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Diet composition and the plasma levels of some peptides regulating pancreatic secretion in the pig

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Summary. The aim of the present work was to study the effect of a modification of diet composition upon the plasma levels of some peptides known to be involved in the hormonal regulation of exocrine pancreas secretion. Six growing Large-White pigs weighing 41 $\pm$ 3.2 kg were fitted with a catheter in a carotid artery ; four ot these pigs were also fitted with permanent fistulae in the pancreatic duct and duodenum. All the pigs were adapted to a control diet (C) during an 8-day period before surgery. In the 8-day post-operative period and a first experimental period of 4 days, they were fed on the same control diet. Three pigs were then fed the experimental diets in the following sequence : fat-rich diet (F) for 7 days, control diet (C) for 7 days, starch-rich diet (S) for 7 days, whereas the other three pigs were fed the same diets over the same time lengths but in inverse sequence : diet S, diet C, diet F. The three diets were isoproteinic (16 % protein) and isocaloric (3 850 cal/kg). The pancreatic secretion and the plasma levels of cholecystokinin (CCK), secretin, pancreatic polypeptide (PP) and somatostatin were analysed during the 4 days of the first experimental period and the last day of each of the other three experimental periods. Total proteins and lipase and amylase activities were determined in pancreatic juice samples collected over the 7 hours following the morning meal. Arterial blood was sampled at 9 h 00 (before meal consumption), 9 h 30, 10 h 00 and every hour until 16 h 00.

The results confirm pancreatic adaptation to the diet, *i.e.* increase of lipase specific activity ($\times$ 1.8) when the pigs ingested 6 times more fat (diet S $\rightarrow$ diet F) per day, and an increase in amylase specific activity ($\times$ 2.3) when they ingested 3 times more starch (diet F $\rightarrow$ diet S) per day. Furthermore, changes in diet composition did not lead to any durable, significant change in plasma peptide levels.

In conclusion, CCK, secretin, PP and somatostatin, known to regulate exocrine pancreas secretion, would not be involved in the mechanisms of pancreatic amylase and lipase adaptation to the amount of carbohydrate and fat ingested by pigs.

Introduction.

It is known in many animals such as rats (Desnuelle, Reboud and Ben Abdeljlil, 1962), dogs (Behrman and Kare, 1969), cattle (Clary *et al.,* 1969), calves (Gorill and Thomas, 1967), chickens (Imondi and Bird, 1967) and pigs (Corring and Saucier, 1972 ; Mourot and Corring, 1979) that pancreatic enzymes adapt to the composition of the diet. The adaptive phenomenon concerns biosynthesis (Wicker, Scheele and Puigserver, 1983 ; Wicker, Puigserver and Scheele, 1984) as well as secretion of pancreatic enzymes (Behrman and Kare, 1969 ; Hulan and Bird, 1972 ; Corring and Saucier, 1972). However, the mechanisms involved in this process are still obscure. According to Wicker, Scheele and Puigserver (1983) and Wicker, Puigserver and Scheele (1984), nutritional regulation of tissue levels of pancreatic enzymes and proenzymes is mediated by changes in the content of active cytoplasmic $mRNA_s$. The factors responsible for this mediation, and likely released by the gastrointestinal tract,are still unknown and one or more hormonal relays have been hypothesized. According to Dick and Felber (1975), Adelson and Rothman (1974) and Simoes Nunes and Corring (1980) an hormonal-type peptide, regulating the biosynthesis of one specific pancreatic enzyme, would be released when there is an increase in the intestinal pool of the hydrolytic products of the substrate degraded by that enzyme (Simoes Nunes, 1982). The peptide regulating biosynthesis of pancreatic amylase would be mainly present in the mucosa of the proximal small intestine (Simoes Nunes, 1982). Other authors (Green *et al.,* 1973 ; Solomon *et al.,* 1978) believe that, if the adaptive mechanisms do include peptides regulating pancreatic secretion, they would be known peptides such as cholecystokinin. Results obtained by Wicker *et al.* (1985) do not support this hypothesis since those authors pointed out that caerulein exerted a predominantly translational control on pancreas enzyme biosynthesis, an effect which differs from the transcriptional control they reported in nutritional regulation (Wicker, Scheele and Puigserver, 1983 ; Wicker, Puigserver and Scheele, 1984).

The aim of the present work was to determine the plasma levels of some peptides regulating exocrine pancreatic secretion in pigs after they had been adapted to diets containing different amounts of carbohydrate and fat.

