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## Papel de la calidad de la grasa de la dieta sobre los niveles postprandiales de secretina, colecistoquinina y polipéptido pancreático en humanos

*Role of the quality of dietary fat on the postprandial levels of secretin, cholecystokinin, and pancreatic polypeptide in humans*

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Running head: Dietary fat and gastrointestinal peptides.

### RESUMEN

Los efectos de la adaptación a dos dietas que diferían en el tipo de grasa, sobre los niveles circulantes de secretina, colecistoquinina y polipéptido pancreático fueron investigados en humanos. También fue examinada la relación, previamente descrita por nosotros, con los resultados que concernían a la secreción de ácido gástrico y la liberación de gastrina,

El estudio incluyó a 18 sujetos colecistectomizados previamente sometidos a un período de adaptación de 30 días a dietas que contenían aceite de oliva (grupo 0) o de girasol (grupo G) como fuente de grasa principal.

Durante el periodo experimental, la estimulación fisiológica se consiguió mediante la ingestión de 200 ml de ácido oleico (grupo 0) o aceite de girasol (grupo S) mezclados con la comida. La ingestión de la dieta no indujo cambios significativos sobre la concentración en plasma de secretina en ninguno de los dos grupos, tampoco fueron observadas diferencias significativas entre dicha concentración plasmática en situaciones basal y postprandial.

Los niveles plasmáticos de colecistoquinina fueron significativamente mayores en el grupo 0 durante un periodo postprandial de 30-120 minutos. El tipo de grasa de la dieta afectó a la respuesta del polipéptido pancreático a la comida, los valores en el grupo 0 fueron significativamente mayores a los del grupo S en cualquier punto durante el período postprandial, a pesar de la significativa liberación en ambos grupos tras la comida.

Se sugirió que la colecistoquinina endógena podría ser responsable de la atenuación de la repuesta secretora de ácido gástrico y de la supresión de la serina sérica previamente observada en los sujetos del grupo 0, a través de un mecanismo mediado por somatostatina (paracrino) o por péptido YY (endocrino). La secretina no parece estar implicada en la inhibición inducida por la grasa de la secreción gástrica en humanos, y es dudoso el papel atribuido al polipéptido pancreático.

PALABRAS CLAVES: Grasa de la dicta; secretina; colecistoquinina; polipéptido pancreático; humano

### ABSTRACT

*The effects of adaptation to two diets differing in the type of dietary fat on the circulating levels of secretin, cholecystokinin, and pancreatic polypeptide, were investigated in humans. A relationship with the results concerning gastric acid secretion and gastrin release previously described by us, was also examined. The study involved 18 cholecystectomized subjects previously submitted to a 30-day adaptation period to diets*

*containing olive (group O) or sunflower oil (group S) as the main fat source. During the experimental period, physiological stimulation was achieved by ingestion of 200 mL oleic acid- (group O) or linoleic acid-enriched (group S) liquid mixed meals. Food ingestion did not induce no significant changes in plasma secretin concentration in any of the groups, and no significant differences were observed between them for basal and postprandial situations. Plasma cholecystokinin levels were significantly higher in group O throughout the 30-120 min postprandial period. The type of dietary fat affected the pancreatic polypeptide response to food, since values in group O were significantly higher than in group S at any point during the postprandial period, thus, despite of significant release in both groups after the meal. It is suggested that endogenous cholecystokinin may be responsible for the attenuated gastric acid secretory response and the suppression of serum gastrin previously observed in the subjects of group O, through a somatostatin-mediated (paracrine) or peptide YY-mediated (endocrine) mechanism. Secretin does not seem to be involved in the fat-induced inhibition of human gastric acid secretion, and a role for pancreatic polypeptide is doubtful.*

