JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2009, 60, Suppl 2, 55-59
www.jpp.krakow.pl

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GROWTH IS DEPENDENT ON THE EXOCRINE PANCREAS FUNCTION IN YOUNG WEANERS BUT NOT IN GROWING-FINISHING PIGS.

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A correlation between the exocrine pancreatic function and growth has been previously demonstrated in growing pigs but the data are inconsistent. This was investigated by studying the growth performance of pigs with exocrine pancreatic insufficiency (EPI) at different ages and maintained under similar conditions. Twelve 7 week old (10.5±1.3 kg) weaners, and twelve 16 week old (43±5 kg) growing-finishing pigs were used in the experiments, and 6 pigs from each group were operated and pancreatic duct-ligated. Starting at 3-5 weeks after the operation, when EPI had developed, weekly recordings of feed consumption and growth were done before, during and after feed supplementation with porcine pancreatin (Creon® 10000). In weaner pigs, EPI caused growth arrest while it did not affect the growth of older pigs, as compared to respective un-operated groups of pigs. The daily feed consumption (DFC) was lower in the weaner EPI-pigs while it was similar in the growing-finishing EPI-pigs, as compared to un-operated pigs. Feed supplementation with Creon® improved the DFC and growth in both the EPI and un-operated pigs. In conclusion, the results showed the importance of the exocrine pancreatic function for growth in weaner pigs, while in older animals it played a minor role in growth. Feed supplementation with pancreatin increased the appetite and ensured an improved feed conversion.

Key words: *growth, appetite, age, exocrine pancreas*

INTRODUCTION

An appropriate pancreatic secretion is essential for the digestion and absorption of food, while exocrine pancreatic insufficiency (EPI) leads to poor digestion and absorption of nutrients (1). It has been claimed that only ~10% of the pancreatic secretory capacity is necessary for proper digestion (2). However, data obtained in our lab have shown that feed conversion and weight gain are closely related to the exocrine pancreatic function in both suckling piglets (3) and in young growing (~20 kg) pigs (4).

When reviewing the literature, the data concerning the role of the exocrine pancreas in the growth and performance of pigs is not consistent. It has been shown in young ~6-8 week-old pigs that experimentally induced EPI, using pancreatic duct ligation, lead to total growth retardation (5, 6), while another study showed only a 50% growth retardation (7) in pigs of the same age. For older pigs of ~30 kg b wt, EPI resulted in total growth retardation, as described by Gregory (8), while only a 25 % growth retardation was observed by Corring and Bourdon in pigs ligated at 40 kg (9). These data indicated that the dependency on the exocrine pancreas for growth decreases with increasing age of the pigs. There are also data showing that the pancreatic secretion differs according to the genotype of the pigs (10).

The aim of the present study was to highlight the role of the exocrine pancreas in growth and performance in an experimental model with pancreatic duct-ligated pigs of different ages from the same breed. A second aim was to explore the relationship between the exocrine pancreatic function, feed intake (appetite) and feed conversion.

MATERIALS AND METHODS

Animals

The study was approved by the Local Animal Ethics Review Committee of Lund/Malmo, Sweden. The experiments were performed on 24 crossbred ((Yorkshire × Swedish Landrace) × Hampshire) pigs of both genders, barrows and gilts, from 6 sows obtained from the Odarslov's research farm, Swedish University of Agricultural Sciences (Alnarp, Sweden). The pigs had been weaned at the age of 4 weeks. In the first experimental set, 6 pigs from 2 sows (3 pigs each) were selected for "early" pancreatic duct ligation surgery at the age of 7 weeks (10.5 ±1.3 kg), and another 6 pigs from the same sows for "late" pancreatic duct ligation surgery at the age of 16 weeks (43 ± 5 kg). In the second set of experiments, un-operated pigs (n = 6) were selected from one sow to weight match the early duct ligated pigs and weight matched un-operated pigs (n = 6) to the late duct ligated pigs were selected from another sow. During the experiments, all pigs were housed individually in pens in the same stable at 22°C and with light from 7.00-19.00. The pigs had free access to water *via* a drinking nipple and had *ad libitum* access to a commercial pelleted feed (Vaxtill 320, Lantmannen, Sweden, (*Table 1*) for one hour, twice daily (08.00-09.00 and 17.00-18.00).

