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Original article

Post-prandial lipase, pepsin and acid secretion of a Heidenhain pouch in the rabbit

JP Perret [1], M Daoud-El Baba [1], I Gros [1], M Descroix-Vagne [2]

[1] *Université Claude-Bernard-Lyon I, IUT A, Laboratoire de Physiologie de la Nutrition, 43, bd du 11-Novembre-1918, F 69622 Villeurbanne cedex;*
[2] *INSERM U45, Hôpital E-Herriot, Lyon, France*

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Summary — The kinetics of the gastric secretion of lipase, pepsin and acid were studied after a meal in Heidenhain-pouch rabbits. After a 24-h fast, feeding immediately stimulated (< 15 min) lipase (x 4.1) and later on pepsin (x 1.8) output which reached respectively 16 and 47% of the output observed after pentagastrin stimulation (64 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 1 h), and which were significantly correlated. Lipase concentration was enhanced earlier and to a greater degree (x 7.3) than pepsin concentration (x 2.5). No stimulation of high basal acid secretion occurred. It was concluded that: 1) gastric lipase secretion is stimulated by feeding in the rabbit; 2) pepsin secretion is stimulated by feeding. The modalities of the secretion of lipase and pepsin are compatible with the existence of distinct secretory cells; 3) acid secretion is not stimulated by feeding. The decrease in acid secretion during the post-prandial phase favors a physiological role for lipase which is altered by low pH. The absence of acid stimulation by feeding in the rabbit, in contrast to other species, requires additional studies on the release of gastrointestinal hormones, namely gastrin, cholecystokinin and somatostatin.

gastric lipase secretion / gastric acid secretion / pepsin secretion / feeding / rabbit

Résumé — Sécrétion post-prandiale de lipase, pepsine et acide d'une poche de Heidenhain chez le lapin. *Les cinétiques des sécrétions de lipase, pepsine et acide d'une poche de Heidenhain ont été étudiées lors de la prise de nourriture chez le lapin. Après un jeûne de 24 h, le repas stimule immédiatement (< 15 min) les débits de lipase (x 4,1) et de pepsine (x 1,9) qui atteignent alors respectivement 21 et 52% de celui obtenu lors de la stimulation maximum à la pentagastrine (64 $\mu g \cdot kg^{-1} \cdot h^{-1}$ pendant 1 h) et sont significativement corrélés. La concentration de lipase augmente davantage que celle de pepsine (x 7,2 vs x 2,5). Le repas ne stimule pas la sécrétion acide dont la valeur basale est élevée. Nous concluons que l'estomac du lapin sécrète une lipase, dont l'activité est favorisée par l'absence d'hypersécrétion acide post-prandiale ; les cinétiques des sécrétions de lipase et de pepsine confirment leur origine cellulaire différente ; les caractéristiques de la libération post-prandiale des hormones gastro-intestinales, en particulier gastrine, cholecystokinine et somatostatine, doivent être établies chez le lapin.*

lipase gastrique / sécrétion acide gastrique / pepsine / prise de nourriture / lapin

INTRODUCTION

Although the activity of preduodenal lipases has been well studied *in vitro*, their mechanism of secretion is largely unknown. Studies performed *in vivo* show that the lipolytic activity of gastric contents in adult volunteers is stimulated by central vagal stimulation (Szafran *et al*, 1971) and pentagastrin (Moreau *et al*, 1988b; Moreau *et al*, 1990b; Szafran *et al*, 1978) but that like secretin, cholecystokinin has no effect (Moreau *et al*, 1988b). In the newborn, lipolytic activity is found in the stomach only after a meal (Fredrikzon and Hernell, 1977); or it disappears from the gastric mucosa after suckling (Perret and Bacques, 1983). These *in vivo* results were often obtained without sufficient care in determining the origin and preservation of the lipase (Fredrikzon and Hernell, 1977; Szafran *et al*, 1971, 1978), and do not demonstrate that gastric lipase is effectively secreted or that it plays a significant physiological role in the digestion of triacylglycerols.

Our study reports for the first time the evolution of the secretions of lipase, acid and pepsin of a Heidenhain pouch after a meal in the rabbit, whose stomach is the richest in lipases amongst all species so far studied (Moreau *et al*, 1988a). As the pouch is no longer in contact with food, the unbuffered juice has a very low pH which might alter lipase: pouch perfusion allows the maintenance of a pH that is compatible with lipase and pepsin stability. The effect of perfusion itself was evaluated on acid and pepsin secretion. The responses were compared to those induced by pentagastrin, which has been shown to be the best lipase stimulant in this species (Perret *et al*, 1993). In order to quantify the amount of lipase secretion, the lipase content of the gastric mucosa was also determined.