**KEY WORDS:** Dietary fat; secretin; cholecystokinin; pancreatic polypeptide; human.

## INTRODUCTION

It is well known that intraduodenal administration of fat inhibits gastric acid secretion and stimulates the release of several gut peptides including secretin and cholecystokinin (CCK) in the rat (1), the dog (2,3), and the human (4,5). These two hormones have been involved in the control of gastric acid secretion. Thus, according to Lloyd et al (6), in dogs CCK plays an important role as enterogastrone in fat-induced inhibition of peptone-stimulated gastric acid secretion by a gastrin-independent mechanism. Investigations carried out in the same species by Konturek et al (7) confirmed a similar effect, but gastric inhibition by fat was accompanied by a decrease in plasma gastrin levels, and these authors proposed that the major mechanism of gastric acid inhibition by CCK was probably the release of somatostatin as a local inhibitor of parietal and G cells. Recent studies (8) show that in humans endogenous CCK exerts a similar inhibitory influence on gastric acid secretion and gastrin release. In contrast, the results of Shiratori et al (9) indicate that

endogenous secretin, rather than CCK, is involved in the hormonal mechanism regulating the inhibition of gastric acid secretion by intestinal oleic acid in the rat.

We recently demonstrated (10) that the type of dietary fat affects gastric acid secretion and release of gastrin and peptide YY (PYY) in man. Many other peptides, including secretin, CCK, and pancreatic polypeptide (PP), are reportedly released in response to intraduodenal administration of fat (4,5,11) but no studies to date have dealt with which kind of dietary fat plays the major role in stimulating the secretion of those hormones or in the inhibition of acid secretion. The aim of this study was to investigate the effects of olive oil (the most common source of fat in the Mediterranean diet, rich in monounsaturated fatty acids) and sunflower oil (a dietary fat rich in polyunsaturated fatty acids) on the plasma concentrations of secretin, CCK, and PP and their relationships to gastrin release and gastric acid secretion.

## MATERIALS AND METHODS

### Subjects

Eighteen non-smoking, non-alcoholic patients with gallstones in the gallbladder, showing current clinical signs or symptoms and awaiting surgery (cholecystectomy), were selected within the population served by the Hospital Clínico, University of Alicante. None of them had

undergone previous pancreatic, gastric or biliary tract surgery. Cholelithiasis and asymptomatic cholelithiasis cases were excluded from the study. The subjects had no history of systemic (arterial hypertension, atherosclerosis, diabetes mellitus), gastric (hiatal hernia, gastric or duodenal ulcer), or gastrointestinal disease of any other etiology (acute or chronic pancreatitis). None of them were

receiving medication known to influence gastrointestinal secretions (or motility) or postprandial hormonal responses. These subjects were chosen because of the large number available, the possibility of strictly controlling the participants according to the experimental protocol, and, finally, the applicability of this ailment to our research. The experimental protocol was approved by the Hospital Ethical Committee, and all subjects gave written consent after being fully informed of the nature and procedures of the study. The patients were divided into two experimental groups, the olive oil group (group O) and the sunflower oil group (group S), according to their dietary habits, particularly the type of dietary fat usually consumed before the study (information gained from a dietary history interview at the beginning of the study). Each group had nine patients, with a mean age of 54.4 ( $\pm 4.04$ , SEM) and 41.7 ( $\pm 3.85$ , SEM) years for group O and group S, respectively.

#### *Experimental protocol and diets*

Before surgery, the patients from both groups were submitted to a 30-day adaptation period to diets in which the only source of dietary fat used to prepare their meals was olive oil (group O) or

sunflower oil (group S); their consumption of food items high in saturated fat was also reduced to avoid interference; four seven-day dietary registrations were done to establish energy intake and composition of the diets, the subjects recording all foods and beverages ingested each day. Careful instruction was given not only regarding the methods for recording amounts of food and drink but also regarding the need to record all additions to foods and the cooking methods. These records were collected at every visit to the hospital, the data quantified, and the energy and nutrient intake evaluated by the computer program Nutrition and Health (General Asde, Valencia, Spain), which we developed at the Institute of Nutrition of the University of Granada. The database used was the «Spanish Food Composition Tables», previously published by us (12). As shown in Table 1, the two groups differed primarily in relation to their polyunsaturated and monounsaturated fat intake, whereas the composition of the remaining part of the adaptation diet was similar.