Surgery

After an overnight fast and premedication with azaperone (Stresnil®, Janssen Pharmaceutica, Belgium, 2.2 mg/kg i.m.), the pigs were anaesthetized using a 0.5-1.5% air mixture of Fluothane® (Astra Lakemedel, Sodertalje, Sweden) using O_2 as a carrier gas at approximately 0.5 or 1 L/min and a close-circuit respiratory system (Komesaroff Medical Developments, Melbourne, Australia). The surgery was performed under aseptic conditions. A 14-18 cm long incision was made posterior to the sternum along the *linea alba*. The accessory pancreatic duct was isolated and ligated at 2 and 3 cm distance from the major duodenal papilla with double silk sutures (Ethicon 0-3, Johnson and Jonson Medical Products, Peterborough, ON, Canada) and then cut between the ligatures. The abdomen was closed with 3 layers of sutures. Post-operative pain was prevented by administration of buprenorphine (Temgesic®, Schering-Plough AB, 0.01 mg/kg i.m.) for 2 days after surgery.

Experimental design

The studies on the duct-ligated pigs started about 3-5 weeks after surgery, it is after the development of EPI (11). The feeding experiments were performed for 3 consecutive weeks, including one week with commercial feed, one week with the same feed supplemented with a pancreatic enzyme preparation and finally again one week on the commercial feed. On the duct ligated pigs, at the age of 7 weeks, the experiment was repeated during week 18 and 19, (*Fig. 1*). During enzyme supplementation, the weaner pigs received 12 capsules of the supplement while the grower pigs were given 36 capsules of enteric-coated porcine pancreatin, (Creon® 10 000, Solvay Pharma GmbH, Hanover, Germany) with each feeding. One capsule of Creon® contains 10 000 units of lipase, 8 000 units of amylase and 600 units of protease, according to European Pharmacopeia. Before feeding, the capsules were opened and the Minimicrosphers™ were mixed with 50-150 ml yoghurt and given to the pigs as an appetizer before access to the standard feed.

The un-operated control pigs were housed in the experimental pens for a 10 day adaptation period before the feeding experiments started. These were performed for 3 weeks, starting with one week with the commercial feed supplemented with Creon® and then two succeeding weeks with only the commercial feed. The pigs were weighed before the morning feeding at the beginning of experiment and after each week of experiment. Feed consumption was recorded directly after each meal for each pig individually.

Postmortem examination

At the end of experiments, the pigs were euthanized with an overdose of sodium pentobarbital and submitted to postmortem examination. The pancreatic area and the pancreatic duct system were examined for pancreatic involution and pathological changes. Sampling of intestinal digesta and pancreatic duct fluid content for pancreatic enzyme analyses was also performed.

Calculations and statistics

To be able to compare the growth and daily feed consumption (DFC – g feed/kg b. wt.) data, between the different aged and sized pigs the values for these parameters were calculated per kg of body weight. The data was analysed with Sigma Stat for Windows 2.0 (Jandel Corporation, San Rafael, CA, USA). A one-way ANOVA was used to test for significant differences between EPI-and respective un-operated pigs. Student's paired t-test was used to compare differences within the same animal during the experimental weeks. Differences were considered to be statistically significant when $P<0.05$.

Table 1. Ingredients and composition of the commercial pig feed used in the experiment

Item	
Ingredients	
Wheat, %	35.5
Barley, %	30.0
Wheat feed flour, %	8.0
Wheat bran, %	5.0
Soya flour, %	5.0
Oats, %	4.0
Fish flour, %	4.0
Beet molasses, %	2.0
Maize gluten, %	1.4
Fatty acids, %	1.0
Monocalcium phosphate, %	0.83
Calcium carbonate, %	0.77
Sodium chloride, %	0.18
Composition	
Water, %	12.0
Crude protein, %	17.5
Lysine, g/kg	11.0
Methionine, g/kg	3.8
Cysteine + Methionine, g/kg	6.9
Threonine, g/kg	6.6
Crude fat, %	4.0
Ashes, %	5.9
Crude fiber, %	4.7
Nitrogen, %	2.8
Calcium, %	0.9
Phosphorus, %	0.7
Potassium, %	0.6
Sodium, g/kg	1.5
Energy, MJ	12.6