Material and methods.

Animals and diets. — Six growing pigs of the Large-White breed were fitted with a catheter in a carotid ; four of these animals were fitted with permanent fistulae in the pancreatic duct and duodenum (Corring, Aumaitre and Rérat, 1972) at a mean live weight of 41 ± 3.2 kg. All the pigs were adapted to a control diet (C) for 8 days before surgery. They were given the same diet for 7 days during post-operative recovery and during the first experimental period of 4 days. Three of the pigs were then given experimental diets in the following sequence : high-fat diet (F) for 7 days, control diet (C) for 7 days, high-starch diet (S) for 7 days ; the other three pigs received the same diets for the same lengths of time in inverse sequence : diet S, diet C and diet F. These three diets (see composition in table 1) were isoproteinic (19 % protein) and isocaloric (3 850 cal/kg). They were given in two daily meals at 9 h 00 and at 16 h 00 at the rate of 800 g of meal each, diluted in water (1/1).

Pancreatic juice sampling and analysis. — At the end of surgery, the animals' pancreatic juice was returned by an automatic apparatus which restituted the juice immediately at a rhythm mimicking normal secretion (Juste, Corring and Le Coz, 1983). This apparatus also permitted us to measure the volume drained and to take perfectly representative continuous samples of about 4 % of the juice collected.

TABLE 1

Composition of the experimental diets in percentages.

	Diet C ([1])	Diet F ([1])	Diet S ([1])
Hydrochloric casein	18.6	18.6	18.6
Cornstarch	47.8	21.8	80.8
Peanut oil	12.0	24.0	4.0
Cellulose Colmacel	8.0	14.0	2.0
Vermiculite	10.0	18.0	1.0
Mineral mixture ([2])	2.5	2.5	2.5
Vitamin mixture ([2])	1.0	1.0	1.0
Antioxidant	0.1	0.1	0.1

([1]) Diet S : high-starch ; diet C : control ; diet F : high-fat.
([2]) Corring, Gueugneau and Chayvialle, 1986.

Pancreatic secretion was thus studied for the 4 days of the first experimental period and the 7th day of each of the other three periods when pancreatic adaptation to each diet was stabilized (Ben Abdeljlil and Desnuelle, 1964). Pancreatic juice was sampled every experimental day over a total of 7 h after consumption of the morning meal.

Total proteins (Lowry *et al.*, 1951) and lipase and amylase activities (Corring *et al.*, 1984) were determined in each sample.

Carotid blood samples and analysis. — Blood samples were taken at 9 h 00 (several minutes before the meal was ingested), 9 h 30, 10 h 00 and every hour afterwards until 16 h 00 on each day of the study of pancreatic secretion. The blood was sampled in tubes on ice containing 10 U of heparin and 500 UKI of Trasylol R per ml of blood. The blood was centrifuged immediately after sampling and the plasma stored at − 30 °C until analysis. Secretin, cholecystokinin, pancreatic polypeptide and somatostatin were assayed in each plasma sample by radioimmunological methods already reported (Corring *et al.*, 1985). The plasma cholecystokinin concentration was measured with antiserum 67 H, the characteristics of which have been reported (Miazza *et al.*, 1985). Synthetic CCK 24-33 (gift from Pr Wunsch was labeled with Bolton and Hunter reagent (NEN) according to Fourmy *et al.* (1982). Porcine CCK 33 (Pr V. Mutt) was used as standard, standard inhibition curves being generated in 20 % charcoal-treated plasma from each animal. The sensitivity limit was 1-2 fmoles per tube, with an ID 50 of 5-9 fmoles per tube according to the individual plasma. Serial dilutions of plasma samples with high endogenous plasma CCK concentrations decreased the tracer binding in a way similar to the standard (Fig. 1). In a previous work, the CCK-like components recognized in porcine plasma were characterized by gel permeation on G50 superfine sephadex (1.5 × 100 cm) after concentration on octadecylsilylsilica cartridges (Sep. Pak, Waters). Three components were identified, respectively, in the elution volumes of CCK 33/39 and of CCK 8, and intermediate to these two forms (Cuber *et al.*, unpublished data).