ANIMALS

French official regulations (decree No 87-849, 19 October 1987) for the care and use of laboratory animals were followed.

Female New Zealand rabbits were obtained from the Élevage Scientifique des Dombes, Chatillon-sur-Chalaronne, France, and maintained *ad libitum* on rabbit chow (UAR) and water. When equipped with the Heidenhain pouch, rabbits received water supplemented with NaCl (0.10%, wt/vol) and KCl (0.02%, wt/vol).

MATERIALS AND METHODS

Bovine serum albumin (BSA; fraction V, essentially fatty-acid free) and taurodeoxycholic acid sodium salt (TDC) were obtained from Sigma Chemicals. Hemoglobin protease substrate and Folin-Cioccalteu's phenol reagent, came from Merck. Tributyrin puriss was from Fluka, pepsin from Worthington Biochem, Corp NJ, pentobarbital from Sanofi, chlorpromazine (Largactil) and extencillin from Specia, ranitidine (Azantac) from Glaxo and pentagastrin (Peptavlon) from ICI Pharma.

Titanium cannulae, described by Gregory (1958), were obtained from Down-Bros and Mayer and Phelps Ltd, Surrey, UK. Sterile linen sutures came from Peters and Robert and Carrière, France.

Surgical procedure

A detailed description of the procedure used in the preparation of the Heidenhain pouch (HP) has been reported by El Baba *et al* (1991). The pouches were isolated from the fundic part of the greater curvature of the stomach. A Gregory's cannula was inserted in the ventral part of the pouch. A recovery period of 1 month was observed.

Experimental procedure

Collection of the gastric secretion

After a 24-h fast with water available *ad libitum* and a collar to prevent coecotrophy, rabbits were placed in a harness. The pouch secretion was collected by 2 procedures, with and without pouch perfusion in each animal in a separate set of experiments.

With the first procedure, the pouch was continuously perfused without inducing any pressure with 2.5 ml recirculating solution of BSA 5% (wt/vol) in NaCl 0.9% (wt/vol) adjusted to pH 5.5 at a rate of 2 $ml \cdot min^{-1}$, with a catheter inserted in the pouch through the cannula (id = 1.9 mm). The perfusate flowed freely from the pouch through the cannula by gravity in a funnel emptying into the vessel where its pH was continuously adjusted to 5.5 with NaOH 0.2 N; the volume of the latter was recorded to provide the acid output per period. The vessel was weighed before and after each 15-min period, the difference giving the amount of gastric juice.

With the second procedure without gastric perfusion, the pouch secretion was directly collected in preweighed tubes.

Three 15-min basal periods were incorporated with 2 preliminary 15-min periods to equilibrate the system in the perfusion protocol.

The rabbits received 6 g of their habitual industrial chow over a 15-min period. The test was continued for 5 to 6 15-min periods (1 to 5 experiments for each of the 6 rabbits in both series).

In separate experiments the rabbits received an intravenous injection of pentagastrin (64 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 1 h).

Analytical procedures

Acid output was directly assessed by the volume of NaOH used to maintain the 5.5 pH during each period in the perfusion experiments. In the non-perfusion experiments, acid concentration was determined in 0.1 ml gastric juice from the pouch with 0.1 N NaOH by pHmeter and an autoburet (Radiometer).

Pepsin and lipase concentrations were determined in duplicate the same day on which the experiment was performed.

The measurement of pepsin as described by Anson (1938) was adapted to low volumes. Incubations were carried out for 10 min at 25°C with 0.2 ml hemoglobin substrate and 50 µl appropriately diluted perfusate. A blank was made for each dosage by adding trichloracetic acid to the substrate before the incubation. Isolation of the soluble products of hemoglobin proteolysis was assured by 3-min centrifugation at 11 000 *g* of the trichloracetic precipitate. Quantification of these products was carried out with Folin–Cioccalteu's phenol reagent. A calibration curve was made with pepsin standards from 12.5 to 150 $\mu g \cdot ml^{-1}$.

The measurement of lipase was adapted from Gargouri (1986a). Emulsification of 0.7 ml tributyrin in 19.3 ml NaCl solution 0.9%, BSA 0.01% and TDC 0.1% (wt/vol) was carried out by sonication for 8 min at 25 W in a 30-ml screw-capped tube dipped in crushed ice. We measured at 37°C with the aid of a pH stat the quantity of butyric acid released at pH 5.5 over a 3-min period after the addition of 0.1 ml perfusate or gastric extract to 1.5 ml emulsion with continuous magnetic stirring and under nitrogen flow. Neutralization was assured with freshly prepared 0.02 N NaOH.