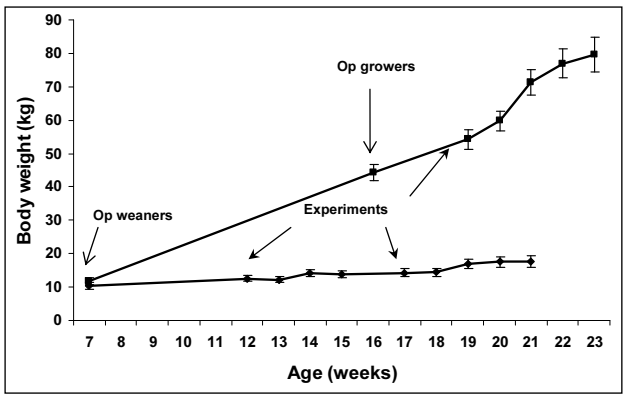

Fig. 1. Body weight gain of pancreatic duct-ligated pigs with exocrine pancreas insufficiency (EPI) during the study period (mean ± SEM, n = 5 and n = 4 respectively for weaners (diamonds) and growing-finishing pigs (squares). Time for operation (Op) of the EPI pigs and time for the feeding experiments are indicated with arrows.

RESULTS

Development of EPI in operated pigs

On the day after surgery and pancreatic duct ligation, the pigs appeared vigorous, willing to eat and showed no symptoms of fever or acute pancreatitis. The feeding experiments started about 4 weeks later when pancreatic involution had progressed and the pigs had adapted to the EPI.

From the 6 duct-ligated weaner pigs, 5 animals showed growth arrest while one still exhibited normal growth. At post-mortem examination, this particular pig showed not involuted pancreas and was consequently excluded from the study. From the 6 duct-ligated growing-finishing pigs, 2 animals showed at the necropsy not fully involuted pancreas and were also excluded from the study. All other duct-ligated pigs showed at the post-mortem examinations pancreatic changes with dilatation of the pancreatic duct system and involution of the pancreatic tissue and therefore were considered to be EPI pigs.

In the young duct-ligated weaners EPI caused total growth arrest (0±0.1 kg/day) during the entire period of the experiments. The growth of the older grower EPI-pigs was not substantially affected and they exhibited a growth of 1.1±0.36 kg/day (*Fig. 1*). This was comparable to the growth of the littermates not subjected to the experiment (1.2±0.35 kg/day).

Table 2. Age, body weight (b. wt.), average daily weight gain - DWG/b. wt. (g/kg), average daily feed consumption - DFC/b. wt. (g/kg) and feed conversion ratio - FCR (kg of feed consumed to gain one kg b. wt.) for pancreatic duct-ligated pigs with exocrine pancreatic insufficiency (EPI) subjected to feeding experiments using a commercial standard feed with and without porcine pancreatin (Creon) supplementation (mean ± SEM). Lower-case letters denotes differences ($p<0.05$) in DWG and upper-case letters denotes differences ($p<0.05$) in DFC between the experimental weeks.