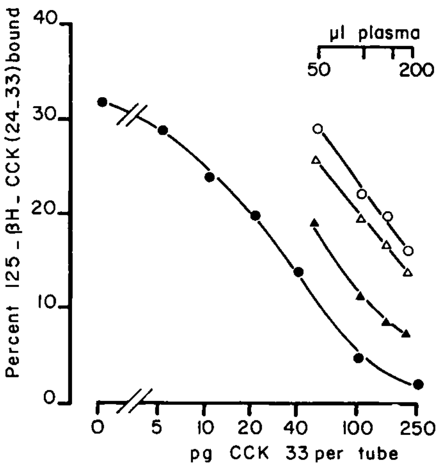

FIG. 1. — *Inhibition curves generated in charcoal-treated porcine plasma,* (final concentration in assay buffer : 20 %) *with serial amounts of* (i) *CCK 33 and* (ii) *three unextracted plasma samples with high endogenous CCK concentrations,* the protein concentration being adjusted with charcoal-treated plasma at all dilution points.

Results.

All the data were processed by the paired Student's t-test. There was no statistical difference between the values found for the two control diet periods, so the means calculated from the whole of the data from these two periods are shown here. Moreover, the order of the dietary sequence did not affect the results and there was no difference in plasma peptide levels between pigs with pancreatic and duodenal fistulae and those with a single carotid catheter.

Pancreatic secretion. — The results given in table 2 show that when the pigs ingested 6-fold more fat per day (transition from diet S to diet F), lipase specific activity increased by 1.8. When 4-fold more starch per day was ingested (transition from diet F to diet S), amylase specific activity increased by 2.3. The mean values during periods when diet C was given were intermediate between the values of diet S and diet F, but only the differences in lipase between diets C and F and in amylase between diets C and S were significant.

The volume of juice drained during the 7 h following meal intake was significantly higher when the pigs had eaten a high-starch diet. This increase was mainly due to the significant increase in the volume secreted during the first postprandial hour (190 ml with diet S *vs* 95 ml with diet C and 112 ml with diet F).

The amount of total proteins secreted over the 7 postprandial hours did not differ significantly from one diet to another.

TABLE 2

Pancreatic secretion in pigs adapted to each of the experimental diets.
Values recorded over the 7 hours following meal intake at 9 h 00.

	Diet C ([3])	Diet F ([4])	Diet S ([4])
Volume (ml)	517 ([5]) ± 33[a]	570 ± 40[a]	815 ± 53[b]
Total proteins (mg)	3 450 ± 275[a]	4 030 ± 486[a]	3 385 ± 310[a]
Lipase ([1])	60.8 ± 9.5[a]	87.4* ± 10.1[b]	48.5 ± 7.3[a]
Amylase ([2])	2 876 ± 453[a]	2 090 ± 386[a]	4 810* ± 517[b]

([1]) Enzyme specific activity : μmoles of fatty acids released minute^{-1}, mg protein^{-1}.
([2]) Enzyme specific activity : units in 1 ml of pancreatic juice after digestion of 1 mg of soluble starch at 37 °C for 30 min, mg protein^{-1}.
([3]) 6 pigs, 30 data.
([4]) 6 pigs, 6 data.
([5]) x ± SEM.
Values on the same line followed by the same superscript are not significantly different ; $P < 0.05$ for a-b.
* $P < 0.05$, difference between diets F and S.

Plasma peptide levels. — An examination of figures 1, 2, 3 and 4 shows two different results. First, there was no overall, permanent effect of diet on the plasma levels of the peptides studied. However, incidental variations, appearing only in some blood samples, were observed for plasma levels of pancreatic polypeptide and somatostatin. Plasma somatostatin was slightly, but significantly, higher with diets F and S at a given level and at the same times as diet C, *i.e.* 3, 4 and 7 hours after meal intake. These variations were greater for pancreatic