The experimental period began after the subjects had recovered from surgery (cholecystectomy by laparoscopy). The test meal (pH 6.33; 294 mosm/L) contained 4.18 MJ/L, and was composed of 17 % of energy as protein, 30 % as fat, 53 % as carbohydrates, vitamins and minerals. It was

**Table 1.** Calculated daily energy and nutrient intakes during 30-day dietary adaptation period\*

	Group S	Group O
Energy (kJ)	6209.4 $\pm$ 1245.2	6786.2 $\pm$ 640.8
Protein (% of energy)	18.2 $\pm$ 2.1	18.6 $\pm$ 1.7
Carbohydrate (% of energy)	38.8 $\pm$ 3.9	39.4 $\pm$ 2.5
Fat (% of energy)	42.6 $\pm$ 3.3	41.6 $\pm$ 2.5
Monounsaturated fat (g)	26.2 $\pm$ 2.9	40.1 $\pm$ 2.6
Polyunsaturated fat (g)	19.8 $\pm$ 2.5	8.3 $\pm$ 0.8
Saturated fat (g)	18.8 $\pm$ 3.2	20.6 $\pm$ 3.8

\* Group S: sunflower oil group. Group O: olive oil group. Each value represents the mean  $\pm$  SD of four seven-day dietary records per subject (nine subjects per group).

prepared by adequately mixing the separate components according to protein (lactalbumin), carbohydrate (maltodextrins) and vitamin-mineral mixture modules (Edda modular, Ibys Nutrición, Madrid, Spain). Olive oil was added to the meal given to group O and sunflower oil to the meal given to group S. The two liquid meals were isoenergetic and isonitrogenous, thus differing only in their fatty acid composition (Table 2).

Each subject was studied on two successive days and after at least 8 h of fasting. Peripheral vein blood samples were taken before and at 30, 60, 120, and 180 min after beginning the slow ingestion of the correspondent liquid test meal (200 mL ingested over 30 min). The complete feeding and sampling procedures were repeated on the second experimental day.

Blood samples were collected in heparinized tubes containing aprotinin (360 Kallikrein Inactivator Units/mL blood; Sigma Chemicals, St. Louis, Missouri) for measurement of the immunoreactive plasma levels of secretin, CCK, and PP. Tubes were placed immediately on ice and, at the end of each experiment, plasma was separated by centrifugation at 4 °C and stored as aliquots at -80 °C until analysis by specific radioimmunoassays.

### Fatty acids determination in diets

The fatty-acid composition of the liquid meals was determined after direct transesterification according to Lepage and Roy (13). Methylated esters were analyzed by gas-liquid chromatography using a Hewlett Packard chromatograph (model 3396, Hewlett Packard, Palo Alto, California) equipped with an automatic injector (Hewlett Packard, model 7673) and a 60-m silica column (ID: 0.32 mm; particle size: 0.20 mm)(SP - 2330, Supelco, Inc., Bellefonte, Pennsylvania).

### Secretin assay

Plasma levels of secretin were measured by a double-antibody radioimmunoassay, using a Daiichi Secretin Immunoassay Kit (Tokyo, Japan). The secretin antibody had been raised in rabbits against synthetic porcine secretin, and showed a cross-reactivity lower than 0.005 % with vasoactive intestinal peptide (VIP), glucagon, motilin and gastrin. Synthetic porcine secretin was used as standard. The minimal plasma secretin concentration detected by this assay was 10 pmol/L. The intraassay and interassay variations were 2.9 % and 8.1 %, respectively.