Treatments	EPI weaners (n = 5)	EPI growing-finishing pigs (n = 4)
Standard feed		
Age (weeks)	12	
Initial b. wt. (kg)	12.6 ± 0.8	
Final b. wt. (kg)	12.3 ± 1.0	
DWG/b. wt. (g/kg)	-3.3 ± 3.6^{a}	
DFC/b. wt. (g/kg)	26.3 ± 1.7^{A}	
FCR	-	
Standard feed + Creon		
Age (weeks)	13	
Initial b. wt. (kg)	12.3 ± 1.0	
Final b. wt. (kg)	14.3 ± 1.0	
DWG/b. wt. (g/kg)	23.4 ±2.1^{b}	
DFC/b. wt. (g/kg)	38.0 ± 2.0^{B}	
FCR	1.65 ± 0.09	
Standard feed		
Age (weeks)	14	19
Initial b. wt. (kg)	14.3 ± 1.0	54.3 ± 2.9
Final b. wt. (kg)	14.2 ± 1.1	59.8 ± 3.0
DWG/b. wt. (g/kg)	4.2 ± 3.3^{a}	20.5 ± 3.3^{c}
DFC/b. wt. (g/kg)	20.5 ± 0.7^{A}	40.4 ± 2.3^{C}
FCR	-	2.15 ± 0.40
Standard feed + Creon		
Age (weeks)	18	20
Initial b. wt. (kg)	14.5 ± 1.2	59.8 ± 3.0
Final b. wt. (kg)	17.0 ± 1.4	71.3 ± 3.8
DWG/b. wt. (g/kg)	21.9 ± 2.4^{b}	24.0 ± 1.6^{c}
DFC/b. wt. (g/kg)	31.2 ± 2.6^{B}	51. 0 ± 3.6^{D}
FCR	1.52 ± 0.26	2.14 ± 0.13
Standard feed		
Age (weeks)	19	21
Initial b. wt. (kg)	17.1 ± 1.4	71.3 ± 3.8
Final b. wt. (kg)	17.5 ± 1.7	77.0 ± 4.4
DWG/b. wt. (g/kg)	3.2 ± 2.0^{a}	10.0 ± 1.6^{d}
DFC/b. wt. (g/kg)	21.2 ± 1.6^{A}	40.9 ± 4.5^{C}
FCR	-	4.24 ± 0.52

Performance of weaner pigs

As presented in *Table 2*, young weaner EPI-pigs subjected to the feeding/performance experiments at an age of 12 weeks (5 weeks after duct-ligation) showed total growth retardation, while their daily feed consumption (DFC/BW) was at a level that should ensure growth. Addition of porcine pancreatin (Creon®) to the feed improved the feed intake (appetite) and significantly increased the daily weight gain, becoming comparable to that of the un-operated pigs of a similar weight. Thus, the feed conversion ratio (FCR) decreased in the EPI-pigs receiving the standard diet, from an "incalculable" value to 1.52 –1.65 kg feed /kg b. wt. after supplementation with Creon®.

In the un-operated pigs of similar weight, the daily weight gain (DWG) was improved from 28.6-30.1 to 46.3 g/kg b. wt. by supplementation of the feed with Creon® (*Table 3*). In addition, the DFC (appetite) was increased from 55 to 61 g/kg b. wt. in the un-operated pigs. The FCR values for the un-operated pigs decreased from 1.35 to 2.01 and 1.87 g/kg b. wt., respectively, in the two weeks after feed supplementation with Creon®.

Performance of growing-finishing pigs

Grower pigs with EPI, subjected to the feeding experiments at week 19 (4 weeks after duct-ligation) showed nearly normal growth as compared to respective un-operated pigs (*Fig. 1*). The addition of Creon® to the feed slightly improved their appetite, as shown by the DFC (40.4 vs. 51.0 g/kg b. wt.) and DWG (20.5 vs. 24.0 g/kg b. wt.) (*Table 2*). The FCR 2.1 did not change from the week before Creon® supplementation. During the week following Creon® supplementation, both the appetite and DWG were reduced in the EPI growing-finishing pigs, and the FCR was essentially increased.

The feeding experiments performed on the un-operated grower pigs showed that Creon® supplementation slightly stimulated the DFC feed intake (52.9 vs. 48.4-47.3), and the DWG (29.7 vs. 22.4-20.2) (*Table 3*). Moreover, the Creon® supplementation decreased the FCR to 1.8 as compared to 2.2 and 2.4 in the weeks after this feed supplementation.

