

• BASIC RESEARCH •

## Ethanol inhibits the motility of rabbit sphincter of Oddi *in vitro*

Réka Sári, Attila Pálvölgyi, Zoltán Rakonczay Jr, Tamás Takács, János Lonovics, László Czakó, Zoltán Szilvássy, Péter Hegyi

**Réka Sári, Attila Pálvölgyi, Zoltán Rakonczay Jr, Tamás Takács, János Lonovics, László Czakó, Péter Hegyi**, First Department of Medicine, Faculty of Medicine, University of Szeged H-6720, Koranyi fasor 10, Hungary

**Zoltán Szilvássy**, Department of Pharmacology, Medical University of Debrecen H-4032, Nagyerdei krt, 98, Hungary

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**Correspondence to:** Péter Hegyi, M.D., Ph.D., First Department of Medicine, University of Szeged, H-6701, PO Box 469, Hungary. hep@in1st.szote.u-szeged.hu

**Telephone:** +36-62-545200 **Fax:** +36-62-545185

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### Abstract

**AIM:** The role of the sphincter of Oddi (SO) in ethanol (ETOH)-induced pancreatitis is controversial. Our aim was to characterise the effect of ETOH on basal and stimulated SO motility.

**METHODS:** SOs removed from white rabbits were placed in an organ bath (Krebs solution, pH7.4, 37 °C). The effects of 2 mL/L, 4 mL/L, 6 mL/L and 8 mL/L of ETOH on the contractile responses of the sphincter were determined. SOs were stimulated with either 0.1 µmol/L carbachol, 1 µmol/L erythromycin or 0.1 µmol/L cholecystokinin (CCK).

**RESULTS:** ETOH at a dose of 4 mL/L significantly decreased the baseline contractile amplitude from 11.98±0.05 mN to 11.19±0.07 mN. However, no significant changes in the contractile frequency were observed. ETOH (0.6%) significantly decreased both the baseline amplitude and the frequency compared to the control group (10.50±0.01 mN, 12.13±0.10 mN and 3.53±0.13 c/min, 5.5±0.13 cycles(c)/min, respectively). Moreover, 0.8% of ETOH resulted in complete relaxation of the SO. Carbachol (0.1 µmol/L) or erythromycin (1 µmol/L) stimulated the baseline amplitudes (by 82% and 75%, respectively) and the contractile frequencies (by 150% and 106%, respectively). In the carbachol or erythromycin-stimulated groups 2-6 mL/L of ETOH significantly inhibited both the amplitude and the frequency. Interestingly, a 4-5 min administration of 6 mL/L ETOH suddenly and completely relaxed the SO. CCK (0.1 µmol/L) stimulated the baseline amplitude from 12.37±0.05 mN to 27.40±1.82 mN within 1.60±0.24 min. After this peak, the amplitude decreased to 17.17±0.22 mN and remained constant during the experiment. The frequency peaked at 12.8±0.2 c/min, after which the constant frequency was 9.43±0.24 c/min throughout the rest of the experiment. ETOH at a dose of 4 mL/L significantly decreased the amplitude from 16.13±0.23 mN to 14.93±0.19 mN. However, no significant changes in the contractile frequency were observed. ETOH at a dose of 6 mL/L inhibited both the amplitudes and the frequencies in the CCK-stimulated group, while 8 mL/L of ETOH completely relaxed the SO.

**CONCLUSION:** ETOH strongly inhibits the basal, carbachol, erythromycin, and CCK-stimulated rabbit SO motility. Therefore, it is possible that during alcohol-intake the

relaxed SO opens the way for pancreatic fluid to flow out into the duodenum in rabbits. This relaxation of the SO may protect the pancreas against alcohol-induced damage.

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### INTRODUCTION

It is well documented that ethanol (ETOH) can cause acute pancreatitis<sup>[1,2]</sup>, but the mechanisms by which alcohol causes this severe pancreatic injury are not clear. Two main hypotheses have been put forward to explain the role of the sphincter of Oddi (SO) in ETOH induced pancreatitis. One is the obstruction-hypersecretion theory which holds that ETOH induces spasm of the SO and can increase the pressure in the pancreatic ductal system, which may lead to the disruption of small pancreatic ducts. Therefore, pancreatic juice can enter the parenchyma evoking acute pancreatitis<sup>[3,4]</sup>. The other is the duodenopancreatic reflux theory which believes that ETOH reduces the SO motility, thus, the reflux of bile, activated enzymes, or other substances into the pancreatic ducts may cause pancreatitis after alcohol ingestion<sup>[5,6]</sup>. Despite these contradictory theories, no data are available concerning the effect of alcohol on physiologically (postprandial)-stimulated SO motility.

