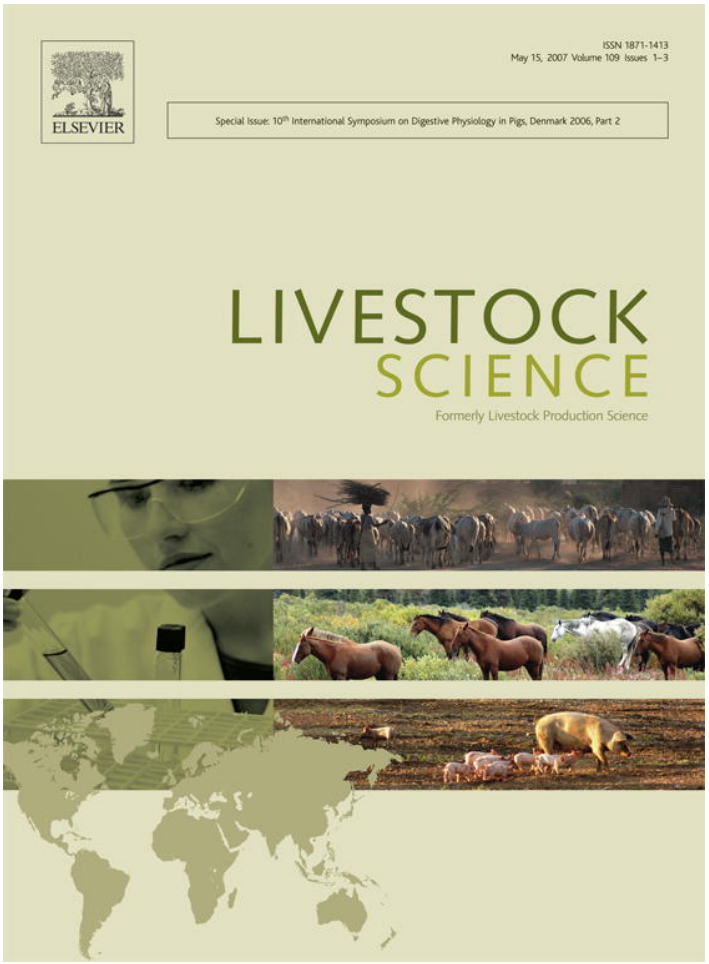

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Attempt to establish a chronic model to study the influence of bile and pancreatic juice diversion on pancreas feedback regulation in conscious pigs ☆

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Abstract

The diversion of pancreatic juice and bile stimulates pancreatic exocrine secretion but the mechanism behind this process is still not clear. The present study investigates the influence of long lasting (10 h) bile diversion or pancreatic juice and bile diversion on the pancreatic secretion in conscious pigs. The experiments were performed on 4 weaned piglets, which had a catheter inserted to the accessory pancreatic duct and bile duct and two cannulas to the duodenum. The depletion of bile alone or both bile and pancreatic juice (PJ) resulted in an increased preprandial pancreatic juice outflow, as compared to controls. Bile diversion increased the pancreatic response to feeding. PJ volume, protein outflow, and trypsin activity values were significantly higher in bile diverted pigs than in control pigs during the prandial and postprandial periods. While in pancreatic juice and bile diverted piglets the PJ protein outflow and trypsin activity slightly increased in response to feeding, their values were lower than those of the control piglets. In conclusion, both pancreatic juice and bile present in the small intestine play an important role in the regulation of the pancreatic juice secretion.

Keywords: Pig model; Pancreatic juice feedback; Bile acids; Bicarbonates

1. Introduction

Pancreatic exocrine secretion in animals and humans is mediated by the neural pathways and gut regulatory peptides; however, a luminal feedback regulation of the secretion which depends on luminal protease activity is believed to play a substantial role as well (Zabielski and Naruse, 1999; Owyang and Logsdon, 2004). In rats, the diversion of pancreatic juice results in pancreatic hypersecretion (Fushiki et al., 1999). In pigs, there is a controversy concerning the existence of feedback regulation. Bile has been known to affect feedback regulation in animal species other than pigs and in humans, but the mechanism remains unclear (Green and Nasset, 1980; Houe et al., 1997). Some researchers suggested that bile acids may stabilize luminal protease activity resulting in inhibition of CCK release, and

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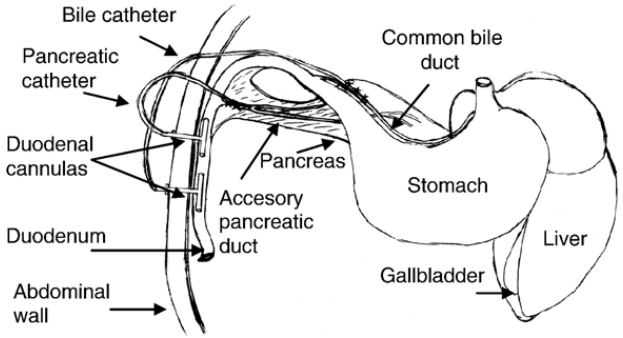