DISCUSSION

The data presented in this study on pigs from the same crossbreed and herd and kept under identical conditions in the same stable, clearly showed that the exocrine pancreatic function is crucial for the growth of young weaner pigs, while for slightly older, grower, pigs it is dispensable. The results indicated that during a critical time period of a few weeks after weaning (i.e., between 7-16 weeks of age, as shown in this study), the digestive system progressed through an important developmental process which resulted in compensatory mechanisms being able to replace the exocrine pancreatic function. In fact, similar observations have been made earlier, but by different investigators and on different animal materials and thus never being evaluated together in an integrated manner. Corring and Bourdon (9) showed that pancreatic duct-ligated growing-finishing pigs lost less than 25% of their capacity for nitrogen

Table 3. Age, body weight (b. wt.), average daily weight gain - DWG/b. wt. (g/kg), average daily feed consumption - DFC/b. wt. (g/kg) and feed conversion ratio - FCR (kg of feed consumed to gain one kg b. wt.) for un-operated pigs subjected to feeding experiments using a commercial standard feed with and without porcine pancreatin (Creon) supplementation (mean ± SEM). Lower-case letters denotes differences ($p<0.05$) in DWG and upper-case letters denotes differences ($p<0.05$) in DFC between the experimental weeks.

Treatments	Weaners (n = 6)	Growers (n = 6)
Standard feed + Creon		
Age (weeks)	10	17
Initial b. wt. (kg)	17.9 ± 0.6	48.8 ± 2.0
Final b. wt. (kg)	23.7 ± 1.1	58.8 ± 1.8
DWG/b. wt. (g/kg)	46.3 ± 3.7^{a}	29.7 ± 2.1^{c}
DFC/b. wt. (g/kg)	61.0 ± 1.4^{A}	52.9 ± 1.4^{C}
FCR	1.35 ± 0.11	1.83 ± 0.14
Standard feed		
Age (weeks)	11	18
Initial b. wt. (kg)	23.7 ± 1.1	58.8 ± 1.8
Final b. wt. (kg)	28.4 ± 1.2	68.0 ± 1.8
DWG/b. wt. (g/kg)	28.6 ± 3.3^{b}	22.4 ± 1.4^{d}
DFC/b. wt. (g/kg)	55.5 ± 2.3^{B}	48.4 ± 1.6^{D}
FCR	2.01 ± 0.16	2.20 ± 0.12
Standard feed (2nd week)		
Age (weeks)	12	19
Initial b. wt. (kg)	26.8 ± 1.0	64.8 ± 1.6
Final b. wt. (kg)	32.4 ± 0.9	74.0 ± 2.0
DWG/b. wt. (g/kg)	30.1 ± 2.0^{b}	20.2 ± 1.5^{d}
DFC/b. wt. (g/kg)	55.3 ± 1.1^{B}	47.3 ± 1.2^{D}
FCR	1.87 ± 0.10	2.40 ± 0.17

retention and protein digestibility. At the same time, Imondi *et al* (5) have reported, as verified by Gregory *et al* (8), a total growth retardation in younger duct-ligated pigs.

In the pig during ontogeny the accessory duct has the function of the main pancreatic duct and pancreatic juice is drained to the duodenum *via* this duct. However, in 10-30% of pigs, both ducts serve the exocrine pancreas (12) and this is probably the reason why some (accessory) duct-ligated pigs still had an unchanged pancreas after the operation. The endocrine pancreatic function appeared intact during the study, since the pigs showed no signs of diabetes mellitus and the levels of insulin and glucose in the duct-ligated pigs were found to be similar to those of the intact pigs (7, 13-15).

The exocrine pancreatic function is crucial to ensure the normal growth of weaner pigs.

In our studies the growth arrest and the lack of a compensatory adaptation mechanism in the young EPI-pigs (duct-ligated at 7 week of age) were obvious. Feed supplementation with porcine pancreatin (Creon®) completely restored the growth of these pigs, improved their appetite and brought the FCR to values acceptable in pig production. Moreover, it was shown that the EPI compensatory mechanisms could not be triggered later in life (at least up to 16 weeks of age in this study), if the pigs had been duct-ligated and developed EPI soon after weaning.