Cholecystokinin (CCK) is generally regarded as the major hormone regulating postprandial SO motility. This regulatory effect of CCK is rather complex. CCK could directly stimulate SO motility in guinea pigs<sup>[7]</sup>, opossum<sup>[8]</sup>, rabbits<sup>[9-11]</sup> and dogs<sup>[12]</sup>. On the other hand, CCK could induce acetylcholine (ACh) and vasoactive intestinal peptide release from pre- and postjunctional sites in the enteric nervous system via CCK<sub>A</sub> and CCK<sub>B</sub> receptors in the canine gastrointestinal tract, which suggests an indirect effect of CCK<sup>[13]</sup>. Others have also demonstrated that the contractile response of the guinea pig SO to CCK consists of a direct effect and an indirect effect mediated by ACh release from postganglionic parasympathetic neurons<sup>[7,14]</sup>.

Motilin is also a key peptide regulating phasic contractile activity of the stomach, duodenum, SO, and gallbladder<sup>[15]</sup>. This regulation is mediated by the migrating myoelectric complex of the gastrointestinal tract<sup>[16]</sup>. Motilin provoked an increase of the SO spike activity in a dose-dependent manner in rabbits<sup>[17]</sup>. Erythromycin, a motilin agonist, has been found to stimulate interdigestive motility of the duodenum and SO in dogs<sup>[18]</sup>, Australian opossum<sup>[19]</sup> and also in humans<sup>[20]</sup>. However, there are no available data concerning the effect of erythromycin on rabbit SO motility.

The parasympathetic nervous system plays an important role in the stimulation of gastrointestinal motility after a meal. The parasympathetic neurotransmitter ACh and its analogues have been shown to stimulate SO motility in different species<sup>[21]</sup>. Furthermore, ACh can be released from postganglionic parasympathetic neurons after hormonal stimuli, as described above.

In this study our aim was to characterise the effects of ETOH on the basal and differently stimulated SO motility in rabbits.

## MATERIALS AND METHODS

### Ethics

The present experiments conformed to the European Guiding Principles for Care and Use of Experimental Animals. In addition, the experimental protocol applied was approved by the local ethical boards of the Universities of Szeged and Debrecen, Hungary.

### Isometric tension measurements

Isometric tension measurements were described in detail previously<sup>[22]</sup>. Biliary SO muscle rings of approximately 6 mm long from adult male New Zealand white rabbits weighing 2–2.5 kg were prepared. The papilla Vateri was eliminated and the ampullary part of the muscle rings of approximately 3 mm long were mounted horizontally on two small L-shaped glass hooks, of which one was connected to a force transducer (SG-O2, Experimetria, Budapest, Hungary) attached to a six channel polygraph (R61 6CH, Mikromed, Budapest, Hungary) for measurement and recording of isometric tension as described<sup>[22]</sup>. One muscle ring was prepared from one animal. The experiments were carried out in an organ bath (5 mL) containing Krebs bicarbonate buffer (in mmol/L: NaCl 118.1, KCl 4.7, MgSO<sub>4</sub> 1.0, KH<sub>2</sub>PO<sub>4</sub> 1.0, CaCl<sub>2</sub> 2.5, NaHCO<sub>3</sub> 25.0, glucose 11.1) which was maintained at 37 °C and aerated continuously with carbogen (50 mL/L CO<sub>2</sub>/950 mL/L O<sub>2</sub>).

### Experimental protocol

The muscle rings underwent brief experimental protocols as follows. Phasic activity of SO: contractile frequencies and their amplitudes were measured over 50 min in each experiment. The initial tension was set at 10 milliNewtons (mN) and the rings were allowed to equilibrate for over 30 min. After that amplitudes and frequencies were recorded for 60 min. In the first 10 min, baseline phasic activity was measured. From the second 10 min, phasic activities were stimulated with 0.1 µmol/L carbachol, 1 µmol/L erythromycin or 0.1 µmol/L CCK. During the last 40 min, ETOH was administered at the doses of 2 mL/L, 4 mL/L, 6 mL/L and 8 mL/L for equal periods (4 times, 10 min). The control SOs received no treatments.