Results are expressed in µEq H^+ or in mg pepsin or in units lipase secreted for 15 min. One unit lipase released 1 µEq butyric acid in 1 min.

Determination of lipase activity in the gastric mucosa

The fresh stomach of 5 non-fasted rabbits was excised at the level of the pericardia, the fundus near the greater curvature, *ie* at the site of the HP, the corpus and the antrum. The mucosa was removed from each sample and weighed, then homogenized in an ice-bath for 20 s with a motor-driven microhomogenizer. Homogenates were centrifuged for 5 min at 10 000 *g* and lipolytic activity measured in the clear supernatant as already described using 0.1 N NaOH. Protein content was determined by the Lowry procedure (1951).

Stastistical analysis

Data obtained for each rabbit were averaged before the group data were pooled. The non-

parametric Wilcoxon test for paired values was used to test the effect of the alimentary stimulus. The non-parametric Mann–Whitney test was chosen to compare the procedure. Correlation coefficients between the acid, pepsin and lipase output were calculated.

RESULTS

Basal secretion

With pouch perfusion, lipase, pepsin and acid output was respectively 4.7 ± 2.1 units, 2.4 ± 1.5 mg and 73 ± 12 μEq over 15 min (fig 1) which represented 4, 26 and 20% of the maximal output obtained with pentagastrin stimulation (respectively 120.0 ± 29.4 units, 9.0 ± 4.3 mg, 364 ± 57 μEq per 15 min). The concentrations of lipase, pepsin and acid are given in table I. No correlation was obtained between the lipase, acid and pepsin output (table II). Lipase and pepsin output was stable throughout the basal periods, while acid declined (40% over 1 h).

Without perfusion, no lipase could be detected. Pepsin output was lower (1.0 ± 0.5 mg per 15 min); the mean acid output was identical (71 ± 7 μEq over 15 min).

Meal stimulated secretion

With pouch perfusion, lipase output rose significantly immediately after the meal and remained high for 75 min (fig 1), while pepsin output rose slowly and was significantly increased after 1 h. The peaks were respectively 4.1- and 1.8-fold the basal level. They reached 16 and 47% of maximal pentagastrin output. Lipase and pepsin concentrations in the gastric secretion were multiplied by 7.3 and 2.5-fold respectively (table I). A positive correlation was observed between the output of lipase and

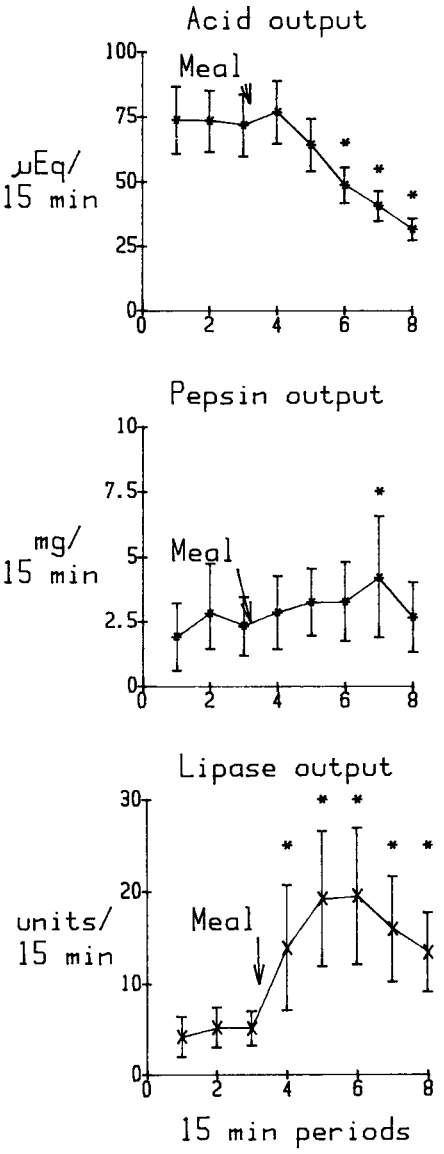

Fig 1. Gastric acid, pepsin and lipase output before and after a meal in rabbits. Gastric secretion was collected by Heidenhain pouch perfusion during basal (period 1 to 3) and after a meal, regular diet (periods 5 to 8). The means and SEM (vertical lines) are the averaged values of 6 rabbits. * Significantly different from basal output (Wilcoxon test), $P < 0.05$.