The role of the exocrine pancreas and EPI compensatory mechanisms in growing-finishing pigs

In contrast to the weaner EPI-pigs, the growth of the slightly older growing-finishing EPI-pigs was comparable to the growth of their un-operated littermates. These older pigs thus showed an ability to adapt to EPI without apparent negative effects on their growth. The compensatory mechanisms for the replacement of exocrine pancreas function are unknown and should be studied in the future.

Firstly, the compensatory role of digestive hydrolysis in the GI tract, with origin other than that of the exocrine pancreas needs to be investigated. Preliminary experiments have shown, as expected, a lack of pancreatic proteinases (trypsin and chymotrypsin) in the EPI pigs while a "new" proteinase (Ac-Phe-β-napthyl amide cleaving) appeared in the small intestinal digesta of these pigs (unpubl.). Secondly, Gregory *et al* (8) have shown profound retrograde growth of bacteria in the small intestine of duct-ligated minipigs and one possibility is that the mechanisms for a compensatory function are related to bacterial digestion. The same authors also showed that Creon supplementation improved the fecal digestibility of fat and protein, while the total digestibility of starch remained the same (8). Further experiments should also include gut wall morphology, and gut hormonal and secretory changes in the intestine in pigs subjected to EPI.

Feed supplementation with Creon® to the EPI growing-finishing pigs improved the daily weight gain slightly, by increasing the appetite, while the FCR was unaffected, as compared to the week following the Creon® addition to the feed. Interestingly, during the second week after Creon® supplementation, the EPI growing-finishing pigs showed an increased FCR (4.15 vs. 2.15). This indicated a "disturbance" by Creon® supplementation in the compensatory mechanism of the EPI pigs, a fact that is intriguing and warrants further exploration.

The role of the exocrine pancreas for the appetite and the FCR

The un-operated pigs, both weaners and growing-finishing pigs, receiving Creon® also exhibited slightly better growth, increased appetite and reduced FCR. These results verified the postulation suggested by Botermans and Pierzynowski (4), that pig performance is correlated to the pancreatic secretory capacity. In fact, even addition of relatively large doses of Creon® could still improve the appetite and FCR. A greater amount of pancreatic enzymes, either in the form of Creon® or a high endogenous juice secretion, might improve the appetite by degrading the CCK-releasing factor in the gut lumen (16) and thus lower CCK secretion and satiety. It would be of interest to know if such a mechanism also is valid for obese humans. It would also be interesting to determine the age whereby feed supplementation with Creon® can still improve growth of muscle mass (protein) in pigs as manifested by a low FCR (below 2) while not in fat mass when FCR is reaching value over 4, and when it cannot.

The ability of Creon® to restore the reduced growth in weaner EPI-pigs and the positive effect on the growth and performance of the older EPI-pigs may be related to components in Creon® other than digestive enzymes (13). We have performed a study showing that young EPI-pigs did not grow even when receiving sufficient nutrients in an elemental form. However, enteral supplementation with Creon® to pigs given the elemental diet almost fully restored the growth of these young EPI-pigs. From these results we postulated the existence of a factor in the exocrine pancreas or released in the presence of pancreatic secretions (or pancreatin) affecting nutrient assimilation in the pig (13).

Implications of the study

The importance and indispensability of exocrine pancreatic function for the growth of young pigs, as well as other production animals should be considered. However, it is not excluded that the relative slow growth and growth retardation seen during different pathological conditions in human

childhood could be related to a limited exocrine pancreatic function (17, 18). The role of the appetite regulating peptides on pancreatic exocrine secretion (19) should be also reconsidered. Scientists, who actually face 'a wall of impossibility' to improve animal performance and production quality, should consider the exocrine pancreatic function as being important to ensure quantitative and qualitative (protein not fat) high body growth. Finally, the pancreatic exocrine function may have an impact on the contemporary issue of obesity.

Acknowledgements: The work was supported by grants from: FORMAS, Sweden; The Royal Physiographic Society in Lund, Sweden; Essentys AB, Lund, Sweden; SGPlus, Malmo, Sweden. All authors have contributed substantially in the performance of the study and in the drafting of the article.

Conflict of interest statement: None declared.

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Received: December 8, 2008
Accepted: April 4, 2009

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