### Drugs and chemicals

All laboratory chemicals (including ions, carbachol, erythromycin, CCK and ETOH) were obtained from Sigma Chemical Company (Budapest, Hungary). CCK and carbachol were dissolved in Krebs solution, while erythromycin was dissolved in dimethyl sulfoxide.

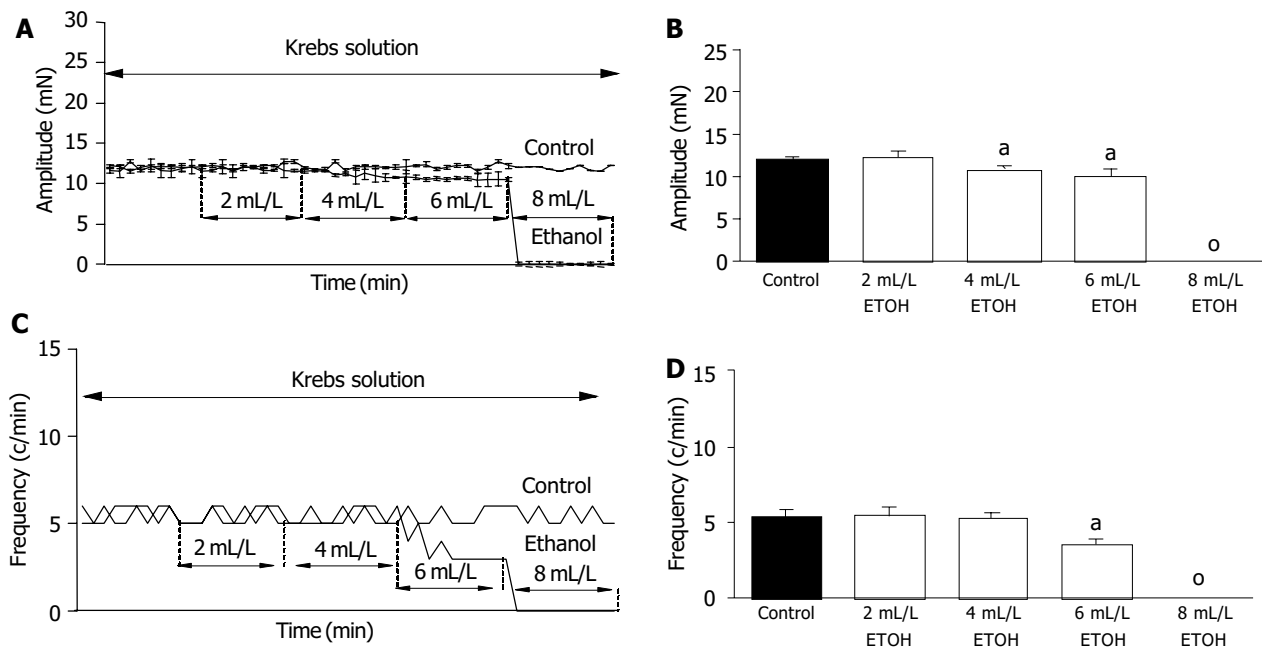
### Data and statistical analysis

Parameters producing the data for evaluation were as follows. The *amplitude of contractions* (mN) was referred to as the difference between peak contractions and relaxations. The average of the amplitudes was calculated every minute (results were expressed as mean±SE, *n* = number of frequencies in a minute). The *frequencies of contractions* (c/min) were calculated every minute. Statistical analysis was performed for 10 min of each of the experiments using either Student's *t*-test (when the data consisted of two groups) or ANOVA (when three or more data groups were compared). Results were expressed as mean±SE, *n* = 5, *P* < 0.05 was considered statistically significant.

## RESULTS

### Effect of ETOH on basal SO motility

The amplitudes and frequencies of the basal SO motility were stable during the control experiments (11.98±0.04 mN and 5.37±0.07 c/min, respectively). ETOH (2 mL/L) had no effects on the baseline amplitudes and frequencies. When ETOH was administered at a dose of 4 mL/L, the baseline amplitude was significantly decreased *vs* the control (11.19±0.07 mN and 11.98±0.05 mN, respectively) (Figure 1A, B). However, no significant changes in the contractile frequency were observed *vs* the control (Figure 1C, D). ETOH (6 mL/L) significantly decreased both the baseline amplitude and frequency *vs* control (10.50±0.01 mN, 12.13±0.10 mN and 3.53±0.13 c/min, 5.50±0.17 c/min, respectively). ETOH (8 mL/L) completely relaxed the SO within 10 s. Therefore, neither the frequencies nor the amplitudes could be detected during the last 10 min of the experiments.



