Changes of Duodenal pH and Pancreatic Exocrine Function after Upper G-I Intraluminal Ethanol Administration

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Many studies have been conducted to present the action of ethanol on exocrine secretion of the pancreas. It has been reported that oral administration of ethanol causes elevation in pancreatic exocrine secretion (Brooks and Thomas 1952; Walton et al. 1962; Llanois 1977). There are also contrasting reports that pancreatic exocrine secretion is suppressed (Dreiling et al. 1952; Tiscornia et al. 1973), and stimulated (Walton et al. 1962) by intravenous administration of ethanol. Noel-Jorand and Sarles (1983) reported that suppressive and stimulative effects exist in accordance with high and low blood ethanol concentration.

However, there appeared to be no reports of studies that have continuously measured variations of the duodenal luminal pH in response to gastrointestinal administration of ethanol. In our study, we simultaneously measured duodenal lumen pH and pancreatic exocrine secretion to determine the effects of gastrointestinal administration of ethanol.
tinal administration of ethanol.

**MATERIALS AND METHODS**

**Experimental model**

Modified Herrera's pancreatic fistula (Herrera et al. 1968) was produced in three mongrel dogs (2 males, 1 female) with a body weight of 16-18 kg. Thomas cannulas (Thomas 1941) were inserted into the stomach and into the jejunum 30 cm caudal from the Treitz ligament to produce gastric and jejunal fistulas (Fig. 1).

**Measurement of duodenal pH and pancreatic secretion**

The experiment was started after a 3-week postoperative recovery period. Specifically, the Herrera dogs were fasted for 18 hr prior to starting the experiment, then were placed on a Pavlov's stand in standing position. As shown in Fig. 1, a micro glass pH electrode (Type CL5DI, Chemical Instruments, Inc., Tokyo) was inserted and fixed in the inner tube of the Herrera's cannula and the duodenal pH was recorded continuously with a recording needle. Changes in the duodenal pH were compared by calculating the area (SpH8) between the pH 8 line and the graphic marker for each 30-min period (Fig. 2).

Pancreatic juice was collected for every 30 min for output measurement. A 1-ml aliquot was taken from the collected pancreatic juice to measure $\text{HCO}_3^-$, and protein, then the remainder returned to the duodenum during the next 30 min. The first 30 min (B fraction) was assumed to represent basal secretion. During the next 30 min (fraction 1), 100 ml of 20% or 40% ethanol was administered by intragastric or intrajejunal infusion, then pancreatic juice sampling (fractions 2-6) was continued up to 150 min following ethanol administration (Fig. 3). Intragastric and intrajejunal administration of ethanol was performed via a Thomas cannula. The pH of the administered ethanol was in the range of 4.9-5.6. $\text{HCO}_3^-$ concentration was measured by the method of Van Slyke (1922), and protein by Lowry's method (1951). Peripheral venous blood was sampled prior to ethanol loading and at 30-min intervals over 180 min after ethanol loading. The sampled blood was used to measure blood ethanol and plasma CCK concentration. Blood ethanol concentration was measured by gas chromatography (Tsukamoto 1970), and plasma CCK concentration by RIA method with a double antibody employing OAL 656 antibody (Hashimura et al. 1982; Himeno et al. 1983).

The above-described measurements were conducted twice on three experimental dogs, a total of six times. Measured values were expressed as means ± standard error (Mean ± s.e.). Means were evaluated by Student's t-test and judged to be significant if $p < 0.05$.

