Low Plasma Levels of Pancreatic Polypeptide in Obesity

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SUMMARY

Plasma levels of pancreatic polypeptide (PP) were studied in a group of 22 normal and 22 obese subjects after an overnight fast. In a second group of 10 normal and 13 obese adults, PP secretion was stimulated by a protein-rich meal. The results indicate lower fasting PP values in the obese subjects and a decreased response during the second phase of the meal-induced secretion. This could suggest a possible role of PP in obesity. DIABETES 29:428–430, June 1980.

Pancreatic polypeptide (PP) was identified during purification of insulin in the chicken[1] and in mammalians.[2] Although the structure of PP and the factors leading to its secretion are fairly well known at present, its role in physiologic and pathologic conditions is still unclear. PP may contribute to the regulation of satiety: in ob-ob mice it has been shown that injection of bovine PP results in reduction of both food intake and weight gain.[3] Similarly, complete regression of the obesity-hyperglycemia-hyperinsulinism syndrome has been observed in NZO mice after intraperitoneal injection of PP.[4]

Based on these experimental data in animals, the aim of this study was to see whether plasma levels of PP are modified in human obesity. For this purpose, plasma levels of PP in the fasting state and after stimulation by a protein-rich meal were compared in obese and normal adults.

METHODS

Subjects and test procedures. After an overnight fast, plasma PP levels were measured at 0800 h in 22 normal volunteers (6 males and 16 females) and in 22 obese adults (5 men and 17 women) (mean weight excess, 65%), with normal glucose tolerance, aged 20 to 40 yr.

In another series of 10 normal healthy (five men and five women) and 13 obese adults (2 men and 11 women), (mean weight excess, 73%) with normal glucose tolerance, of mean age 30.1 and 28.8 yr, respectively (no significant age difference), provocative testing was performed.

In the two series, all subjects were on the same standard hospital diet (9.2 kJ, 300 g carbohydrate) before testing. A protein-rich breakfast (2.5 kJ, 80 g protein) consisting of cheese (100 g), ham (50 g), powdered milk (40 g), bread (30 g), tea, and sugar (10 g) was rapidly ingested. Plasma PP, insulin, glucagon, glucose, and free fatty acid (FFA) levels were determined 15 min before, at the onset, and 5, 10, 20, 30, 60, 120, 180, and 240 min after ingestion.

Assays. Plasma PP was determined by radioimmunoassay using human PP as a standard and bovine PP as a tracer after labeling by I^{125} with chloramine-T followed by purification on Biogel P2 and P10 columns. Binding was achieved using rabbit anti-hPP serum (lot 615-1054 B-248-19). These products were the generous gift of Dr. R. Chance. Bound and free fractions were separated by precipitation with anti-rabbit serum.

Plasma glucose was determined using an AutoAnalyzer, FFA according to Dole's method, and plasma insulin and glucagon were measured with commercial radioimmunoassay kits (kits from Sorin and Hypolab).

Statistical analysis. Differences in plasma values between obese and control subjects were analyzed using the Student's *t* test.

RESULTS

Fasting plasma PP levels were significantly lower ($P < 0.001$) in the obese subjects (14.49 ± 2.75 pmol/L) compared with controls (27.1 ± 2.6 pmol/L).

Figure 1 shows the results obtained after ingestion of the protein-rich breakfast:

–Control subjects displayed a biphasic response with an initial rise in plasma PP reaching 118.5 ± 16.1 pmol/L after 5 min, followed by a decrease to 88.5 ± 19.0 pmol/L at 30 min. A second prolonged rise in plasma PP was then observed, extending to 240 min, with a maximum of 144.7 ± 17.3 pmol/L at 180 min.

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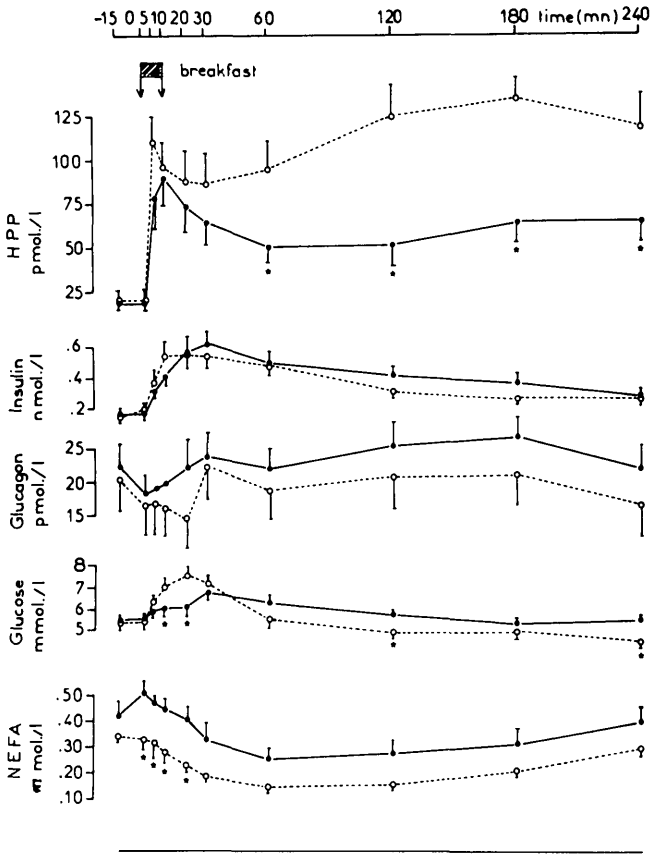