**Figure 1** Basal SO motility inhibited by ETOH. Sphincter of Oddi (SO) was exposed to increasing doses of ethanol (ETOH; 2 mL/L, 4 mL/L, 6 mL/L and 8 mL/L). Each concentration of ETOH was administered for 10 min. A: Effect of ETOH on the baseline amplitude. Representative experiments of the control and the ETOH-treated groups are shown. B: Summary of the effect of ETOH on the baseline amplitude. mean±SE, *n* = 5, <sup>a</sup>*P* < 0.05 *vs* the control; o: no contractile activity. C: Effect of ETOH on the contractile frequency. Representative experiments of the control and the ETOH-treated groups are shown. D: Summary of the effect of ETOH on the contractile frequency. mean±SE, *n* = 5, <sup>a</sup>*P* < 0.05 *vs* the control; o: no contractile activity.

### Effect of ETOH on carbachol-stimulated SO motility

Carbachol (0.1  $\mu\text{mol/L}$ ) stimulated the baseline amplitude by 82% and the contractile frequency by 150%. This carbachol-stimulated SO motility was stable during the experiment (Figure 2A-C). ETOH (2 mL/L) significantly inhibited both the amplitude and frequency vs the carbachol-stimulated group ( $19.42 \pm 1.16$  mN,  $20.81 \pm 0.49$  mN and  $12.32 \pm 0.16$  c/min,  $12.91 \pm 0.10$  c/min, respectively) (Figure 2A-D). ETOH (4 mL/L) further reduced the amplitude ( $13.92 \pm 0.49$  mN) and the frequency ( $9.24 \pm 0.21$  c/min) of the SO motility. ETOH (6 mL/L) decreased the contractile frequency of the SO by 50% ( $4.61 \pm 0.46$  c/min). However, it did not modify the amplitude frequency ( $12.23 \pm 0.22$  mN). Interestingly, a  $4.20 \pm 1.47$  min administration of 6 mL/L ETOH suddenly and completely relaxed the SO.

### Effect of ETOH on erythromycin-stimulated SO motility

Erythromycin (1  $\mu\text{mol/L}$ ) stimulated the baseline amplitude by 75% and the contractile frequency by 106%. This erythromycin-stimulated SO motility was constant over the experiment. ETOH (2 mL/L) significantly inhibited both the amplitude and the frequency vs the carbachol-stimulated group ( $19.10 \pm 0.25$  mN,  $19.65 \pm 0.45$  mN and  $9.66 \pm 0.29$  c/min,  $10.45 \pm 0.20$  c/min, respectively). ETOH (4 mL/L) significantly decreased both the amplitude ( $16.27 \pm 0.33$  mN) and the frequency ( $8.32 \pm 0.22$  c/min), (Figure 2E-H). Administration of 6 mL/L ETOH caused a further decrease in the amplitude and frequency ( $11.85 \pm 0.41$  mN and  $4.10 \pm 0.37$  c/min, respectively). Similar to that seen in the carbachol-stimulated group, a  $4.10 \pm 0.55$  min administration of 6 mL/L ETOH suddenly and completely relaxed the SO.

### Effect of ETOH on CCK-stimulated SO motility

CCK (0.1  $\mu\text{mol/L}$ ) stimulated the baseline amplitude from  $12.37 \pm 0.05$  mN to  $27.4 \pm 1.82$  mN within  $1.60 \pm 0.24$  min. After this peak, the amplitude decreased to  $17.17 \pm 0.22$  mN and was constant during the experiment. The frequency peaked at  $12.8 \pm 0.2$  c/min, after which the constant frequency was  $9.43 \pm 0.24$  c/min throughout the rest of the experiment. ETOH (2 mL/L) mildly decreased the amplitude frequency ( $16.13 \pm 0.23$  mN and  $17.05 \pm 0.14$  mN), but had no effect on the contractile frequency of the SO ( $9.32 \pm 0.15$  mN and  $9.50 \pm 0.31$  mN). ETOH (4 mL/L) further decreased the amplitude frequency from  $16.13 \pm 0.23$  mN to  $14.93 \pm 0.19$  mN, but still had no effect on the contractile frequency of the SO ( $9.82 \pm 0.23$  c/min). ETOH (6 mL/L) further decreased the amplitude and frequency of the SO to  $12.13 \pm 0.11$  mN and  $7.26 \pm 0.27$  c/min, respectively. ETOH (8 mL/L) resulted in complete relaxation of the SO within 10 s (Figure 2 I-L). After this time neither frequencies nor amplitudes could be detected during the remaining part of the experiments.