**Table 2.** Fatty acid composition of liquid test meals\*

	Group S	Group O
Oleic (C18:1 n-9)	29.03 ± 0.66 <sup>†</sup>	61.89 ± 2.00
Linoleic (C18:2 n-6)	42.16 ± 1.70 <sup>†</sup>	5.06 ± 0.12
Monounsaturated	29.67 ± 0.66 <sup>†</sup>	63.08 ± 1.95
Polyunsaturated	44.62 ± 1.55 <sup>†</sup>	8.19 ± 0.14
Saturated	25.93 ± 1.93	29.03 ± 1.86
U/S <sup>‡</sup>	2.99 ± 0.30	2.51 ± 0.23

\* Expressed as grams per 100 g total fatty acids. Mean ± SEM (n = 6)  
<sup>†</sup> Significant differences ( $P < 0.05$ ) between the two diets.  
<sup>‡</sup> Ratio of unsaturated to saturated fat.

### *Cholecystokinin assay*

A commercially available radioimmunoassay kit (Peninsula Laboratories GMBH, Belmont, California) with 80 % specificity for the sulfated CCK[26-33]octapeptide was employed to determine the plasma concentration of this hormone by a double-antibody procedure. CCK[26-33]octapeptide was used as standard. The sensitivity of the assay was 10 pmol/L, and the coefficients of variation within and between assays were 4.3% and 5.6%, respectively. The antiserum, generated in rabbits against synthetic CCK[26-33]octapeptide showed a cross-reaction equal to 63%, 14% and 100% with CCK[27-33], CCK[30-33] fragments and porcine CCK-33, respectively, and did not cross-react (< 0.1%) with vasoactive intestinal peptide (VIP) nor human PP. The cross-reactivity with gastrin in this assay, assessed by Gomez Cerezo et al (14), was 4.2%.

### *Pancreatic polypeptide assay*

For assay purposes, antiserum against pure bovine PP (Eurodiagnostica, Malmö, Sweden) was used in a final dilution of 1:20,000. The labelled peptide [synthetic human PP, iodinated by the chloramine-T method, and purified by high-performance liquid chromatography (HPLC)], was also purchased from Eurodiagnostica. Highly purified (99 % HPLC purity) synthetic human PP (Sigma Chemicals) was used as standard after serial dilution (from 480 to 0 pmol/L) in assay buffer. This was a sodium barbital buffer, 0.02 mol/L, pH 8.60, containing bovine serum albumin (2 g/L), and sodium azide (0.0077 mol/L). Plasma specimens and standards were tested as 100 ml aliquots in duplicate, adding 500 ml of diluted PP antiserum and either 100 ml of assay buffer (unknown) or 100 ml of PP-free plasma (standard), the latter obtained by processing fresh plasma through a

Sep-Pak C18 cartridge (Millipore Corporation, Milford, Massachusetts). After incubation for 72 h at 4 °C, one-hundred microliters of labelled PP were added and the tubes incubated for an additional 24 h. Free and bound peptides were separated by the addition of 50 ml diluted normal rabbit serum (Eurodiagnostica) and 500 ml goat antirabbit-IgG antiserum (Eurodiagnostica), previously diluted with assay buffer containing polyethyleneglycol 6000 (75 g/L). The mixture was incubated at 20-25 °C for 45 min and then centrifuged at 1700 g for 15 min at 4 °C. Finally, the pellet radioactivity was counted. The assay had a detection limit of 3 pmol/L. The antiserum chosen was free (0.03 %) of cross-reactivity with tetragastrin, human gastrin-17 and -34, porcine gastric inhibitory peptide, CCK-39, secretin, pancreatic glucagon, insulin and adrenocorticotrophic hormone 1-39, showing a cross reaction equal to 120 % with bovine PP. The intraassay and interassay coefficients of variation were 5.6 % and 5.7 %, respectively.

