PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 159, 245–248 (1978)

Fluctuations of Human Pancreatic Polypeptide in Plasma: Effect of Normal Food Ingestion and Fasting[1] (40324)

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The secretion of human pancreatic polypeptide (hPP) is stimulated by food ingestion (1, 2). Since this response persists for several hours (1), it could be predicted that under the common dietary habit of three meals a day plasma hPP would be elevated above fasting levels during most of the daytime. Thus, we have examined the daily fluctuations of circulating hPP in normal individuals subjected to such a meal schedule and in an inverse situation, i.e., during prolonged fasting. In addition, the effect of the ingestion of a low-calorie, bulky meal as well as tap water on hPP secretion was examined.

Materials and methods. Healthy, nonobese subjects participated in this study. Their ages ranged from 20 to 24 years. Informed consent was obtained. In a group of seven male volunteers hPP plasma levels were measured at 30-min intervals from 8:30 to 24:00 hr while on the following meal schedule: breakfast at 9:00 hr (a cup of coffee with milk and two croissants); lunch at 13:00 hr (300 g of boiled spaghetti, 200 g of grilled beef, and one pear); dinner at 20:00 hr (vegetable salad, 200 g of boiled hake, 50 g of white bread, and one pear). In a second group of 12 volunteers (eight males and four females) fasting was maintained for 84 hr. They received water *ad libitum* and 40 mEq of K^+ daily. Upon termination of the experiments, a body weight loss of 3.5±0.2 kg was recorded. Blood samples were obtained 12, 18, 24, 36, 42, 48, 60, 66, 72, and 84 hr after the last meal, which was taken in the evening (21:00 hr) prior to the observation period. Volunteers were admitted to our clinical research center on the afternoon preceding the experiments. In further experiments, six volunteers (three males and three females) were given either 400 g of vegetable salad (250 g of asparagus and 150 g of lettuce) or 500 ml of tap water on two different days. These tests were performed after an overnight fast.

The collection and processing of blood samples has been previously described (3). Plasma glucose was determined by means of a commercial glucose-oxidase preparation (Biochemica Test Combination, Boehringer Mannheim GmbH). Radioimmunoassay was used to estimate insulin (4), glucagon (5), and hPP (6). Results are expressed as means±SEM. Differences between values were calculated for significance by paired *t* test analysis.

Results. Figure 1 shows the daily fluctuations of plasma hPP levels in a group of seven subjects kept on a conventional meal schedule. Mean fasting hPP concentration was 61 ± 15 pg/ml. Ingestion of each meal was followed by a sustained hPP elevation. After breakfast plasma hPP rose to 158±35 pg/ml at 11:30 hr ($p < 0.01$) while lunch and dinner elicited more marked increases (551±131 pg/ml at 15:00 hr, $p < 0.01$; 640±153 pg/ml at 20:30 hr, $p < 0.01$, respectively). It is noteworthy that between meals circulating hPP did not return to basal values. As expected, following each meal the concentrations of glucose and insulin in plasma increased in a parallel fashion.

In view of the apparent association of hPP secretion with the consumption of food, we tested the effect of a low-calorie, bulky meal on plasma hPP (Fig. 2). This meal elicited a sixfold increase of hPP concentration with only a small rise of plasma insulin and glucose. The ingestion of even 500 ml of tap water (Fig. 3) more than doubled the levels of circulating hPP.

In Fig. 4 are depicted the mean hPP, glucagon, insulin, and glucose plasma levels for a group of 12 volunteers subjected to 84 hr of fasting. Basal (after a 12-hr overnight fast) hPP concentration was 61 ± 16 pg/ml. Prolonging of fasting resulted in an increase of circulating hPP, which became statistically

[1] Supported in part by a grant (12-130-77) from the Instituto Nacional de Previsión, Spain.

0037-9727/78/1592-0245$01.00/0

significant 24 hr after the last meal (181 ± 53 pg/ml, $p < 0.02$) and persisted elevated during the remainder of the experimental period. It is remarkable that for each day plasma hPP showed a distinct pattern, with a progressive rise from 9:00 to 21:00 hr and a subsequent decline during the night. The overall curve, however, exhibited an ascending trend. Finally, during fasting plasma glucose and insulin declined while glucagonemia rose.

