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Development of Exocrine Pancreas Function in Chronically Cannulated Pigs During 1–13 Weeks of Postnatal Life

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Summary: The development of exocrine pancreas function was studied in Swedish Landrace pigs surgically fitted with a chronic pancreatic duct catheter and a duodenal re-entrant cannula. The juice secretion and output of total protein and trypsin activity were followed before (basal secretion) and after feeding (postprandial secretion) during the first 1–13 weeks of life. The results showed that throughout the suckling period, up to 4–5 weeks of age, the basal pancreas function remained low and the secretory response to feeding, i.e., nursing sow milk, was also low. After weaning, the pancreatic juice secretion as well as the output of protein and trypsin activity markedly increased with respect to both basal and postprandial levels. Furthermore, the enzyme composition of the pancreatic juice changed qualitatively during this period. During the first 2 weeks of life, the intravenous administration of cholecystokinin (CCK) and secretin did not stimulate exocrine function, but a significant effect was achieved from 3–4 weeks of age. These results showed that there was both an increase in exocrine pancreas function and a qualitative change in the hydrolytic enzyme pattern during porcine postnatal ontogeny, apparently correlated with the changes in diet around weaning. An increase in the response of the pancreas to hormonal stimulation was also observed during the suckling period. **Key Words:** Exocrine pancreas, development—Pig—Cholecystokinin—Secretin—Weaning—Trypsin.

The mammalian digestive tract undergoes important periods of functional changes during ontogeny (1); the first change takes place from the last part of the fetal period to birth, preparing the fetus for enteral nutrition. Another period occurs around weaning, during the change from a milk diet to one based on solid food. The ontogeny of the pancreas has been studied in several species by measuring changes in protein content and/or proteinase activities in homogenates from pancreata from individuals of different ages (2–5). In other studies, samples from intestinal contents have been used for such measurements (6,7). The results of these studies generally agree, showing an increase in pancreas function with age. The studies, however, have not considered the dynamic processes of secretion, both under basal conditions and after stimulation, and thus can only provide limited information about detailed changes in the secretatory capability of the pancreas of developing individuals. These problems were partly overcome in a recent study where the secretion in anesthetized piglets of different ages was investigated in acute experiments (8).

The purpose of this investigation was to study quantitative and qualitative changes in pancreas function and regulation in pigs during postnatal development in a herd under normal management. This was accomplished using a recently developed model for the long-term collection of pancreatic juice in young pigs fitted with a chronic pancreatic duct catheter and a re-enterant duodenal cannula (9).

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MATERIALS AND METHODS

Animals

The experiments were carried out on purebred Swedish Landrace pigs (*Sus scrofa*) obtained from a production herd (Department of Farm Buildings, Swedish University of Agricultural Sciences, Lund, Sweden) where complete management, health, and production data were maintained (10). From the second week of life, all suckling pigs had free access to a creep feed containing 16.5% crude protein (Växtfor, Lantmännen, Stockholm, Sweden) onto which the pigs were weaned at 4–5 weeks of age.

At 1–8 weeks of age, the animals (Table 1) were surgically fitted with a pancreatic duct catheter that was exteriorized via an abdominal cannula and a duodenal re-enterant T cannula (9). A catheter was also implanted into the right jugular vein for peripheral blood sampling. After the operation, the pigs usually recovered from the anesthesia within 12 h and suckling pigs could be returned to their litters. Pigs weaned on the day of operation, or later, were moved and kept in separate cages, and had contact with each other. The pancreatic catheter was connected to the re-enterant duodenal T cannula on the day after operation and maintained there between experimental samplings. The cannulas and the catheter were properly secured and protected using adhesive tape.