### *Statistical evaluation*

Two studies were carried out on each of two consecutive days for each patient, and the overall mean of the studies was used to calculate the group mean (nine subjects per group) and the standard error of the mean. For statistical comparisons within the groups (above resting values), a one-way analysis of variance was made (Oneway Procedure, SPSS/PC v. 6.1, Chicago, Illinois), and *a posteriori* mean comparisons were done using the Duncan's multiple-comparison test. Differences in hormone measurements between the two dietary groups at the same time points, as well as between the two liquid meals (fatty acid composition) were tested for significance by Student's *t* test (T-Test Groups Procedure, SPSS/PC v. 6.1).  $P < 0.05$  was considered statistically significant.

## RESULTS

Fasting concentrations of plasma secretin ( $17.72 \pm 1.19$  pmol/L in group O vs  $16.52 \pm 3.09$  pmol/L in group S), CCK ( $28.25 \pm 5.33$  pmol/L in group O vs  $20.65 \pm 2.22$  pmol/L in group S), and PP ( $141.9 \pm 18.1$  pmol/L in group O vs  $97.9 \pm 13.7$  pmol/L in group S) were similar in both experimental groups (Fig. 1, 2, and 3).

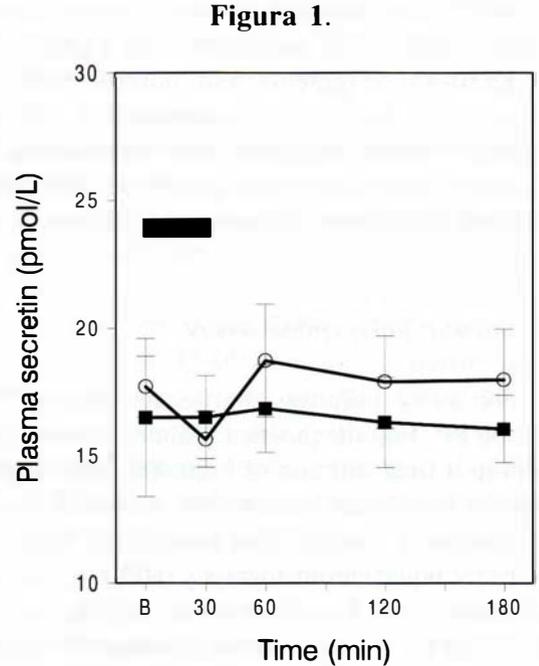
No marked changes in secretin levels were found in group O nor in group S after food ingestion (Fig. 1). The presence of food in the digestive tract did not result into significant changes for plasma CCK concentration in either group, although a trend to increase was observed in group O 30 min after the beginning of the meal. As a consequence, plas-

ma CCK levels in group O were significantly higher ( $P<0.05$ ) than in group S throughout the 30-120 min postprandial period (Fig. 2).

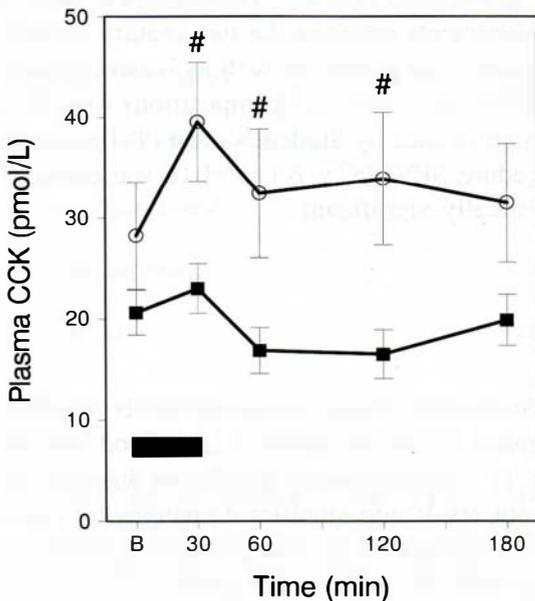
Liquid food ingestion induced significant increases ( $P<0.05$ ) in plasma PP concentration for both groups. The peak occurred in the first 30 min after the meal started. In group O, plasma PP remained significantly higher

( $P<0.05$ ), as compared to the fasting values, until the end of the experimental period, while a decrease was observed in group S from the second postprandial hour onwards. At any point during the postprandial period, plasma PP concentration was significantly higher ( $P<0.05$ ) in group O than in Group S (Fig. 3).