## DISCUSSION

It has been widely known for a long time that ETOH may evoke acute pancreatitis<sup>[23]</sup>. The role of SO in the pathogenesis of alcohol-induced acute pancreatitis has also been suggested<sup>[3,6]</sup>. However, the effect of ETOH on SO is controversial. On the one hand, it has been demonstrated that ETOH reduces the SO pressure<sup>[3,6]</sup>. On the other hand, alcohol was found to induce spasm of the SO<sup>[24,25]</sup>. These contradictory results indicate that much more information is needed to clarify the effect of ETOH on SO motility.

To investigate these issues, we tested the effect of four different concentrations of ETOH on the resting SO motility. ETOH (2 mL/L) had no effect on the basal SO motility. This result is in accordance with the findings of Cullen *et al.*<sup>[26]</sup>. They reported that ETOH at a dose of 2 mL/L had no significant effect on the baseline amplitude and the contractile frequency of SO in opossum. ETOH (4 mL/L) mildly decreased the baseline amplitude of the spontaneously contracting SO, but had no effect on the contractile frequency. When ETOH concentration

was elevated to 6 mL/L, both the baseline SO contractile amplitude and the frequency were decreased (13%, 34% respectively), while 8 mL/L of ETOH completely relaxed the SO.

Next we tested the effect of different doses of ETOH on physiologically stimulated SO motility (carbachol, erythromycin and CCK). We tested 3 different stimuli at the ED<sub>50</sub> doses. Carbachol was used to mimic the activity of parasympathetic nervous system, while CCK and a motilin receptor agonist erythromycin were administered to mimic neurohumoral stimuli.

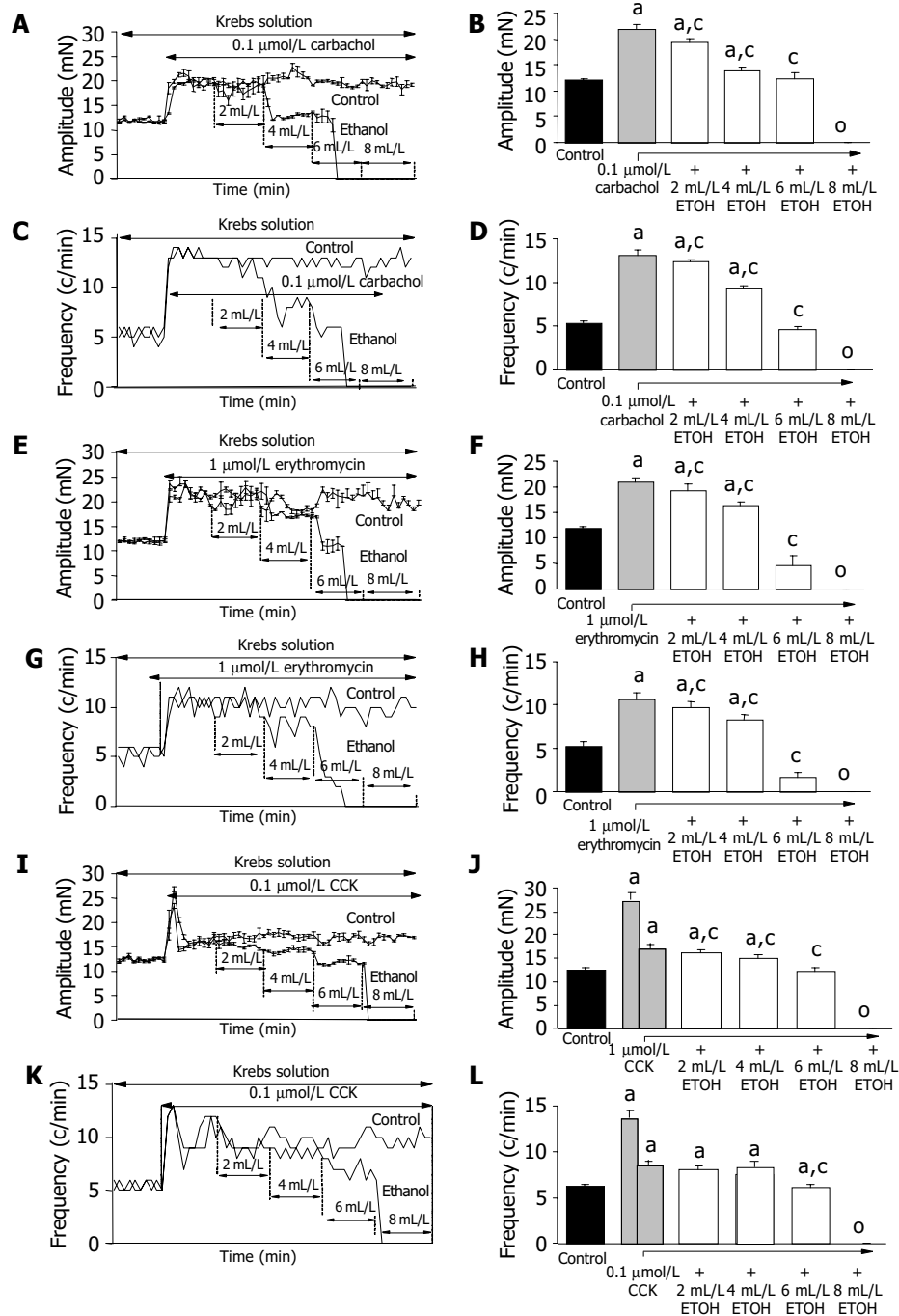
Carbachol (0.1  $\mu\text{mol/L}$ ) stimulated the frequency (150%) and the amplitude (82%) of SO contractions. ETOH (2 mL/L) decreased the baseline amplitude and frequency of the carbachol-stimulated SO by the same rate (12%). ETOH (4 mL/L) decreased the amplitude of SO motility to the basal level, but the frequency still remained elevated. A 4-5 min administration of 6 mL/L ETOH completely relaxed the SO. These results demonstrate that ETOH may inhibit the activity of SO motility stimulated by the parasympathetic nervous system in a dose-dependent manner. Moreover, we can conclude that ETOH has a stronger effect on the contractile amplitude than on the frequency of SO.