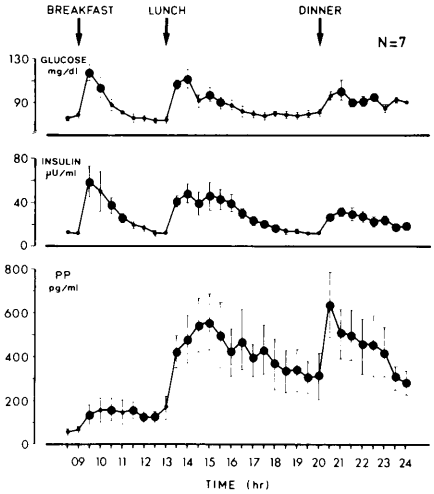

FIG. 1. Daily fluctuations of plasma pancreatic polypeptide in normal subjects under conditions of normal food ingestion (mean±SEM). The large dots represent statistically significant differences from the baseline values.

Discussion. The foregoing data confirm the stimulatory effect of food intake on pancreatic polypeptide secretion in man. The fact that the ingestion of a fiber-rich meal as well as plain water provokes hPP release suggests that the hPP response to food represents in part a nonspecific effect, perhaps the consequence of gastric distention as pointed out by Schwartz *et al.* (7). Furthermore, our results demonstrate that under normal dietary conditions, the successive postprandial rises of circulating hPP maintain its levels above fasting values throughout the daytime. Although the physiological role of pancreatic polypeptide remains enigmatical, it is suspected to have the category of a digestive hormone since the administration of the bovine peptide in dogs modifies gastric and pancreatic secretion as well as gastrointestinal and bile duct motility (8). Contextually, the persistent elevation of plasma hPP may be thought to exert a tonic influence on some of these processes. On this basis, in conditions of food deprivation a decrease of circulating hPP could be

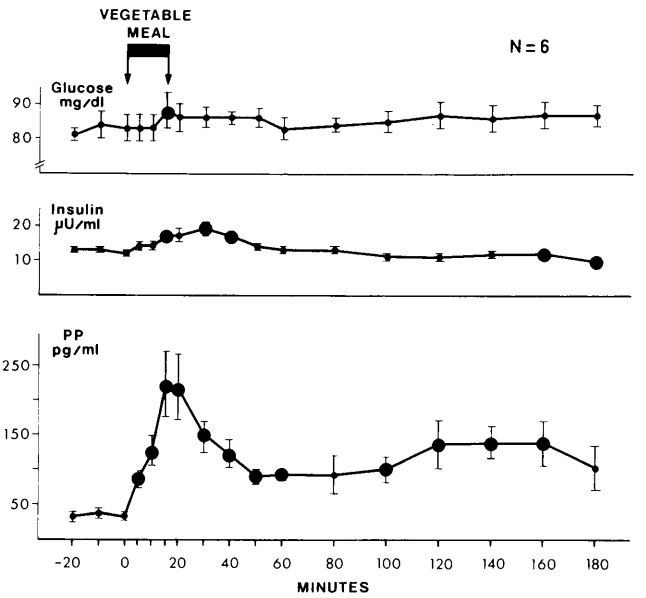

FIG. 2. Effect of ingestion of a vegetable meal on pancreatic polypeptide plasma levels in normal subjects (mean±SEM). The large dots represent statistically significant differences from the baseline values.

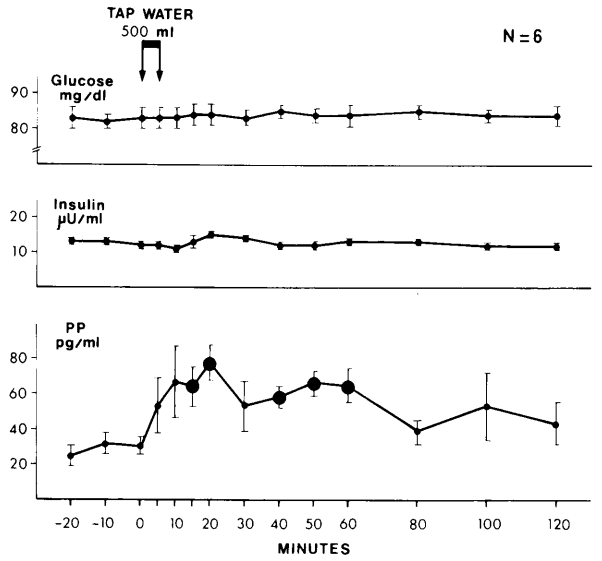

FIG. 3. Effect of tap water ingestion on pancreatic polypeptide plasma levels in normal subjects (mean±SEM). The large dots represent statistically significant differences from the baseline values.