Experimental Procedure

Beginning 2–3 days after surgery, collections of pancreatic juice were made before and after food ingestion, on every second day starting at 8 a.m. The pigs, two at a time, were slightly restrained in an upright position in canvas slings during the collection period. For preweaned pigs, 4 × 15 min consecutive collections were done starting 30 min after removal from the sow. The pigs, together with their unoperated littermates, were then returned to the sow for 30 min and allowed to nurse, and then moved to the slings again for four additional collections of 15 min each. For weaned pigs, 3 × 30 min juice collections were made after a 2 h fasting period. The animals were then fed the weaning diet, 10 g/kg of body weight, and water ad libitum during a 30 min period, after which additional 3 × 30 min collections were made.

In a limited number of experiments, secretin and cholecystokinin, CCK-33 (KabiVitrum, Stockholm, Sweden), 0.5 U/kg, were given as i.v. injections and juice was collected for a 5-min period. During the collections, pancreatic juice was entirely diverted into plastic tubes held in an ice bath. The volume was measured and the samples were stored at −20°C until analyses. Blood samples of 2 ml were taken 30 min before and after feeding, and 2 m*M* EDTA + 500 KIU Trasylol (Bayer, Leverkusen, West Germany) were added. The samples, immediately ice chilled, were centrifuged and plasma was harvested and stored at −20°C until analysis.

TABLE 1. *Number of animals, weaning age, and duration of experiments, starting from the day the pigs were operated*

Number of pigs	Experimental period [age (days)]	Weaning age (days)
2	1–7, 1–14	—
2	3–10	—
2	18–39, 18–75	27
3	27–42	33
1	29–84	29
1	40–77	40
1	49–81	27
2	51–73, 51–89	37
2	57–90	32

Analysis

Pancreatic juice was analyzed for total protein using the Lowry method (11), modified to be performed on 96-well microplates, with bovine serum albumin (BSA) (A-7638, Sigma Chemical Co., St. Louis, MO, U.S.A.) as a standard. Trypsin activity was measured using a micromodification of the original method of Erlanger et al. (12). Fifty microliters of juice and 150 μl 0.2 *M* Tris-HCl buffer, pH 7.8, containing 0.05 *M* $CaCl_2$ were placed in the wells of a microplate. Activation of the juice was done by preincubation of the plate for 20 min at 37°C and 15 min at room temperature with 0.12 mg/ml enterokinase (Sigma) added to the Tris buffer. The reaction was then started by adding 100 μl of substrate solution containing 1 mg/ml Na-benzoyl-DL-arginine-*p*-nitroanilide (Sigma). The change in absorbance at 405 nm was followed for 45 s (at room temperature) on a spectrophotometer with a built-in kinetic program (Uniscan II, Labsystems OY, Helsinki, Finland). The trypsin activity was expressed as units (U) and defined as the amount of enzyme that hydrolyzed 1 μmol of substrate/min. For each experiment day, each sample collected was analyzed separately. The results from before (basal) and after feeding were then averaged

for each experiment day and compared statistically using Student's t test.

Identification of proteinases in pancreatic juice was made after electrophoretic separation in 1% agarose gels containing 0.037 M Ca–veronal buffer at pH 8.6, using acetylphenylalanine-β-naphthylester (Ac–Phe–βNE, Sigma) as a substrate, as previously described in detail (13).

The glucose level in the blood was estimated using the Reflocheck system (Boehringer, Mannheim, West Germany).

RESULTS

In this study, the postnatal development of exocrine pancreas function in the pig was evaluated as the secretion of pancreatic juice and total protein, and the activity of a specific enzyme, trypsin, with all values expressed per kg of body weight. During the preweaning period, i.e., the first 4–5 weeks of life, the secretion of pancreatic juice before feeding (basal conditions) remained low, at about 0.5 ml/kg/h (Fig. 1A), as did the output of protein (≈1 mg/kg/h, Fig. 1B) and trypsin activity (≈0.2 U/kg/h, Fig. 1C). Nursing did not significantly affect the levels of these parameters.