FIGURE 1. Hormonal and metabolic responses to protein-rich meal in 10 normal weight (○---○) and 13 obese (●—●) subjects; asterisks denote statistically significant differences ($P < 0.05$).

Males had slightly higher basal PP levels than females, but over the entire test, they displayed a lower rise in plasma PP levels. So, we considered males and females as a whole for the control group.

–A similar PP secretion pattern was found in the obese group. Nevertheless, although the first plasma peak was not significantly different from that in the controls (spike at 10 min; mean value, 96.6 ± 16.6 pmol/L), plasma PP values throughout the second rise were significantly lower (P between 0.02 and 0.002) in the obese subjects.

–Regarding the other measured plasma components, insulin and glucagon levels were not significantly different between obese and control subjects, whereas glucose levels in the obese group were slightly lower ($P < 0.05$ at 10 and $P < 0.01$ at 20 min) during the first 60 min after ingestion and slightly higher ($P < 0.01$ at 120 and 240 min) thereafter.

Plasma FFA levels were higher in the obese subjects than in the controls [significant difference ($P < 0.02$) at 0, 5, 10, and 20 min after ingestion], but both groups displayed parallel patterns during the test.

DISCUSSION

Results of this study show that plasma PP levels in obese individuals after an overnight fast and during the second phase of secretory response to a protein-rich meal are lower than in nonobese healthy adults.

Plasma PP levels increase with age,[5] but in our series obese and normal weight subjects had the same age range and mean. Lower PP levels in females than in males have been reported.[6] An excess of female representation in the obese group cannot explain the results observed in our study. Indeed, the sex ratio was the same among the control (6 M, 16 F) and obese subjects (5 M, 17 F) in whom basal PP levels were compared.

In the provocative test study, the control group comprised a lower proportion of females (5/10) than did the obese group (11/13). Normal females had, in fact, slightly lower basal PP levels than did normal males. But these levels increased more than those of males after stimulation at all times of sampling (statistical analysis was not performed because of the small number of subjects of the two sexes). Therefore, the larger number of females in the obese group cannot be responsible for the decreased poststimulative PP levels observed.

Decreased PP levels found in the obese could be the result of increased metabolic clearance. However, PP is not metabolized but is eliminated in its active form by the kidney.[7] Even though glomerular flow is slightly increased in the obese, this phenomenon does not suffice to account for these lower PP levels.

Accordingly, we are led to suggest the presence of decreased secretion of PP in the obese. As previously described by Fajans,[8] Adrian,[9] and Schwarz,[10] a biphasic PP secretory response is observed. The first phase seems to be mainly under vagal control.[11] Conversely, the second secretory phase would depend not only on vagal control but also on poorly recognized metabolic or hormonal factors.[9,11] It is interesting to note that the difference we observed between control and obese subjects was found during this second secretory phase.

This difference in plasma PP levels does not seem to be related to any of the other hormonal parameters studied, since the latter did not differ between the two groups.

Hypoglycemia stimulates and hyperglycemia suppresses PP secretion.[12] The slightly higher plasma glucose levels in the obese group during the second secretory phase might account for suppressed PP secretion in these cases. However, the slight difference in plasma glucose levels between obese and control subjects (5.78 ± 0.16 versus 4.99 ± 0.28 mmol/L at 120 min and 5.56 ± 0.11 versus 4.64 ± 0.23 mmol/L at 240 min) is not sufficient to explain the significant differences found in PP levels. Accordingly, the decreased PP response in the obese does not seem to be secondary to hyperglycemia.

Conversely, a possible influence of FFA levels cannot be excluded.

In obese animals, it is difficult to confirm the presence of an increased or decreased number of PP-secreting cells. A decreased number of pancreatic PP cells has been reported in the Zucker rat, which is genetically obese.[13] Malaisse-Lagae reported[3] a relatively decreased number of PP cells among the increased total cell population of the islets of the ob-ob mice. However, Gingerich[14] found that the PP content of the pancreas in ob-ob mice was greater than that in control mice. Likewise, the number of PP cells per islet was increased in the ob-ob mice. Nevertheless, it should be noted that these mice present islet hyperplasia and that the relative volume of the PP cells within the islets is less than normal.