Table I. Concentrations in HP secretion (mean ± SEM) of lipase, pepsin and acid in basal, after meal and pentagastrin stimulation (the number of rabbits is given in parentheses).

	Lipase ($U \cdot mh^{-1}$)	*Pepsin* ($mg \cdot mh^{-1}$)	*Acid* ($\mu Eq \cdot mh^{-1}$)
Basal	9.2 ± 5.5 (6)	4.6 ± 2.3 (6)	144 ± 8 (6)
Meal	66.8 ± 35.7* (6)	12.3 ± 4.5* (6)	159 ± 8* (6)
Pentagastrin	216 ± 96* (6)	13.9 ± 4.7* (6)	166 ± 6* (6)

* Significantly different from basal (Wilcoxon test, $P < 0.05$).

pepsin after the meal (table II). Acid output was not stimulated by the meal (fig 1). Following a transient non-significant rise, a progressive and significant 47% fall was observed over 1 h following the meal. This decline was not different from the 40% drop observed during basal period. The pouch perfusion with pH 5.5 NaCl alone without BSA as a buffer led to a 10-fold weaker lipase secretion, while pepsin and acid secretion were unchanged.

Without pouch perfusion, no lipase could be found after the meal in the gastric juice, with a pH which always remained at < 1. Feeding induced an increase in pepsin output with a maximum (4.1 ± 2.4 mg per 15 min) which did not differ from that obtained by perfusion (fig 1). Acid output was not increased by feeding and continued to decrease as in the basal condition (45 ± 18%).

Localization of lipase-secreting cells

As indicated in table III, lipase-secreting cells were mainly located in the pericardial and fundic areas. The HP was roughly equal to 20% of the fundic area. The maximal meal-induced lipase output per 15 min was ≈ 10% of the total lipase content. Such a comparison is only indicative, since newly-synthesized lipase was not taken into account.

Table II. Correlation (r) between basal and meal stimulated lipase, acid and pepsin output of rabbit HP secretion.

	Acid/Lipase	*Acid/Pepsin*	*Lipase/Pepsin*
Basal: periods 1–3			
n	24	24	24
r	−0.313	−0.016	0.060
Meal: periods 4-7			
n	24	24	24
r	−0.241	−0.068	0.642*

n: Number of pairs tested; * significant correlation.

Table III. Lipase activity (expressed in units: U) in the gastric mucosa of 5 non-fasted rabbits (mean ± SEM).

Area	*U/g fresh mucosa*	*U/mg protein*	*Total activity (U)*
Pericardial	286 ± 146	5.7 ± 2.9	410 ± 226
Fundus	391 ± 192	9.6 ± 4.8	1 083 ± 497
Corpus	63 ± 28	1.6 ± 0.7	300 ± 192
Antrum	25 ± 16	0.8 ± 0.5	40 ± 20

DISCUSSION

The aim of this study was to determine how gastric lipase is effectively secreted in the rabbit. Our study shows for the first time that feeding stimulates lipase secretion together with pepsin secretion, while acid secretion is not influenced by food intake.

In order to collect gastric juice free of contamination by nutriments, saliva or pancreatic juice, we isolated a gastric pouch at the level of the fundic region of the greater curvature. As rabbit gastric lipase activity is impaired in pure gastric juice with a pH < 1 (Perret, 1982) as in the dog (Carriere *et al*, 1992), the pouch was perfused with an isotonic 5% BSA solution in NaCl 0.9% at pH 5.5. This value was chosen for 3 reasons. First, the pH of gastric contents is > 2 in the rabbit (Marty and Raynaud, 1966) and above the critical pH for irreversible inactivation of lipase. Secondly, the perfusate is used directly to measure the lipase activity which is maximum at pH 5.5. Thirdly, this pH also prevents the inactivation of pepsin, which occurs at pH > 5.5.

The rise in pepsin and lipase output after the meal is positively correlated, but the differences in the secretion kinetics (lipase peak preceding pepsin peak) and the variations in the ratio between the 2 enzymes are in accordance with the existence of distinct lipase- or pepsin-secreting cells (Moreau *et al*, 1990a). The rise in HP lipase output is not a result of the decreased acid output which could protect lipase from inactivation since the acid concentration of the HP secretion increases. Moreover, pentagastrin stimulation simultaneously enhanced acid and lipase output.

