The Effect of Intravenous Infusion of Atropine on Pancreatic Exocrine Secretion in Sheep

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Abstract The effect of intravenous infusion of atropine on the pancreatic exocrine secretion in sheep was examined. Atropine was infused for 60 min at the dose of 0.01, 0.1, 0.5, 1, 10, 20 and 30 $\mu\text{g}/\text{kg} \cdot \text{min}$. The flow rate of pancreatic juice was decreased by atropine at the dose of 0.1, 0.5, 1, 10, 20 and 30 $\mu\text{g}/\text{kg} \cdot \text{min}$ and its decreased level was maintained during infusion period except for the first 10 min. The mean reduction rates at the doses above 0.5 $\mu\text{g}/\text{kg} \cdot \text{min}$ were reached almost equal level of 74.3%. Atropine also decreased protein concentration and amylase activity in pancreatic juice of which the reduction rates were 51.3% and 45.1%, respectively. These results indicate that the considerable part of basal juice flow and enzyme secretion are mediated by the cholinergic mechanisms. *Jpn. J. Zootech. Sci.*, 56 (11): 905-910, 1985

Key words: Exocrine pancreas, Atropine, Sheep

It has been well known that the pancreatic exocrine secretion was mainly controlled by vagal nerve activity and gastrointestinal hormones. The effects of vagal mechanisms and their functional importance on the control of pancreatic secretion, however, remains incompletely understood in part because of species differences¹⁾. In sheep, the dominance of humoral control in maintenance of basal rate of secretion was mentioned by TAYLOR²⁾.

In this study, the effect of intravenous infusion of atropine on pancreatic exocrine secretion was examined to know the role of cholinergic nervous activity in the basal rate of secretion.

Materials and Methods

Five sheep, weighing 39-45 kg, were chronically catheterized with silastic tubing (4 mm O.D., 2 mm I.D.) inserted into the common bile duct at two places; one near the duodenum for collection of pancreatic juice and the other near the gall bladder for collection of bile. The common bile duct was ligated immediately distal to both catheter insertions. A third catheter was inserted into the duodenum to return the pancreatic juice and bile. In addition, a silastic tubing (1.53 mm O.D., 0.75 mm I.D.) was inserted into the jugular vein to infuse atropine. The animals were kept in individual crates and fed orchard-grass hay (100 g) and alfalfa pellets (2.5% of body weight) once a day at 19:00. Water was available *ad libitum*. Pancreatic juice and bile were returned to the duodenum of each sheep at about the rate of

production by means of a peristaltic pump.

The flow rate of pancreatic juice was measured for every 10 min from 16:00 to 17:30 and an aliquot of 100 μ l were taken for analyses. Intravenous infusion of atropine (as atropine sulfate, Wako Pure Chemical, Osaka, Japan) was started at 16:30 and continued for 60 min at the rate of 0.01, 0.1, 0.5, 1, 10, 20 or 30 μ g/kg $\cdot$ min. The rate of infusion was 1 ml/min in each experiment.

Protein concentration was determined by the method of LOWRY *et al.*³⁾ using bovine serum albumin as a standard. Amylase activity was assayed by the method of BERNFELD⁴⁾, with slight modification as described by KANNO⁵⁾. The activity unit was defined as the amount of enzymes which produced 1 mg maltose/min from starch.

The results were analyzed statistically by the Student's *t*-test.

Results

The flow rates of pancreatic juice began to decrease immediately after the onset

Fig. 1. Changes in pancreatic juice flow of sheep induced by intravenous infusion of atropine at the dose of 0, 0.01, 0.1, 0.5, 1, 10, 20 and 30 μ g/kg $\cdot$ min. Each value represents mean of five experiments.

Fig. 2. Dose-response of atropine for pancreatic juice flow in sheep plotted as a percentage of the mean value before infusion. Each value represents mean $\pm$ SE of five experiments. * indicates a significant difference from the value of saline infusion ($P < 0.01$).

of atropine infusion, reaching nearly minimal value in 2nd 10 min of infusion period and remained decreased throughout the experimental period when atropine was infused at 0.5, 1, 10, 20 and 30 $\mu\text{g}/\text{kg} \cdot \text{min}$. Infusion of saline or atropine at the dose of 0.01 $\mu\text{g}/\text{kg} \cdot \text{min}$ had no effect on the flow rate. At a dose of 0.1 $\mu\text{g}/\text{kg} \cdot \text{min}$ of atropine very modest decrease in flow rate was observed (Fig. 1). The relation between the dose of atropine and the response of pancreatic juice flow is shown in Fig. 2, in which the mean flow rate of pancreatic juice during the latter half of infusion period was expressed as a percentage of the mean value before infusion. The rates of juice flow were almost minimal above the dose of 0.5 $\mu\text{g}/\text{kg} \cdot \text{min}$, declining to the mean value of only 25.7%.

The relation between the dose of atropine and the response of protein concentration in pancreatic juice is shown in Fig. 3, in which the value only in final 10 min

Fig. 3. Dose-response of atropine for protein concentration in pancreatic juice in sheep. The value of final 10 min of infusion period was plotted as a percentage of the mean value before infusion. Each value represents mean $\pm$ SE of five experiments. *indicates a significant difference from the value of saline infusion ($P < 0.01$).