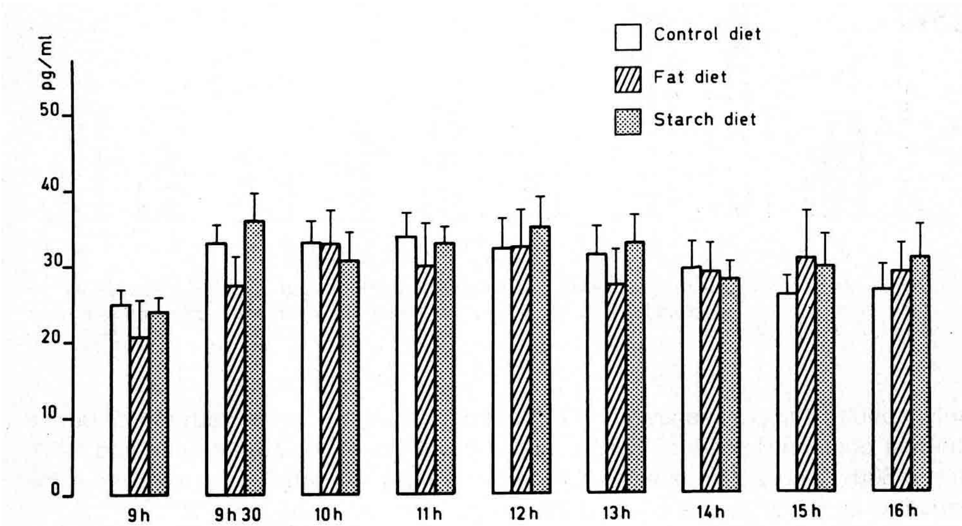

FIG. 2. — *Variations in plasma cholecystokinin levels in relation with the diet ingested.*

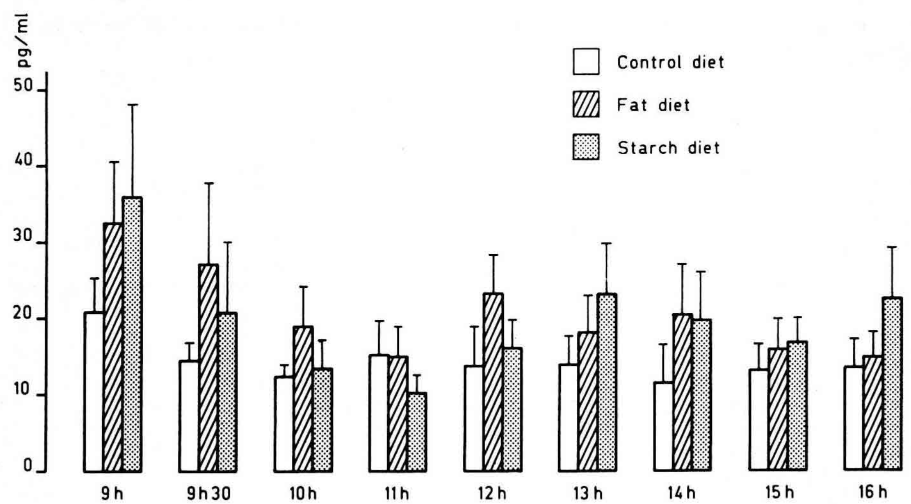

FIG. 3. — *Variations in plasma secretin levels in relation with the diet ingested.*

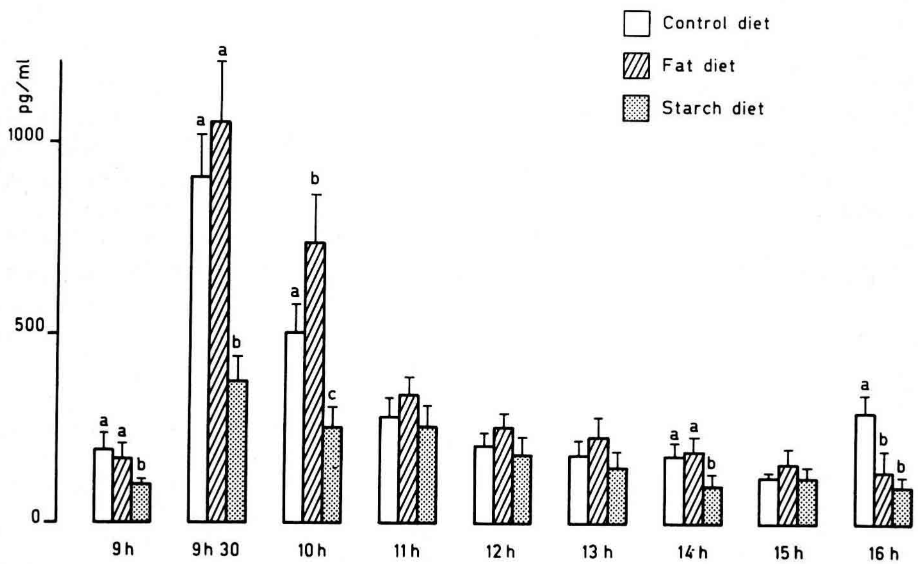

FIG. 4. — *Variations in plasma pancreatic polypeptide in relation with the diet ingested.* At the same sampling time, differences between values are significant when the superscript is not the same. $P < 0.05$ for a, b, c.

polypeptide ; the plasma level of this peptide was clearly lower with diet S during the first postprandial hour. This decrease was 60 % at the 30th minute and 50 % at the 60th minute compared to the control values. Although very low, the same variation occurred at the 5th and 7th hours after the meal.