Studies of plasma PP levels have been rarely reported in animal experiments, undoubtedly because of the difficulties

in measuring plasma PP values in rodents. Nevertheless, Gates[4] reported that plasma PP is decreased in the NZO mouse.

The hypothesis, suggesting the existence of a circulating satiety factor, was advanced after the parabiosis experiments of Coleman in ob-ob mice.[15,16] These animals seem to possess a functioning satiety center, which remains sensitive to the satiety factor produced by lean mice.

Finally studies, showing that injections of PP induce weight reduction and decrease appetite in the ob-ob mouse[3] and reduce hyperglycemia, hyperinsulinism, and weight gain in the NZO mouse,[4] seem to indicate that PP may be needed in the regulation of food intake in certain types of genetic obesity in animals.

Our results, showing decreased PP levels after fasting and during the late postprandial phase in obese adults, are compatible with the suggestion that PP may somehow be active in satiety and may be reduced to a variable degree in certain types of human obesity. However, it should be kept in mind that factors other than PP may be different in obese subjects and the differences observed in normal and obese individuals may not necessarily play a causative role in the pathogenesis of the obesity.

REFERENCES

[1] Kimmel, J. R., Pollock, H. J., and Hazelwood, R. L.: A new pancreatic polypeptide hormone. Fed. Proc. *30*:1318, 1971. (Abstr.)

[2] Chance, R. E., and Jones, W. E.: Polypeptides from bovine, ovine, human and porcine pancreas. US Patent Office Pat. 3,842,063, 1974.

[3] Malaisse-Lagae, F., Carpentier, J. L., Patel, Y. C., Malaisse, W. J., and Orci, L.: Pancreatic polypeptide: a possible role in the regulation of food intake in the mouse. Hypothesis. Experientia *33*:915–16, 1977.

[4] Gates, R. J., and Lazarus, N. R.: The ability of pancreatic polypeptide (APP and BPP) to return to normal the hyperglycemia, hyperinsulinemia and weight gain of New Zealand obese mice. Horm. Res. *8*:189–202, 1977.

[5] Floyd, J. C., Jr., Fajans, S. S., Pek, S., and Chance, R. E.: A newly recognized pancreatic polypeptide: plasma levels in health and disease. Recent Prog. Horm. Res. *33*:519–70, 1977.

[6] Bakir, S. M., Gates, R. J., and Lazarus, N. R.: Low levels of pancreatic polypeptide in non-diabetic obese women. 10th IDF Congr., Vienna 1979. Amsterdam/New York, Excerpta Medica Publ., ICS 481, Abstract 34.

[7] Boden, G., Master, R. W. P., and Owen, O. E.: Hepatic and renal extraction of endogenous human pancreatic polypeptide (HPP). Scand. J. Gastroenterol. *13* (Suppl. 49):28, 1978. (Abstr.)

[8] Floyd, J. C., Jr., and Fajans, S. S.: A newly recognized human pancreatic islet polypeptide: concentrations in healthy subjects and in patients with diabetes mellitus. Diabetes *25* (Suppl. 1):330, 1976. (Abstr.)

[9] Adrian, T. E., Bloom, S. R., Besterman, H. S., Barnes, A. J., Cooke, T. J., Russel, R. C., and Faber, R. G.: Mechanism of pancreatic polypeptide release in man. Lancet *1*:161–63, 1977.

[10] Schwartz, T. W., and Rehfeld, J. J.: Mechanism of pancreatic polypeptide release. Lancet *1*:697–98, 1977.

[11] Schwartz, T. W., Stadil, F., Chance, R. E., Rehfeld, J. E., Larson, L. I., and Moon, N.: Pancreatic polypeptide response to food in duodenal ulcer patients before and after vagotomy. Lancet *1*:1102–05, 1976.

[12] Marco, J., Hedo, J. A., and Villanueva, M. L.: Relationship between plasma glucose and human pancreatic polypeptide (HPP) concentrations in normal subjects. Diabetologia *13*:216, 1977. (Abstr.)

[13] Larsson, L. I., Boder, G. B., and Shaw, W. N.: Changes in the islets of Langerhans in the obese Zucker rat. Lab. Invest. *36*:593–98, 1977.

[14] Gingerich, R. L., Gersell, D. J., Greider, M. H., Finke, E. H., and Lacy, P. E.: Elevated levels of pancreatic polypeptide in obese-hyperglycemic mice. Metabolism *27*:1526–31, 1978.

[15] Coleman, D. L.: Effects of parabiosis of obese with diabetes and normal mice. Diabetologia *9*:294–98, 1973.

[16] Coleman, D. L.: Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. Diabetologia *14*:141–48, 1978.