The effect of ETOH was almost the same on erythromycin-stimulated as on carbachol-stimulated SO. ETOH (2 mL/L) mildly decreased the baseline amplitude and frequency by 10%. ETOH (4 mL/L) decreased both the amplitude and the frequency of erythromycin-stimulated SO. A 4-5 min administration of 6 mL/L ETOH completely relaxed the SO, as it was found during carbachol-stimulation.

Finally, the effect of ETOH was tested on CCK-stimulated SO motility. CCK stimulated the baseline amplitude and the contractile frequency of SO by 39 % and 74%, respectively. ETOH (2 mL/L) mildly decreased the baseline amplitude (6 mL/L), but had no effect on the frequency of the SO. ETOH (4 mL/L) further decreased the baseline amplitude. Interestingly, 4 mL/L ETOH still had no effect on the contractile frequency. When the concentration of ETOH was increased to 6 mL/L, both the baseline amplitude and the contractile frequency of SO were decreased (29% and 23% respectively). ETOH (8 mL/L) immediately and completely relaxed the SO as it was seen during the study of unstimulated SO.

Taken together, ETOH inhibited the basal and neurally (carbachol), humorally (erythromycin, a motilin agonist) and neurohumorally (CCK) stimulated SO motility in a dose-dependent manner. Viceconte *et al.*<sup>[6]</sup> suggested that alcohol might cause a hormone-mediated relaxation, but they could not exclude a nervous or direct mechanism. Cullen *et al.*<sup>[26]</sup> demonstrated that 2 mL/L ETOH could decrease the frequency of H<sub>2</sub>O<sub>2</sub>-stimulated SO motility. These findings suggest that the main effect of alcohol is direct, independent of a specific neural and/or humoral pathway. Interestingly, we have to note that the inhibitory effect of ETOH was more pronounced during carbachol or erythromycin stimulation than during CCK stimulation. Therefore, we could not totally exclude a marginal specific effect of ETOH. There is no data available concerning the effect of low doses of ETOH on the SO in human. However, gastric absorption accounted for 30% of ETOH administered with food<sup>[27]</sup>, therefore, during a low alcohol-concentrated-fluid (2-5%) intake, small doses of alcohol may be found around the SO. These findings need further investigation.