Secondly, whatever the diet, the plasma levels of somatostatin, pancreatic polypeptide and cholecystokinin increased after meal consumption whereas that of secretin tended to decrease.

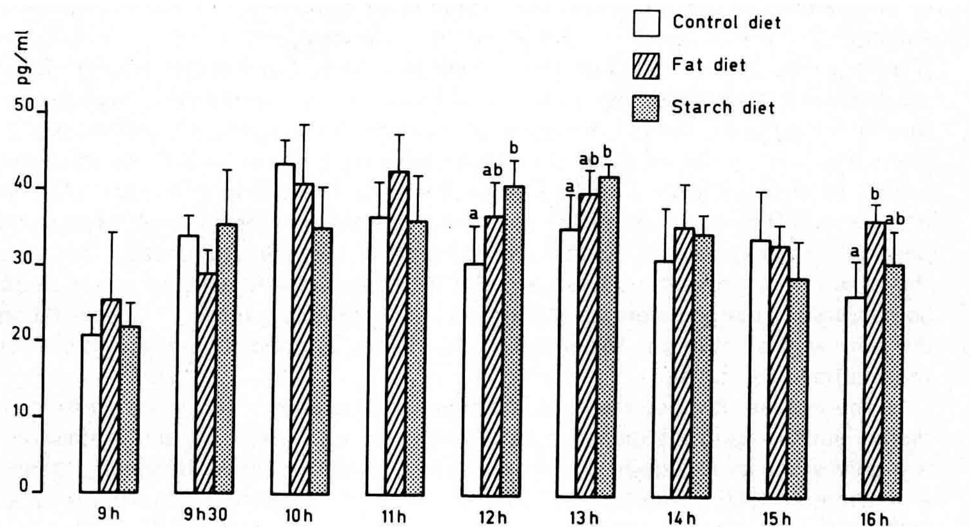

FIG. 5. — *Variations in plasma somatostatin in relation with the diet ingested.* At the same sampling time, differences between values are significant when the superscript is not the same. P < 0.05 for a, b.

Discussion.

The aim of the present work was to study the plasma levels of some peptides regulating pancreatic secretion in pigs when the same animal was adapted to the consumption of various isoproteinic and isocaloric diets but with different levels of fat and carbohydrate. Pancreatic secretion was studied in 4 out of 6 pigs to check whether the pancreatic enzymes could adapt to the amounts of fat and carbohydrate ingested. The results obtained confirm that amylase activity increased when the pigs ingested more starch and that lipase activity also augmented when fat ingestion augmented. This confirms data reported before on pancreatic juice (Corring, 1977) and tissue (Mourot and Corring, 1979) in the same species.

Besides the description of this adaptive process, it is necessary to determine the mechanism(s) involved. According to certain authors (Green *et al.,* 1973 ; Solomon *et al.,* 1978), the peptides regulating pancreatic secretion would play an essential role in determining pancreatic adaptation to the diet. In the present study, the plasma levels of secretin and cholecystokinin, which are known as powerful stimulators of exocrine pancreatic secretion, were not affected by the increase in fat or starch intake. It is suggested that those two hormones would not play a major role in the nutritional regulation of the lipase or amylase secretion ; this agrees with results obtained by Wicker *et al.* (1985).

Despite the rather small number of pigs studied, which could explain the absence of significant differences, some significant variations in the plasma levels of pancreatic polypeptide and somatostatin were observed. It is rather difficult to estimate the part of starch and fat intake in those variations. In two recent studies (Corring, Gueugneau and Chayvialle, 1986 ; Langlois, Corring and Février, 1987), we observed that in pigs eating raw soybean or a diet containing a high percentage of wheat bran, the plasma levels of secretin and vasoactive intestinal peptide were significantly higher at all the same sampling times than the corresponding values determined with a heated soya diet or a low-wheat bran diet. We can assume that if there is any effect of a dietary factor on plasma levels of digestive peptides, it has to be expressed by a lasting change in the latter levels. This is not the case in the present study where plasma levels of pancreatic polypeptide and somatostatin changed significantly at only some sampling times. These variations did not seem to have any relationship to a change in pancreatic enzymes and are thus difficult to explain.