After weaning, at 4–5 weeks of age, the basal levels of all parameters increased during the first weeks, reaching about 1–2 ml/kg/h, 4–8 mg/kg/h, and 2–4 U/kg/h, respectively, at 9 weeks of age (Fig. 1A–C). The ingestion of solid food resulted in a significantly increased postprandial secretion in comparison to the basal values, reaching about 4 ml/kg/h for juice outflow, 20 mg/kg/h for protein output, and 10 U/kg/h for trypsin activity.

The protein concentration in pancreatic juice increased significantly after feeding but did not change with age, when the pre- and postweaning periods are compared (Table 2). The trypsin activity in juice increased after feeding in the postweaning period and did show an increase with age.

During the first 2 weeks of life, the combined i.v. administration of cholecystokinin (CCK) and secretin had no effect on the pancreatic juice secretion, in comparison to the basal values (Table 3). However, pigs 3–4 weeks of age of older responded, in most cases significantly, to this hormonal stimulation for all three parameters studied. The secretion, both basal and stimulated, increased significantly with age, with the exception of the basal levels of trypsin.

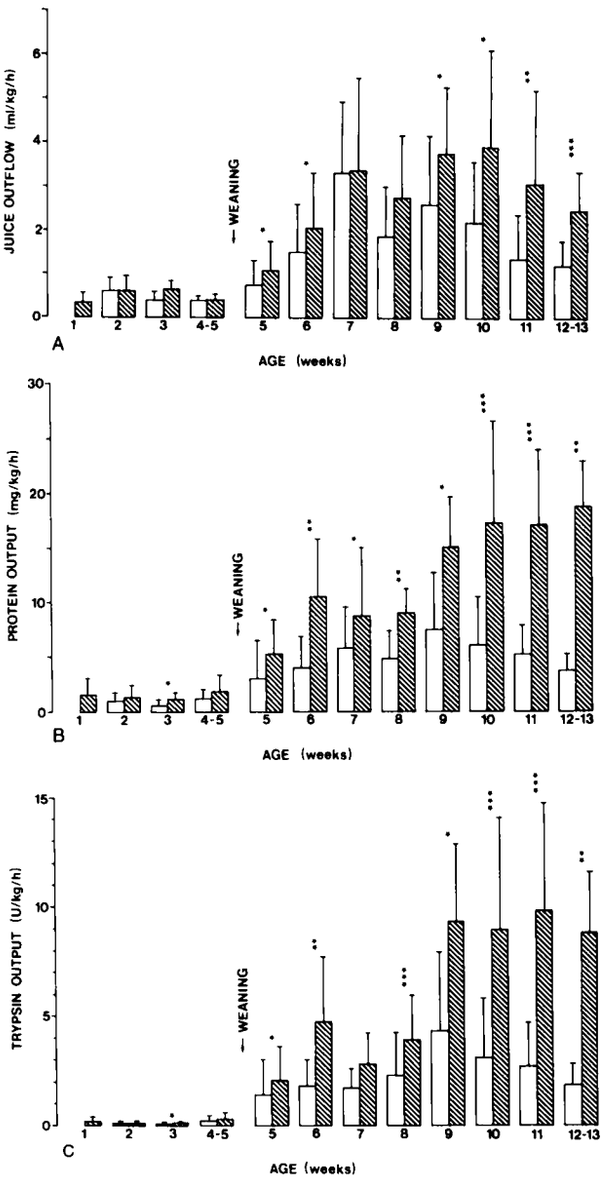

FIG. 1. Levels (mean ± SD; number of experiments as in Table 4) of pancreatic juice secretion **(A)**, output of total protein **(B)**, and trypsin activity **(C)** during 1.0–1.5 h before feeding (white bars) and 1.0–1.5 h after feeding, either sow milk before weaning or solid food after weaning (hatched bars), according to age in chronically catheterized pigs. Statistical analysis was done using paired Student's t test for the comparison of the basal and postprandial data for each age group where $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

The serum glucose levels, measured as an indicator of food ingestion and digestion, increased postprandially during the entire period studied, both after the consumption of sow milk and solid food (Table 4).