Fig. 1. Schematic presentation of bile and pancreatic duct catheterization and cannulas implantation in the duodenum of the pig for chronic studies of pancreatic juice and bile secretion.

others are of the opinion that the inhibition of plasma CCK is achieved due to enhanced somatostatin release by the bile (Koop et al., 1996). Methodological difficulties in studying the secretion of both pancreatic juice and bile simultaneously may contribute to the lack of data concerning the interplay relationship between these secretions and their importance in modulating the intestinal stimuli influencing the exocrine pancreatic secretion. In some species, like the rat, it is very difficult to separate the pancreatic juice from bile because of the anatomical features of these animals (Kato et al., 1999). However, in pigs the accessory pancreatic duct and the common bile duct reach the duodenum separately, and as far as we know there is no suitable model for studying these processes chronically. Thus our aim was to develop a pig model suitable for studying the pancreatic juice and bile secretion in pigs.

2. Materials, methods, techniques

The animal studies were approved by the Local Ethical Committee. An experimental model was developed to allow collection and reintroduction or diversion of pancreatic juice or both pancreatic juice and bile simultaneously in the pig. Under general halothane anesthesia, a silicone catheter was inserted to the accessory pancreatic duct and two silastic cannulas were placed in the duodenum according to the method described by Pierzynowski et al. (1988). The bile duct was catheterized according to the method of Lundin et al. (1991) with modifications (Fig. 1). The studies were carried out on 4 weaned pigs randomized to all the treatments according to the Latin square principle protocol. In the control pigs (n=4, B+, PJ+), the pancreatic juice (PJ) and bile (B) were returned to the duodenum, while in the experimental pigs pancreatic juice was reintroduced, but bile was diverted (n=4, B− , PJ+) or both bile and pancreatic juice were diverted (n=4, B− ,PJ−). Collection of PJ and bile lasted 5 h

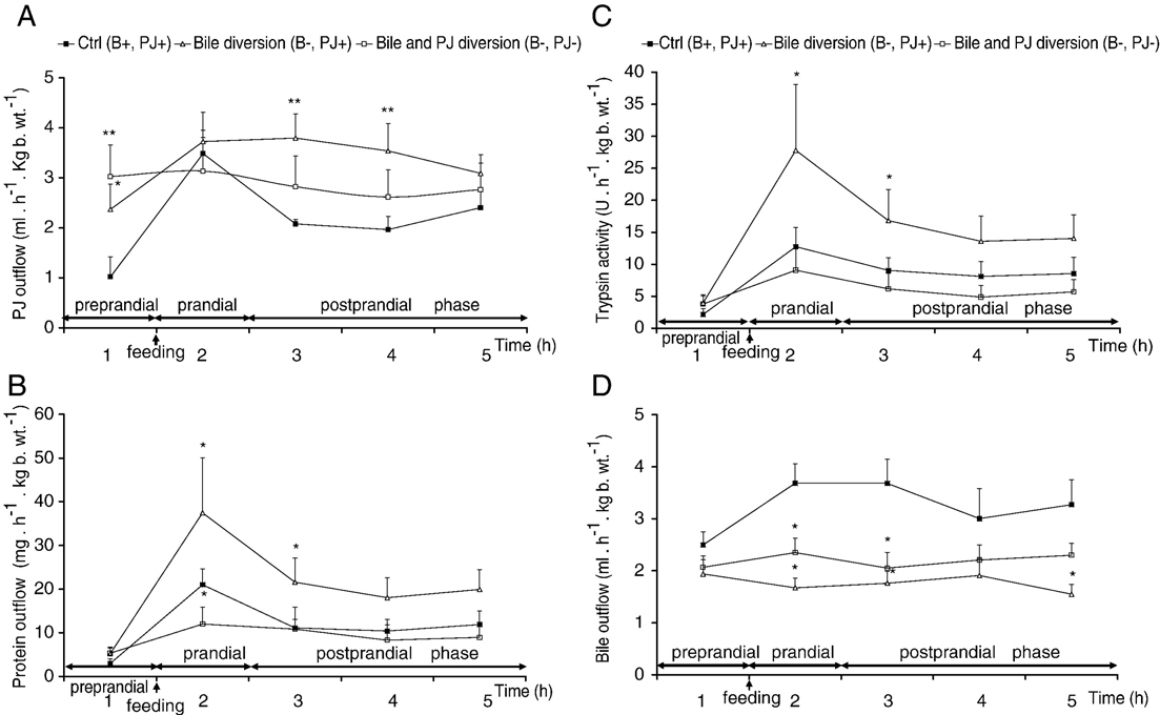

Fig. 2. (A) Pancreatic juice (PJ) outflow, (B) protein outflow, (C) trypsin activity and (D) bile outflow in control (B+ , PJ+), bile diverted (B− , PJ+) and both bile and pancreatic juice diverted pigs (B− , PJ−). Bile and PJ diversion lasted 10 h before experiments. Mean values±SE.