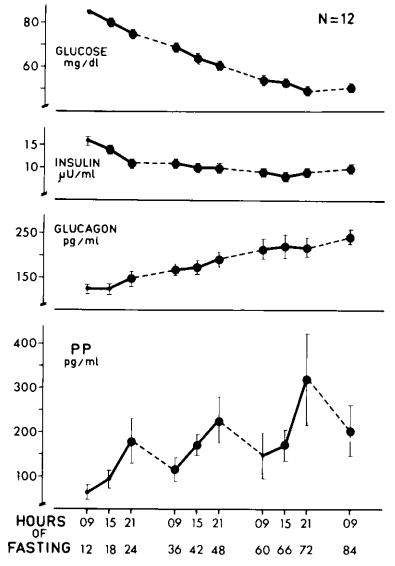

FIG. 4. Pancreatic polypeptide plasma levels during prolonged fasting in normal subjects (mean±SEM). The large dots represent statistically significant differences from the baseline values.

expected, as reported for gastrin (9). However, prolonged fasting resulted in a progressive increase of this factor in blood, an observation in agreement with that of Floyd and associates (1). Moreover, in the absence of food intake plasma hPP showed circadian variations, with higher concentrations in the late evening than in the preceding and subsequent morning. A similar pattern was observed by the above-mentioned authors with determinations at 8:00 AM and 4:00 PM. In interpreting the rise of plasma hPP during fasting, the concomitant decline of glycemia should be considered, since even a modest fall of blood sugar provokes hPP secretion (1, 6). Also, as described for glucagon (10), the possibility of diminished metabolic clearance of hPP should be contemplated. However, either of these alternatives fails to explain the circadian oscillations of hPP. Current evidence indicates that parasympathetic stimulation induces hPP secretion (11, 12) and, thus, changes in vagal tonus may affect circulating hPP. Accordingly, the reduction of vagal tonic activity associated with sleep (13) could be responsible for the low hPP plasma levels found in the morning. In man, during a 24-hr fast a circadian rhythm of gastric acid secretion, with greater output in the evening than in the morning has been documented (14). The relationship between this phenomenon and the parallel changes of hPP remains speculative.

In any case, the understanding of the paradoxical rise of plasma hPP in both anabolic (feeding) and catabolic (fasting) situations awaits a better knowledge of the biological activity of this putative hormone.

Summary. In this work we have examined the daily fluctuations of circulating hPP in normal individuals subjected to a conventional meal schedule (breakfast, lunch, and dinner) as well as during food deprivation for 84 hr. In addition, we have tested the effect of ingestion of a low-calorie, fiber-rich salad as well as 500 ml of tap water on hPP secretion.

Ingestion of each meal was followed by a sustained hPP elevation. Between meals, circulating hPP did not return to basal values. Both the vegetable meal and the water load evoked hPP release, suggesting that the hPP response to food intake is partially a nonspecific effect. In the fasted group, plasma hPP rose significantly 24 hr after the last meal and persisted elevated for the remainder of the experimental period. Moreover, in this condition hPP showed circadian variations, with higher values in the late evening than in the preceding and subsequent morning.

Since pancreatic polypeptide is suspected to possess gastrointestinal functions, its elevation in plasma throughout the daytime in conditions of normal feeding may be thought to exert a tonic influence on some digestive process. On this basis, the increase of hPP during prolonged fasting appears paradoxical and, indeed, the explanation of this phenomenon awaits a better knowledge of the biological activity of this peptide.

The expert technical assistance of Ms. Ana Ramírez, Ms. Pilar García, and Ms. Begoña Samper is gratefully acknowledged.

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Received May 16, 1978. P.S.E.B.M. 1978, Vol. 159.