TABLE 2. *Protein concentration and trypsin activity (mean ± SD) in pancreatic juice before (basal) and after feeding (postprandial) at various ages in pigs fitted with chronic pancreatic duct catheters*

Age (weeks)	n	Protein (mg/ml)		Trypsin (U/ml)	
		Basal	Postprandial	Basal	Postprandial
1–5	27	3.9 ± 5.6	5.7 ± 8.4*	0.7 ± 1.4	1.0 ± 2.1
5–13[a]	60	3.5 ± 2.3	5.9 ± 3.9***	1.7 ± 1.2	2.8 ± 2.2***

n = number of experiments.
Statistically significant differences were evaluated between basal values and those after feeding using paired Student's *t* test and between the age groups with Student's *t* test, where $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$.
[a] Weaned pigs.

The enzyme pattern in the pancreatic juice changed qualitatively during postnatal ontogeny (Fig. 2). During the first weeks of life, chymotrypsin A and B, elastase II, and anodal trypsin dominated. The existence of "fetal–neonatal" proteinase(s) during this period was indicated by the presence of two to three activity bands located in the anodal section of the electopherogram; these bands disappeared with age. After weaning, cathodal trypsin appeared in the enzyme pattern and chymotrypsin C increased markedly in activity, while the other enzymes showed no major changes.

DISCUSSION

This investigation is the first to obtain and measure both quantitatively and qualitatively pure pancreatic secretion in conscious young animals during postnatal development. The pig, of convenient size for surgical procedures and having a rapid growth, appeared to be an ideal animal model for this purpose. The results showed that, throughout the suckling period, exocrine pancreas function was low, i.e., both the secretion before feeding (basal secretion) and the secretory response to feeding sow milk were poor. After weaning, pancreatic secretion was significantly increased, and the qualitative enzyme composition of the juice markedly changed. These results agreed well with previous studies of the enzyme contents of pancreatic homogenates and/or intestinal contents in growing pigs (2–4,7) and in other mammalian species during postnatal development (14).

The relatively low pancreas function observed during the suckling period should be evaluated with respect to several factors. First, dam's milk is an easily digested food (2), and thus it is likely that

TABLE 3. *Secretion of pancreas juice, output of protein, and trypsin activity (mean ± SD) before and after stimulation with secretin and CCK-33, 0.5 U i.v./kg of body weight, at various ages in pigs fitted with chronic pancreatic duct catheters*

Age	n	Basal	Secretin + CCK
1–2	5		
Volume, ml/kg/h		0.7 ± 0.4[a]	1.1 ± 0.6[ef]
Protein, mg/kg/h		1.3 ± 1.0[c]	1.6 ± 0.6[i]
Trypsin, U/kg/h		0.1 ± 0.1	0.2 ± 0.1[l]
3–4 weeks	5		
Volume, ml/kg/h		0.4 ± 0.2[a]	2.1 ± 0.5[eg]***
Protein, mg/kg/h		0.7 ± 0.7[d]	4.3 ± 2.8[j]
Trypsin, U/kg/h		0.1 ± 0.1	0.4 ± 0.2[m]*
5–6 weeks (weaned pigs)	5		
Volume, ml/kg/h		0.5 ± 0.2[a]	1.9 ± 0.7[e]*
Protein, mg/kg/h		1.8 ± 1.9[c]	5.3 ± 3.6[j]*
Trypsin, U/kg/h		1.0 ± 1.0	2.8 ± 2.4[n]
8–13 weeks (weaned pigs)	6		
Volume, ml/kg/h		3.1 ± 2.2[b]	8.0 ± 3.9[h]**
Protein, mg/kg/h		10.9 ± 10.1[c]	29.1 ± 16.4[k]***
Trypsin, U/kg/h		5.0 ± 5.1	13.3 ± 9.5[o]**

n = number of experiments.
Statistically significant differences were evaluated between basal values and those after hormonal stimulation (horizontal) using paired Student's *t* test, where $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$, and between the age groups (vertical) with Student's *t* test, where different letter superscripts indicate differences at the $p < 0.05$ level in between values for each parameter group.