(1 h preprandial, 1 h prandial and 3 h postprandial) during the morning feeding. Pancreatic juice and bile secretion were collected in 30 min-periods, measured and 1.5 ml samples were stored at −20 °C until analyses. The remaining PJ and bile were reintroduced into the duodenum during the next collection period or kept chilled for reintroduction after the experiments were finished. Pancreatic juice was analyzed for total protein content using the method described by Lowry et al. (1951). Trypsin activity was measured according to the method described by Pierzynowski et al. (1990). One-way ANOVA followed by unpaired Student *t*-test was used for the comparison of two sets of data. The differences were recognised as significant when $p<0.05$. Statistical analysis was done with InStat v2.03 software (GraphPad Software Inc., San Diego, CA, USA).

3. Results

During the preprandial period, in the bile diverted (B− , PJ+) and both bile and pancreatic juice diverted pigs (B− , PJ−), the pancreatic juice outflow increased significantly as compared to the control pigs (B+, PJ+). In the prandial phase, the pancreatic juice outflow increased in the control and bile diverted pigs ($p<0.05$), while in both bile and PJ diverted pigs, PJ outflow did not increase. In the postprandial phase, PJ outflow decreased in the control pigs but not in bile diverted pigs, which differed significantly ($p<0.01$) from the controls. In the bile and PJ diverted pigs, PJ outflow did not change and showed intermediate values between control and bile diverted pigs (Fig. 2A). The pancreatic juice protein outflow of experimental pigs did not differ significantly from that of the controls in the preprandial phase (Fig. 2B), while in the prandial phase, it was significantly higher in the bile diverted pigs ($p<0.05$). In contrast to this, the B− , PJ− pigs showed significantly lower protein outflow than the controls. During the postprandial phase, the protein outflow decreased in the control and B− , PJ− pigs, but it was still significantly higher in the B− PJ+ as compared to controls ($p<0.05$). Similar trends were observed in the PJ trypsin activity (Fig. 2C). Bile outflow did not differ significantly between the experimental and control pigs in the preprandial phase; however, a tendency toward lower values was seen in the B− , PJ+ and B− , PJ− pigs (Fig. 2D). The bile outflow in control pigs increased in the prandial phase and slightly decreased during the postprandial phase. Contrary to this, bile outflow did not increase either in the prandial or in the postprandial phase in B− , PJ+ and B− , PJ− pigs. The low bile outflow in experimental pigs differed significantly from control values in the prandial and postprandial phase (Fig. 2D).

4. Discussion

In this work we present the results from the experiments carried out on a pig model elaborated to investigate the role of the bile and pancreatic juice in the luminal stimuli modulating the exocrine pancreatic secretion in the periprandial period. The long lasting diversion of bile and PJ demonstrated that during the interdigestive period the secretion of the PJ is augmented but only in terms of volume, because protein outflow and trypsin activity did not change. This could be due to the lack of bicarbonate in the small intestine and subsequent increased secretin release by the acidic chyme entering the duodenum. On the other hand, intraduodenal infusion of bicarbonate instead of bile did not prevent the elevated PJ outflow in the pig (Valverde et al., unpublished). During the digestive period, the lack of bile in the small intestine evoked an increased response to feeding. This was not due to the lack of pancreatic enzymes, since PJ was reintroduced into the duodenum and its protein content and trypsin activity were high. Under these conditions, pancreatic proteases could be autodigested in the intestinal lumen, as suggested by Green and Nasset (1980), leading to a decreased food protein cleavage and increased protein loss from the small intestine. Long lasting diversion of both bile and PJ caused an elevated PJ outflow within the time of the observations, but did not influence either protein outflow or trypsin activity. On the other hand, the low bile outflow in the experimental pigs is due to the interruption of the enterohepatic circulation of the bile acids salts, since only *de novo* synthesized bile acids are responsible for bile secretion under these conditions (Anwer et al., 1975).

5. Conclusions

A suitable model for chronic studies of pancreatic juice and bile secretion and their interrelationships in pigs has been developed. The diversion of bile strongly influences the secretion of the PJ during the interdigestive and digestive period.

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