[16] Furthermore, metabolic studies have shown that steroids do not influence glucose-induced insulin secretion but do exert effects on insulin-mediated glucose metabolism, specifically nonoxidative glucose disposal.[41] So far, the abnormalities shown in our study in group P do not seem to be due to immunosuppressants.

Cephalic-phase glucagon release was demonstrated in group C but not in group P. The absence of cephalic-phase glucagon release in group P is somewhat surprising. Since group P subjects have their own native pancreas releasing glucagon, one would expect to find cephalic-phase glucagon release in this group similar to that observed in group C. In contrast, in group P the mean AUC of plasma glucagon during the meal was virtually identical to that of the premeal period (897.3 ± 71.9 *v* 884.5 ± 80.6 ng/L · min). When AUC data are examined on an individual basis, one can see that only patient no. 3 showed a nonnegligible increase in glucagon AUC during the meal with respect to both AUCs measured in the minute 0 to 10 and 11 to 20 intervals of the fasting period. The difficulty in distinguishing cephalic-phase glucagon release in transplanted patients may be related to alterations of the native pancreas. Defects of α-cell release in diabetic patients have been previously described,[42] which may be correlated with deterioration of the parasympathetic system.[43] Indeed, some impairment in the α-cell release of the native pancreas of group P is suggested by the fact that despite the double α-cell mass, fasting glucagon levels did not reach the high values observed in a previous study in the early posttransplant period[24] and were only slightly higher than those measured in normal subjects.

Results obtained during the basal fasting state (0 to 20 minutes) confirm that group P subjects have higher serum insulin and C-peptide levels than normal subjects, in keeping with previous reports.[28-30] One possible explanation is that basal β-cell release is increased in group P because of insulin resistance.[17,18] Another factor contributing to higher insulin levels is the abnormal anatomic site of the pancreas. Since the vessels of the pancreas are anastomosed to the iliac vessels (general circulation) and not to the portal vein, secreted insulin reaches the systemic circulation by escaping first-pass hepatic extraction.[31]

In conclusion, no evidence of cephalic-phase insulin and glucagon release during food ingestion was observed in group P, whereas the test was effective in eliciting cephalic-phase insulin and glucagon release in group C. The absence of cephalic-phase insulin and glucagon release could be due to denervation of the grafted pancreas and to deterioration of the parasympathetic system of the native pancreas, respectively. Our findings may have clinical implications, since these early alterations in insulin and glucagon release could contribute to the impairment in glucose tolerance frequently observed in successfully pancreas-transplanted patients.

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