We find that lipase activity is as high in the fundic as in the pericardial mucosa, in contrast to the immunocytochemical estimations of Moreau *et al* (1990a). We estimate that 10% fundic lipase content is secreted in 15 min at peak ouptut after feeding. As carbamylcholine is a potent stimulus of HP lipase, pepsin and acid secretions in the rabbit (Perret *et al*, 1993), parasympathetic denervation probably minimizes the secretory response. Comparison of lipase output measured under the same conditions shows a higher postprandial response in the HP rabbit than in the cat. Basal-, cholinergic- and pentagastrin-stimulated secretions are also higher. However, this provides evidence that in the cat the HP mucosa is not as rich in lipase due to the preferential localization of this enzyme near the cardia (Descroix-Vagne *et al*, 1993; Perret *et al*, 1993). Our data support the possibility that a potentialization of pancreatic lipase can in fact occur

in vivo, as has been suggested by *in vitro* studies (Gargouri *et al*, 1986b; Bernbäck *et al*, 1989).

The increase in pepsin output observed during perfusion can arise from a low concentration of topical acid, as has been observed in man (Smith and Torres, 1990) and from osmotic changes, as described in the rat (Puurunen and Westermann, 1978). A reflex arising from the distension of the pouch or the presence of BSA in the perfusate are excluded respectively by the mode of perfusion which avoids such a distension and the similitude of the data obtained with non-protein perfusate. The increase in pepsin induced by feeding was identical with and without pouch perfusion.

We confirm the existence of a high basal acid secretion which is not specific to the rabbit since it has been described in man (Wormsley and Grossman, 1965), the rat (Komarov *et al*, 1944) and the pig (Meritt and Brooks, 1970), whereas it is null in carnivorous animals (Emas and Grossman, 1967). The high basal secretion observed cannot be attribued to the presence of alimentary residues in the stomach, since stomach emptiness was verified after a 24-h fast with a collar to prevent coecotrophy in anesthetized rabbits before HP surgery. This confirms what has been shown, *ie* that several h after emptying, the acid output of a fistulated rabbit stomach reached 50% of the level obtained during pentagastrin stimulation (Redfern *et al*, 1991).

We have shown, for the first time that feeding does not stimulate acid secretion in the rabbit. The absence of acid stimulation is contrary to what has been observed in the dog (Wasunna *et al*, 1971) and the cat (Vagne *et al*, 1982). Several hypotheses might be advanced to explain the lack of acid stimulation by feeding: 1) gastrin is not the major stimulant of acid secretion in the rabbit; 2) gastrin is a major stimulant, but antral acidification does not inhibit gastrin release; 3) the food given to the rabbit does not release enough gastrin; 4) the food also releases acid secretion inhibitors such as somatostatin or cholecystokinin which could be a weak gastrin agonist in the rabbit as in the dog (Johnson and Grossman, 1970) and man (Brooks and Grossman, 1970); 5) cholinergic innervation plays a crucial role in pentagastrin-stimulated acid secretion, as has been described by Mulvihill *et al*, (1989). We previously found (Perret *et al*, 1993) that the maximally effective dose of pentagastrin for HP acid secretion is much higher than that determined by Redfern *et al*, (1991) in the innervated stomach: 64 *vs* 10 $\mu g \cdot kg^{-1}$, but this is the case for many species. Similar to observations on HP, these authors showed that the high basal acid output is observed in the denervated as well as in the innervated stomach of gastric fistulated rabbits. The increase of acid concentration in meal-stimulated HP secretion rules out the possibility of an increased buffering effect which could lead to an underestimation of acid secretion. The gastric perfusion used to prevent lipase inactivation, which could elicit a local sympathetic reflex which inhibits gastric acid and pepsin in dogs (Magee, 1976), is probably not involved in the acid inhibition since a similar response was obtained without perfusion and acid and pepsin responses were opposite.

In conclusion, the secretion of gastric lipase is immediately and strongly stimulated by a meal in the rabbit. This secretion is positively correlated with that of pepsin which arises a little later, but is not accompanied by a rise in acid secretion. This favors the activity of lipase in the gastric lumen and a synergy between gastric and pancreatic lipase suggested by *in vitro* experiments. This conclusion cannot be strictly generalized to other mammals in which gastric acid secretion is stimulated by a meal. Isolated rabbit gastric glands or

cells require a physiological study of the gastric secretion in the isolated pouch to elucidate the mechanism of gastric secretion and the role of gastrointestinal hormones, namely gastrin, somatostatin and cholecystokinin, whose release is not fully understood in the rabbit.

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