Fig. 4. Dose-response of atropine for amylase activity in pancreatic juice in sheep. The value of final 10 min of infusion period was plotted as a percentage of the mean value before infusion. Each value represents mean $\pm$ SE of five experiments. *indicates a significant difference from the value of saline infusion ($P < 0.01$).

of the infusion period was expressed as a percentage of the mean value before infusion, because of delayed response of protein release to atropine infusion. Intravenous infusion of atropine at the dose of 1, 10, 20 or 30 $\mu\text{g}/\text{kg} \cdot \text{min}$ decreased the protein concentration in pancreatic juice to 48.9% (mean of the values at the higher four doses) of the pre-infusion value of $45.8 \pm 1.5 \text{ mg/ml}$ (mean $\pm$ SE, $n=120$).

The relation between the dose of atropine and the response of amylase activity in pancreatic juice is shown in Fig. 4, in which the results are presented in the same manner as in the protein concentration. Intravenous infusion of atropine at the dose of 1, 10, 20 or 30 $\mu\text{g}/\text{kg} \cdot \text{min}$ decreased the amylase activity in pancreatic juice to 54.9% (mean of the values at the higher four doses) of the pre-infusion value of $4641 \pm 159 \text{ units/ml}$ (mean $\pm$ SE, $n=120$).

Thus, outputs of protein and amylase in pancreatic juice, which were calculated as release rate by multiplying the content of pancreatic juice by the flow rate, decreased after atropine infusion by 87.5% and 85.9%, respectively.

Discussion

Intravenous infusion of atropine at the higher doses resulted in about 75% reduction in pancreatic juice flow. This indicates that the cholinergic mechanisms could be mainly involved in the basal secretion of sheep pancreatic juice. The dose dependent response was not observed at higher doses than 1 $\mu\text{g}/\text{kg} \cdot \text{min}$, reaching almost similarly minimal levels. This also indicates that the dose of 1 $\mu\text{g}/\text{kg} \cdot \text{min}$ was enough to block the cholinergic effects to the exocrine pancreas. The great decreases of protein and amylase outputs in pancreatic juice induced by atropine indicate that the major part of enzyme secretion in pancreatic juice is also mediated by the cholinergic mechanisms. It seems very difficult to clarify whether the main effect of atropine is caused via the directly masked cholinergic responses in the pancreatic cells or via the indirect cholinergic effects to the exocrine pancreas. In pigs, a large increase in enzyme output was reported to be caused by vagal stimulation while the response to CCK-PZ was relatively small, suggesting that the vagal nerve might exert a quantitatively greater influence on the secretion of pancreatic juice than in other species⁶⁾. A similar observation in sheep was obtained by REYNOLDS and HEATH⁷⁾. The direct effect of vagal nerve may play a considerable role in the pancreatic exocrine secretion in sheep. It should be considered, however, that the blockade of cholinergic mechanisms by atropine might be also involved in the inhibition of endogenous release of gastrointestinal hormones, since KONTUREK *et al.*^{8,9)} reported that the endogenous releases of secretin and CCK-PZ from intestinal mucosa were inhibited by atropine. Gastrin which is known to be secreted through the cholinergic mechanism^{10,11)} has been reported to increase the exocrine pancreatic secretion in rats^{12,13)}, rabbits¹⁴⁾, cats^{15,16)} and dogs^{17,18,19,20,21)}. Therefore, the possibility is not excluded that decreased secretion of these gastrointestinal hormones by atropine caused at least a part of decreased pancreatic exocrine secretion. Indirect effect of reduced secretion of secretin and CCK-PZ through the inhibition of entering the acids into duodenum is also

presumed. The inhibition of gastrointestinal motility by atropine which was shown by BUENO & FIORAMONTI²²⁾ also may have some effect on secretion of gastrointestinal hormones through the decreased contact of gastrointestinal contents to mucosa.

Further experiments to determine the effect of atropine on the endogenous release of gastrointestinal hormones and on the action of exogenous gastrointestinal hormones to the exocrine pancreas will help to clarify the quantitative role of cholinergic mechanisms on pancreatic exocrine secretion.

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めん羊の腓外分泌に及ぼす静脈内アトロピン注入の影響

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めん羊の腓外分泌に及ぼす静脈内アトロピン注入の影響を明らかにするために、本試験を行なった。アトロピンは、0.01, 0.1, 0.5, 1, 10, 20 および 30 $\mu\text{g}/\text{kg} \cdot \text{min}$ の投与量で 60 分間注入した。腓液流量は、0.1, 0.5, 1, 10, 20 および 30 $\mu\text{g}/\text{kg} \cdot \text{min}$ のアトロピン注入により減少し、最初の 10 分間を除き注入期間中一定レベルを維持した。1 $\mu\text{g}/\text{kg} \cdot \text{min}$ 以上の投与量では減少率がほぼ

等しく、その平均減少率は 74.3% であった。アトロピンはまた、腓液中のタンパク濃度およびアミラーゼ活性を低下させ、その減少率はそれぞれ、51.3% および 45.1% であった。これらの結果は、通常の腓液流量および酵素分泌量のかなりの部分が、コリン作動性機序を介していることを示している。

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