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Fig. 1. Left side: Experimental design for intragastric infusion. Right side: Experimental design for intrajejunal infusion.
RESULTS

Changes of duodenal pH

The mean value of SpH₈ before intragastric infusion (hereafter abbreviated to i.g.) of 20% ethanol was 14.1 cm²/30 min. However, this value increased significantly after ethanol infusion, reaching a maximum of 51.0 cm²/30 min in fraction 2, decreasing gradually thereafter. SpH₈ prior to 40% ethanol i.g. was 9.2 cm²/30 min, but this value increased significantly after ethanol infusion, reaching a maximum value of 40.3 cm²/30 min in fraction 3. The mean value of SpH₈ prior to intrajejunal infusion (hereafter abbreviated to i.j.) of 20% ethanol was 11.7 cm²/30 min. However, this value increased after ethanol infusion, reaching a maximum value of 66.3 cm²/30 min in fraction 4. SpH₈ prior ethanol i.g. was 11.5 cm²/30 min, but this value increased significantly after ethanol infusion, reaching a maximum value of 55.6 cm²/30 min in fraction
4. SpH₈ decreased gradually thereafter, returning to near the pre-infusion value in fraction 6 (Fig. 4)

**Changes of pancreatic exocrine secretion**

**Pancreatic juice output**

Changes of pancreatic juice output were similar to those of SpH₈. Specifically, the mean value of fraction B was 2.5 ml/30 min, but this increased gradually after 20% ethanol i.g., reaching 10.4 ml/30 min in fraction 2, which was a 4.2 times higher level than that of fraction B. However, the mean value of pancreatic juice output returned to close the pre-infusion level in fraction 6. Output in the B fraction prior to 40% ethanol i.g. was 2.7 ml/30 min, but this...
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reached a maximum value of 8.2 ml/30 min in fraction 4, which was 3.1 times higher level than that of fraction B. This was followed by a gradual decrease. After 20% ethanol i.j. there was a clear increase in pancreatic juice output to the maximum value of 19.8 ml/30 min in fraction 4, which was a 6.6 times higher value than that of fraction B. After 40% ethanol i.j., output peaked at 11.3 ml/30 min in fraction 4, but it was lower than those after 20% ethanol i.j. (Fig. 5).

**HCO₃⁻ output**

Pancreatic HCO₃⁻ output increased significantly after 20% ethanol i.j. administration, reaching 1.7 mEq/30 min in fraction 4, which was a 14.8 times higher value than that of fraction B. The pattern of changes in pancreatic bicarbonate output after 40% were similar to those after 20% ethanol i.j. administration, but the increase was less than that after 40% ethanol i.j. administration.

![Bicarbonate Output Graph](image)

**Fig. 6.** Changes of pancreatic bicarbonate output after ethanol infusion. Symbols are the same as in Fig. 4. *n = 6.* *p < 0.05; **p < 0.01.*

![Protein Output Graph](image)

**Fig. 7.** Changes of pancreatic protein output after ethanol infusion. Symbols are the same as in Fig. 4. *n = 6.* *p < 0.05.*
Protein output in pancreatic juice

Protein output increased after i.g. and i.j. infusion of ethanol. Protein output after 20% ethanol i.j. increased more compared with the levels after 20% and 40% ethanol i.g., but the value was lower than that obtained after 20% ethanol i.j. (Fig. 7).

Integrated values of pancreatic exocrine secretion after ethanol infusion

Changes in the pancreatic exocrine secretion after administration of ethanol i.g. and i.j. were compared from the basic integrated values of SpH₈ of each fraction, pancreatic juice output, bicarbonate output, and protein output during 180 min after ethanol infusion (Fig. 8). Although statistically significant differences were not obtained, increases were noted in SpH₈, and in pancreatic juice, bicarbonate and protein outputs after G-I administration of ethanol. Furthermore, a higher response was observed in the i.j. group than in the i.g. group.

Correlation between duodenal intraluminal pH and pancreatic juice output

Correlation between SpH₈ and pancreatic juice output in all experiments was derived by regression. SpH₈ values greater than 40 cm²/30 min showed a significant positive correlation with pancreatic juice output after i.g. infusion with \( y = 0.42x - 13.8 \) \((p < 0.01, \rho = 0.62)\), and after i.j. infusion with \( y = 0.48x - 13.6 \) \((p <

![Integrated values of pancreatic exocrine secretion after ethanol infusion](image_url)

Fig. 8. Integrated values of pancreatic exocrine secretion after ethanol infusion. Symbols are the same as in Fig. 4. \( n = 6 \). \(*p < 0.05\).
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However, SpH₈ values less than 40 cm²/30 min were not significantly correlated with pancreatic juice output in either of the i.g. or i.j. groups (Fig. 9).