The inhibitory effect of ETOH on SO motility may have an important pathophysiological role. ETOH has been found to increase basal pancreatic flow rate and protein output<sup>[28,29]</sup>, thus, elevating the intraluminal pressure in the pancreatic ductal system. The relaxation of SO opens the way for pancreatic fluid to flow out into the duodenum, thus, preventing the pancreas from the damage by the elevated intraluminal pressure during acute ETOH administration. It is hard to believe, that a duodeno-pancreatic reflux against the high pancreatic-juice-flow could play a decisive role in the pathogenesis of alcohol-induced



**Figure 2** Effect of ETOH on carbachol, erythromycin, CCK stimulated SO motility. All of the SOs were stimulated by 0.1  $\mu\text{mol/L}$  carbachol for 40 min. Different concentrations of ETOH were administered as described in Figure 1. A: Effect of ETOH on the carbachol-stimulated baseline amplitude. Representative experiments of the control (carbachol-treated) and the ETOH-carbachol-treated groups are shown. B: Summary of the effect of ETOH on the carbachol-stimulated baseline amplitude. mean $\pm$ SE,  $n = 5$ ,  $^aP < 0.05$  vs control,  $^cP < 0.05$  vs the carbachol-stimulated group, o: no contractile activity. C: Effect of ETOH on the contractile frequency. Representative experiments of the (carbachol-treated) and the ETOH-carbachol-treated groups are shown. D: Summary of the effect of ETOH on the carbachol-stimulated contractile frequency. mean $\pm$ SE,  $n = 5$ ,  $^aP < 0.05$  vs control,  $^cP < 0.05$  vs the carbachol-stimulated group, o: no contractile activity. E: Effect of ETOH on the erythromycin-stimulated baseline amplitude. Representative experiments of the control (erythromycin-treated) and the ETOH-erythromycin-treated groups are shown. F: Summary of the effect of ETOH on the erythromycin-stimulated baseline amplitude. mean $\pm$ SE,  $n = 5$ ,  $^aP < 0.05$  vs the control,  $^cP < 0.05$  vs the erythromycin-stimulated group, o: no contractile activity. G: Effect of ETOH on the contractile frequency. Representative experiments of the control (erythromycin-treated) and the ETOH-erythromycin-treated groups are shown. H: Summary of the effect of ETOH on the erythromycin-stimulated contractile frequency. mean $\pm$ SE,  $n = 5$ ,  $^aP < 0.05$  vs the control,  $^cP < 0.05$  vs the erythromycin-stimulated group, o: no contractile activity. I: Effect of ETOH on the carbachol-stimulated baseline amplitude. Representative experiments of the control (CCK-treated) and the ETOH-CCK-treated groups are shown. J: Summary of the effect of ETOH on the CCK-stimulated baseline amplitude. mean $\pm$ SE,  $n = 5$ ,  $^aP < 0.05$  vs the control; o: no contractile activity. In the 0.1  $\mu\text{mol/L}$  CCK-treated group, the first column represents the peak amplitude of contractile frequencies. The second column represents the constant amplitudes after the peak.  $^aP < 0.05$  vs the constant amplitude of the CCK-treated group. K: Effect of ETOH on the contractile frequency. Representative experiments of the (CCK-treated) and ETOH-CCK-treated groups are shown. L: Summary of the effect of ETOH on the CCK-stimulated contractile frequency. mean $\pm$ SE,  $n = 5$ ,  $^aP < 0.05$  vs the control; o: no contractile activity. In the 0.1  $\mu\text{mol/L}$  CCK-treated group, the first column represents the peak of frequencies. The second column represents the constant frequencies after the peak.  $^cP < 0.05$  vs the constant frequency of the CCK-treated group.

acute pancreatitis. Furthermore, it is also well documented that SO relaxants<sup>[30-32]</sup> and endoscopic sphincterotomy<sup>[33,34]</sup> have beneficial effects during acute pancreatitis, which argue against the duodeno-pancreatic reflux theory. All in all, we think that the response of SO motility to ETOH administration is protective against pancreatic injury rather than harmful to the pancreas.

In conclusion, ETOH can strongly inhibit the basal, carbachol, erythromycin, and CCK stimulated SO motility in rabbits, and it is possible that SO opens the way for the pancreatic fluid to flow out into the duodenum. This relaxation of the SO may prevent the pancreas against alcohol-induced damage.

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