TABLE 4. *Serum glucose levels in mmol/L before (basal) and 30 min after food stimulation (postprandial) in pigs during postnatal development*

Age (weeks)	n	Basal (mmol/L)	Postprandial (mmol/L)
1	7	4.2 ± 0.9	4.9 ± 1.0*
2	7	6.2 ± 1.4	8.1 ± 1.8**
3	4	5.2 ± 0.1	5.9 ± 0.4**
4–5	9	5.6 ± 0.7	6.9 ± 1.9*
5[a]	12	5.0 ± 0.6	6.7 ± 1.9**
6[a]	14	5.7 ± 0.8	6.4 ± 0.9**
7[a]	6	4.8 ± 0.4	6.6 ± 1.6**
8[a]	8	4.6 ± 0.6	6.3 ± 2.1**
9[a]	5	4.9 ± 0.3	5.9 ± 1.4**
10[a]	5	4.6 ± 0.3	6.0 ± 1.3**
11[a]	6	5.2 ± 0.9	7.1 ± 1.6**
12–13[a]	4	5.0 ± 0.6	8.8 ± 1.5**

n = number of experiments.
Statistically significant differences between basal and postprandial values were evaluated with Student's *t* test; $*p < 0.05$ and $**p < 0.01$.
[a] Weaned pigs.

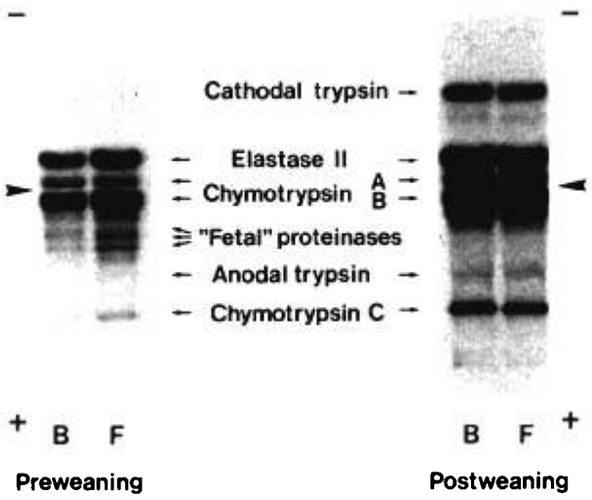

FIG. 2. Enzyme activities in activated pancreatic juice from a pig sampled before (B) and after feeding (F) at 4 weeks (preweaning) and 11 weeks of age (postweaning). After electrophoretic separation in agarose gel at pH 8.6 and incubation with the substrate Ac–Phe–βNE, the enzyme bands were identified according to Ohlson et al. (13) and Weström et al. (5), as indicated by the arrows. An arrowhead indicates the site of sample application. Cathode is at the top of the figure.

there is no requirement for a high pancreatic secretion at this stage. The suitability of a milk diet is demonstrated by the fact that it enables the pigs to quadruple their body weight during the first 3 weeks of life. Second, the qualitative enzyme content of the pancreatic juice rather than the quantitative content may be of importance for the requirements of milk digestion. As far as we are aware, the qualitative aspect of pancreatic juice with respect to digestion has not been studied in any detail. Third, intracellular degradative processes may be of some importance during this period, since macromolecular uptake into the enterocytes does not stop until the fetal type are replaced by the adult type, a process taking about 3 weeks to complete in the distal small intestine (15,16). In the suckling rat, ileal enterocytes are considered to be the site of intracellular degradation of nutrients after uptake (1).