Correlation between duodenal intraluminal pH and HCO₃⁻ output

SpH₈ values greater than 40 cm²/30 min showed a significant positive correlation with bicarbonate ion output after i.g. infusion with \( y = 0.038x - 1.35 \) (\( p < 0.05, =0.495 \)), and after i.j. infusion with \( y = 0.052x - 1.73 \) (\( p < 0.01, =0.61 \)).

Fig. 10. Correlation between SpH₈ and pancreatic bicarbonate output. SpH₈ values greater than 40 cm²/30 min showed a significant correlation with pancreatic bicarbonate output after intragastric (●——) and intrajejunal (○——) ethanol infusions.
However, SpH₈ values less than 40 cm²/30 min were not significantly correlated with bicarbonate ion output in either of the i.g. or i.j. groups (Fig. 10).

**Changes of blood ethanol levels and plasma CCK concentration**

**Blood ethanol levels**

Blood ethanol levels 90 min after infusion of 20% and 40% ethanol i.g. increased to 1.14 mg/ml and 2.15 mg/ml, respectively, then reached a plateau, which was maintained until the end of the experiment. The maximum blood ethanol levels at 90 min after i.j. infusion of 20% ethanol and at 60 min after 40%

![Graph showing blood ethanol levels](image1)

**Fig. 11.** Blood ethanol levels after intragastric and intrajejunal ethanol infusions were always similar throughout all the experiments. •, 20% ethanol, intragastric; ○, 40% ethanol, intragastric; ▲, 20% ethanol, intrajejunal; △, 40% ethanol, intrajejunal. n = 6.

![Graph showing plasma CCK concentration](image2)

**Fig. 12.** Changes of plasma CCK concentration after ethanol infusion. Only 40% intrajejunal ethanol infusion decreased plasma CCK concentration. •, 20% ethanol, intragastric; ○, 40% ethanol, intragastric; ▲, 20% ethanol, intrajejunal; △, 40% ethanol, intrajejunal. n = 6. *p <0.05; **p <0.01.
ethanol i.j. administration were 1.03 mg/ml and 2.33 mg/ml, respectively. These values were maintained almost without change until the end of the experiment. Regardless of the administration route, almost identical blood ethanol levels were maintained dose dependently (Fig. 11).

**Plasma CCK concentration**

Mean plasma CCK concentration before i.g. infusion of 20% ethanol was 7.0 pg/ml and this value remained almost unchanged after infusion. Furthermore, there was almost no change in the mean plasma CCK concentration after infusion of 40% ethanol i.g., similar to the case with 20% ethanol. Plasma CCK value decreased slightly after infusion of 20% ethanol i.j. The mean plasma CCK concentration before i.j. infusion of 40% ethanol was 10.6 pg/ml, but exhibited a significant decrease in each of fractions 1 to 6 after infusion (Fig. 12).