The release of most gastrointestinal peptides is enhanced by the presence of dietary substrates in the digestive tract lumen. Among these, fat and protein have a highly stimulatory effect on the release of cholecystokinin (Hopman, Jansen and Lamers, 1985 ; Stubbs and Stabile, 1985), somatostatin (Chayvialle *et al.*, 1980 ; Penman *et al.*, 1981) and pancreatic polypeptide (Scarpello, Vinik and Owyang, 1982 ; Fink *et al.*, 1983). On the other hand, carbohydrate, and particularly glucose, has very little effect (Chayvialle *et al.*, 1980 ; Owyang, Scarpello and Vinik, 1982 ; Hopman, Jansen and Lamers, 1985). In the present study, the pigs ingested the same amount of protein since the diets were isoproteinic, but they consumed different amounts of fat. Fat would therefore be expected to have an effect on the release of cholecystokinin, somatostatin and pancreatic polypeptide, particularly if a high-fat diet was ingested. The results obtained seem to be contradictory, except for a value of pancreatic polypeptide one hour after diet F was ingested ; however this value is difficult to interpret. We believe that this contradiction stems from the fact that the action of fat on peptide release has only been studied in short-term experiments in humans or non-adapted animals and thus in very different conditions than the ones in the present study.

Finally, in the patterns of all the plasma peptides studied after the ingestion of any one of the diets, we found a postprandial increase in cholecystokinin, somatostatin and pancreatic polypeptide, confirming in pigs observations in humans and other animal species (Schwartz *et al.*, 1976 ; Wass *et al.*, 1980 ; Chayvialle *et al.*, 1980). On the other hand, plasma secretin level did not augment, which agrees with results on humans (Pelletier, Chayvialle and Minaire, 1978).

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Résumé. *Composition du régime alimentaire et taux plasmatiques de quelques peptides de régulation de la sécrétion pancréatique chez le Porc.*

Le but du travail était d'étudier, chez le Porc, l'effet d'une modification de la composition du régime alimentaire sur les taux plasmatiques de quelques peptides connus pour leur rôle dans la régulation hormonale du pancréas exocrine. Six porcs Large White d'un poids vif moyen de 41 $\pm$ 3,2 kg ont été munis d'un cathéter dans une artère carotide ; quatre d'entre eux ont également été munis de fistules permanentes du canal pancréatique et du duodénum. Tous les animaux ont été adaptés à un régime témoin (C) sur une période de 8 jours avant l'intervention chirurgicale. Pendant une période de récupération post-opératoire de 8 jours et une première période expérimentale de 4 jours, ils ont été nourris du même régime témoin. Puis trois porcs ont reçu les régimes expérimentaux selon la séquence suivante : régime riche en lipides (F) pendant 7 jours, régime témoin (C) pendant 7 jours, régime riche en amidon (S) pendant 7 jours, tandis que les trois autres porcs recevaient les mêmes régimes, mais selon une séquence inverse : régime S, régime C, régime F. Les 3 régimes étaient isoprotéiques (16 % protéines) et isocaloriques (3 850 cal/kg). La sécrétion pancréatique et les taux plasmatiques de cholecystokinine (CCK), sécrétine, polypeptide pancréatique (PP) et somatostatine ont été analysés durant les 4 jours de la première période expérimentale et le dernier jour de chacune des trois autres périodes expérimentales. Les protéines totales et les activités de la lipase et de l'amylase ont été déterminées dans les échantillons de suc pancréatique collecté au cours des 7 h qui ont suivi le repas du matin. Le sang artériel a été recueilli à 9 h (avant consommation du repas), 9 h 30, 10 h et chaque heure jusqu'à 16 h.

Les résultats confirment en premier lieu l'adaptation pancréatique au régime, c'est-à-dire une augmentation de l'activité spécifique de la lipase ($\times$ 1,8) quand les porcs ont ingéré 6 fois plus de lipides par jour (régime S $\rightarrow$ régime F) et une augmentation de l'activité spécifique de l'amylase ($\times$ 2,3) quand ils ont ingéré 3 fois plus d'amidon par jour (régime F $\rightarrow$ régime S). En second lieu, la modification de la composition du régime alimentaire n'a induit aucune variation significative et durable du taux plasmatique des peptides.

En conclusion, les peptides : CCK, sécrétine, PP et somatostatine, connus pour leur rôle dans la régulation de la sécrétion exocrine du pancréas, ne seraient pas impliqués dans les mécanismes de l'adaptation de l'amylase et de la lipase aux quantités de glucides et de lipides ingérés par le porc.

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