It was observed in this study that pancreatic secretion did not increase in response to feeding during the preweaning period. Due to the frequent suckling periods, in pigs about once per hour, the milk flow to the intestines appears to be more or less constant, and therefore the pancreas may actually be in a continual state of slight stimulation. The rise in blood glucose level after feeding observed both before and after weaning would, however, speak against this interpretation. The youngest piglets studied (1–2 weeks old) did not show any pancreas response to the secretagogues, CCK and secretin, a result in agreement with previous studies both on the piglet (8) and other young mammals (14,17,18). This indicated that the pancreas of the young piglet may be unable to respond fully to feeding. From 3–4 weeks of age, the potential secretory capacity of the pancreas considerably increased, since a greater response to stimulation by CCK and secretin was found, although the secretory response to feeding milk still was low. Thus, in addition to an inability of the preweaning pig to respond to feeding, milk per se may be a weak stimulator of the exocrine pancreas.

A second phase of pancreas development started around 4–5 weeks of age, apparently associated with the time the pig began to consume appreciable amounts of creep feed, a process abruptly accelerated by weaning. This gradually led to an increase in both basal and postprandial pancreatic secretion, in addition to a change in the enzyme pattern in the juice. Several new hydrolytic enzymes became detectable during this period, e.g., cathodal trypsin became the major form of the two trypsins present in the fully weaned animal. Furthermore, as shown in a previous study, protease E and elastase I appear and chymotrypsin C and amylase activities increase, while the "fetal–neonatal" proteinase(s) disappears (5). The increase in pancreatic protein output with age depended on an increased volume secreted per body weight basis, since the protein concentration in juice did not increase with age. This agreed with the observation that the pancreas/body weight ratio increases after the third week of life in the pig (3).

The occurrence of a partially new set of pancreatic enzymes and the general increase in the output of protein and enzymes around weaning constitute developmental adaptations taking place for the digestion of solid food. The more complex enzyme pattern of the weaned pig, with several isoenzyme forms often of opposite charge, may confer an advantage in that the utilization of a wide variety of nutrients is possible. These changes in pancreas function appear to coincide with other developmental changes in the porcine digestive tract. An increase in stomach acid secretion and a shift in the stomach hydrolases from chymosin to pepsin has been observed during this period (19,20). Moreover, the activities of the intestinal brush-border hydrolases, maltase, and sucrase increase, while that of lactase decreases (2). Again, these develop-

mental changes probably all reflect the digestive tract adaptations necessary to cope effectively with a changed and increased dietary repertoire.

In this study, the pancreas changes coincided with weaning at an age of 4–5 weeks, but more generally these changes appear to be more related to the profound dietary changes rather than to weaning or age. Corring et al. (3) showed that nursing pigs reached pancreatic maturation, i.e., exhibited increased enzyme levels, at 3–4 weeks of age concomitant with a change in the diet, since the piglets began to ingest significant amounts of creep feed at that time.

The quantitative and qualitative postnatal changes in the pancreas and in the entire gastrointestinal tract of the pig, as exemplified above, appeared to be consequences of a developmental program, probably initiated and controlled by endocrinological signals (14). Several gastrointestinal hormones may be candidates for such regulation; insulin, secretin, and cholecystokinin all affect pancreatic enzyme production and secretion (21–24) as well as pancreas growth (25,26). These hormones have also been shown to be involved in adaptations of the pancreas to the diet in the adult (27,28). In pigs kept under standard production conditions, weaning is an artificial and abrupt process. In addition to the sudden loss of milk and the profound dietary change, it is most certainly a stressful situation for the piglet, probably resulting in adrenal stimulation. Glucocorticoids have been shown to induce ontogenic changes in the digestive tract and pancreas in the rat (1,29) and the piglet (30,31).

We believe that this animal model, under more controlled conditions, e.g., controlled consumption of creep feed, might be useful for further evaluating the influence of dietary and endocrine changes or determining the more distinct age effects on the postnatal development of the exocrine pancreas.

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