**DISCUSSION**

We continuously measured duodenal pH and the pancreatic exocrine secretion response after upper G-I intraluminal administration of ethanol. The influence to the duodenal pH of intragastric ethanol infusion itself was negligible in this model. According to the results, duodenal pH decreased and pancreatic exocrine secretion was stimulated after i.g. or i.j. ethanol infusion. The mechanism of these responses after i.g. ethanol infusion, as indicated by Imamura et al. (1985), is probably elevation of gastric acid secretion by the infused ethanol. This elevation in turn, increases the duodenal intraluminal acid load, thereby inducing secretin secretion which causes a secondary stimulation of pancreatic juice secretion. Furthermore, Hirschowitz(1956) and Woodward et al. (1957) have reported finding extensive elevation of gastric acid secretion after i.g. ethanol infusion. They suggested that the mechanism of this elevation was stimulation of the antrum by the infused ethanol leading to secretion of gastrin. Woodward et al. (1957) additionally demonstrated that elevation of gastric acid secretion occurred after irrigation of Thiry's jejunal fistula with ethanol. The mechanism for this phenomenon was explained by Way et al. (1975), who proposed participation of the humoral factor entero-oxyntin, which is secreted by the upper intestine. There was no dose dependency between SpHs and concentration of infused ethanol. It is supposed that the duodenal pH is defined by the sum of gastric acid secretion and pancreatic exocrine secretion. From the results of our study, we also believe that decrease in the duodenal intraluminal pH resulting from i.g. and i.j. ethanol infusion, is caused by elevated gastric acid secretion, which leads to the stimulation of pancreatic exocrine secretion. This strongly indicates the existence of entero-oxyntin in the small intestine.

In our experiment, upper G-I infusion of 20% ethanol induced a stronger pancreatic exocrine secretion response than infusion of 40% ethanol, implicating the involvement of blood ethanol concentration in the mechanism. Noel-Jorand and Sarles (1983) reported that in their experiment using dogs, a blood ethanol
concentration of 1.5 mg/ml or more tended to suppress pancreatic exocrine secretion. The blood ethanol concentrations in our experiment were approximately 1.0 mg/ml after 20% ethanol infusion and 1.5 mg/ml after 40% ethanol infusion. Accordingly, it appears that the lower pancreatic exocrine secretion response in 40% ethanol infusion group compared with the 20% ethanol infusion group may be explained by the higher blood ethanol concentration after 40% ethanol infusion. With regard to correlation between duodenal intraluminal pH and pancreatic exocrine secretion, Meyer et al. (1970) did not measure duodenal pH, but loaded dog's duodenum with various acids, including hydrochloric acid, sulfuric acid, phosphoric acid, lactic acid and citric acid, and found that when the pH of the infused acid was 4.5 or lower, output of bicarbonate in the pancreatic juice increased. And they suggested that a pH of 4.5 in the duodenum is threshold value for stimulation of pancreatic bicarbonate secretion. In our experiment, in order to quantify change in pH, we derived the area (SpH₈) included between the pH 8 line and the graphic marker for each 30 min period. We found that SpH₈ values greater than 40 cm²/30 min were positively correlated with pancreatic juice and pancreatic bicarbonate outputs, suggesting that in our experiment, an SpH₈ value equal to 40 cm²/30 min is a threshold value for stimulating pancreatic juice and pancreatic bicarbonate secretion.

With regard to correlation between duodenal pH and plasma CCK concentration, Chen et al. (1985) reported that in their experiment using dogs, plasma CCK concentration increased when the duodenal pH was lowered by hydrochloric acid. In contrast, Fried et al. (1984) reported that the integrated CCK value and the plasma CCK concentration decreased 120 min after consumption of 60 ml of 45% ethanol by humans. Moreover, Larson et al. (1985) reported the absence of changes in plasma CCK after intragastric or intravenous administration of ethanol to dogs. In our experiment, although the duodenal pH decreased, there was no change or only a slight change in the plasma CCK concentration.

From the above statement, it can be seen that a definitive opinion does not exist about the relationship between plasma CCK concentration and either duodenal pH and ethanol administration. In our study, although elevation of plasma CCK concentration was not observed, a slight increase was noted in pancreatic protein output. As suggested by Noel-Jorand, this result points to a mechanism of parasympathetic-nerve-mediated promotion of pancreatic protein secretion by elevation of the blood ethanol level.

From the above-described results, we conclude that changes in duodenal pH and the pancreatic exocrine stimulation response resulting from upper G-I intraluminal ethanol administration mainly via the mechanism of gastric acid secretion.

References

1) Brooks, F.P. & Thomas, J.E. (1952) The effect of alcohol on canine pancreatic