**Fig 1.** Time-course evolution of plasma secretin concentration after the administration of a liquid meal containing olive (○) or sunflower oil (■) as the fat source to two separate groups of cholecystectomized subjects previously adapted for 30 days to oleic acid- and linoleic acid-enriched diets, respectively. B denotes the fasting values. The meal was ingested within 30 min (dark bar). Values represent the mean  $\pm$  SEM of two experiments on each subject (nine per group).

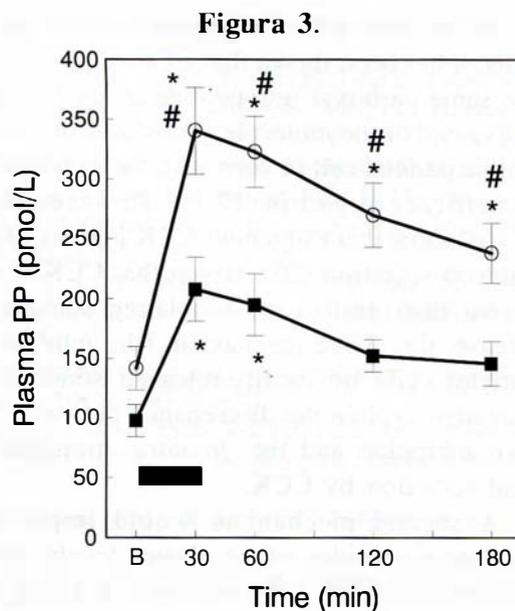


**Figura 2.**



**Fig 2.** Time-course evolution of plasma cholecystokinin concentration after the administration of a liquid meal containing olive (○) or sunflower oil (■) as the fat source to two separate groups of cholecystectomized subjects previously adapted for 30 days to oleic acid- and linoleic acid-enriched diets, respectively. B denotes the fasting values. The meal was ingested within 30 min (dark bar). Values represent the mean  $\pm$  SEM of two experiments on each subject (nine per group). # Mean values for the two dietary groups were significantly ( $P<0.05$ ) different at paired time points.

**Fig 3.** Time-course evolution of plasma pancreatic polypeptide concentration after the administration of a liquid meal containing olive (○) or sunflower oil (■) as the fat source to two separate groups of cholecystectomized subjects previously adapted for 30 days to oleic acid- and linoleic acid-enriched diets, respectively. B denotes the fasting values. The meal was ingested within 30 min (dark bar). Values represent the mean  $\pm$  SEM of two experiments on each subject (nine per group). \* Mean values for each group were significantly ( $P < 0.05$ ) different from the fasting ones. # Mean values for the two dietary groups were significantly ( $P < 0.05$ ) different at paired time points.



## DISCUSSION

The control of secretin and CCK release by dietary fat is a current area of interest in clinical nutrition. Whereas secretin, rather than CCK, is involved in the hormonal mechanism regulating the inhibition of gastric acid secretion in the rat (9), CCK seems to be the most important factor both in dogs (6,7) and humans (8). In a previous work (10), we found that fat-induced inhibition of human gastric acid secretion depended on the type of dietary fat. Thus, the adaptation to a diet containing olive oil as the main source of dietary fat results in an attenuated gastric secretory function in response to a liquid meal, compared with a diet containing sunflower oil. Moreover, the effects of olive oil are associated with a suppression of serum gastrin. In the present study, we investigated the influence of these two dietary fats upon the release of secretin, CCK, and PP, to know whether or not a relationship can be established with the results concerning gastric acid secretion and gastrin release previously described by us.

In the light of our data, it appears that the type of dietary fat does not affect the plasma secretin response to food ingestion. The consumption of the liquid meals was followed by a lack of changes in plasma CCK concentrations in group S, and by a slight postprandial rise in group O, such that values significantly higher

were observed in the latter throughout the major part of the postprandial period, a logical finding if we take into account that oleic acid (the major fatty acid in olive oil) is one of the most potent stimulus for CCK release known to date (15). In addition, the subjects of group O evidenced a diminished gastric acid secretory function and gastrin release in relation to those from group S (10). Thus, the overall results concur with the findings of Konturek et al (16), who reported that endogenous CCK released by a fatty meal inhibits gastric acid responses, this action involving a suppression of plasma gastrin.

The exact role of CCK as a mediator of the inhibition of gastric acid secretion and gastrin release remains unclear, although two mechanisms could account for these effects. First, a negative feed-back mechanism controlling gastrin secretion and mediated by CCK could exist. *In vitro* experiments have shown that CCK can potently stimulate somatostatin release from isolated canine fundic mucosal cells (17). It is also well documented that gastrin secretion is under somatostatin control in rats (18). Under our experimental conditions, we were not able to find a postprandial increase in plasma somatostatin levels in either of the experimental groups (10), but CCK might act by enhancing the local paracrine or neurocrine release of somatostatin

in the vicinity of the G cells or even the parietal cells. It has been shown that CCK-8, which shares the same carboxyl tetrapeptide as gastrin at the active end of the molecule, stimulates the isolated canine parietal cell *in vitro* with the same potency and efficacy as gastrin (17,19). However, studies *in vivo* show that exogenous CCK inhibits gastrin-induced secretion (20). Given that CCK is more potent than gastrin in stimulating somatostatin release, the above mechanism (the inhibition of parietal cells by locally-released somatostatin) may also explain the discrepancy between the *in vivo* inhibition and the *in vitro* stimulation of acid secretion by CCK.

A second mechanism would imply other inhibitory peptides which plasma levels increase after intestinal fat or the ingestion of a fatty meal, with their release being mediated, at least in part, by CCK. One possible candidate could be PP. Certainly, oleic acid (the main fatty acid in the diets and experimental meals consumed by the group O subjects, in which we found a reduced gastric response and gastrin release) has demonstrated to be a potent releaser of PP (21). In addition, the intestinal phase of physiologic release of PP is mediated to a large extent by CCK (8,22). In the present study, liquid food ingestion induced significant increases in plasma PP concentration in both experimental groups, but the values achieved in group O were significantly higher than those in group S at any point during the postprandial period, which is consistent with the findings of Fink et al (21) and also with our CCK data. However, PP appears to be a rather weak inhibitor of gastric acid secretion (23), so we should rule it out as the

mediator of the observed inhibitory effect of olive oil. Another candidate could be peptide YY (PYY). Indeed, in our previous report (10), we suggested that PYY, whose plasma concentrations were consistently higher in group O than in group S, may be involved in the diminished acid secretory response observed in the former group, since this peptide had been shown to cause a marked reduction in pentagastrin- (24) and vagally-induced (25) human gastric secretion when administered in physiological doses. Furthermore, although distal perfusion with oleic acid produces PYY release (26), probably through the direct stimulation of the PYY cell in the ileo-colonic mucosa (27), recent evidence also indicates that postprandial release of PYY may be, in part, mediated by CCK (28-30). Thus, the results from our previous (10) and present work support the existence of a role for PYY in CCK-mediated fat-inhibition of gastric acid secretion.

In summary, adaptation for 30 days to two diets that only differ in the type of dietary fat (olive and sunflower oil) leads to different patterns in the CCK response to a liquid mixed meal, the subjects fed the olive oil-enriched diet showing the highest values. It is suggested that endogenous CCK may be responsible for the attenuated gastric acid secretory response and the suppression of serum gastrin observed in the subjects of group O (10), through a somatostatin-mediated (paracrine) or a PYY-mediated (endocrine) mechanism. Endogenous secretin does not seem to be involved in the fat-induced inhibition of human gastric acid secretion. The type of dietary fat affects the postprandial PP response, although an influence upon gastric secretion is unclear.

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