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# The Action of Intravenous Ethanol on Gastric Secretion[1] (39925)

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Intravenous infusion of ethanol will stimulate gastric secretion but the mechanism is still uncertain.

Although histamine had been a powerful candidate as the mediator (1) this has been disputed by Daves *et al.* (2). They found that intravenous infusion of ethanol did not increase the histamine concentration in peripheral blood, gastric juice, gastric mucosa, or urine.

Many controversial hypotheses such as direct effect on parietal cells (2) and central stimulation followed by activation of the vagi (3) have been postulated.

Recently Becker *et al.* (4) demonstrated that ethanol caused the release of gastrin into the antral vein. The present experiments were designed to test the hypothesis that gastrin is the mediator through which ethanol stimulates gastric secretion by examining ethanol-stimulated juice for those qualities of composition and pharmacology unique to gastrin.

*Methods.* Nine dogs weighing about 18 kg were used. Four of them had gastric fistulae and Heidenhain pouches, and the other five had gastric fistulae and innervated antral pouches. The former were used in the experiments with ganglionic blocking agents and with the cervical vagal block, and the latter were the subjects for experiments with antral pouch acidification.

Animals were fasted for 18 hr before the experiment and were kept in stands during the experiment. Gastric juice was collected for 10-min intervals by simple drainage from the fistula and by washout technique from the Heidenhain pouch. Samples for pepsin estimation were immediately acidified with 12 M HCl to pH 2 if necessary.

Ethanol was always given as a 10% solution diluted with 0.9% saline by intravenous infusion at a rate of 4 ml/min for 60 min. The ganglionic blocking agent (pentolinium tartrate) was given subcutaneously in doses sufficient to relax the nictitating membrane, usually 1 mg/kg, at the start of the ethanol infusion.

Atropine was given intramuscularly (1 mg), superimposed on the ganglionic blocking agent, after 60 min of the ethanol infusion.

The cervical vagi were blocked by infiltration anesthesia using 2% Xylocaine to both nerves 30 min after starting the ethanol infusion. The completeness of the block was confirmed by observing tachycardia and relaxation of the nictitating membrane.

For antral acidification, 0.1 *N* HCl was pumped at 10 ml/min through the lumen of the antral pouch via a narrow tube. Drainage was by gravity.

In these experiments the ethanol infusion was started after the acid lavage had reduced the resting secretion from the stomach almost to zero. Time-control studies were conducted in each dog on a separate day. In these ethanol was given without any other drugs or treatment for 60 min. In the antral pouch animals, the antral pouch lumen was kept neutral with 0.15 *M* citric acid–Na citrate buffer adjusted to pH 7, which was pumped through it as described above.

The results were compared with those of typical experiments at identical time intervals from the start of ethanol infusion or, in some experiments, increase over pre-ethanol basal secretion was calculated. Basal secretion was collected for at least 30 min before every experiment and the mean of the last two collections was used for calculations. In either case significance was judged by a paired *t* test.

Acid was titrated to pH 7 by Radiometer autotitrator, and pepsin was estimated by Anson's method (5).

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Both acid and pepsin are expressed as output per 10 min.

*Results.* Intravenous infusion of ethanol stimulated fistula acid and pepsin secretion. It also stimulated Heidenhain pouch acid but not pepsin secretion (Table I, Figs. 1 and 2).

After ganglionic blockade, ethanol stimulated neither fistula acid (Fig. 1A) nor pepsin secretion (Fig. 1B). These were not significantly different from the basal secretion and during one collection period after ganglionic blockade fistula acid and pepsin secretion was below basal ($P < 0.05$). Atropine abolished both acid and pepsin secretion from the fistula.

Ganglionic blockade diminished basal pepsin secretion from the pouch (Fig. 2B). Acid secretion from the Heidenhain pouch was less after pentolinium than in the control study but statistical significance was obtained in only one collection period. Indeed, for 40 min from the start of ethanol infusion, pouch acid secretion was higher than the basal secretion.

Atropine brought about a significant decrease down to basal levels in pouch and fistula (Fig. 2A).

Cervical vagal block did not suppress the ethanol-stimulated gastric secretion (Table 2).

In antral pouch dogs, after antral acidification to pH 1, ethanol no longer stimulated fistula acid or pepsin secretion. The small

TABLE I. THE EFFECT OF ETHANOL ON ACID AND PEPSIN SECRETION (CONTROL).[a]

| | Basal ↓[b] | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min |
|---|---|---|---|---|---|---|---|
| Fistula $H^+$ (mequiv/10 min) | | | | | | | |
| Mean | 0.6139 | 0.8501 | 1.911[c] | 2.2573[d] | 2.2037[d] | 1.8739[c] | 1.8178[c] |
| ± SE | 0.1548 | 0.2938 | 0.5509 | 0.40 | 0.4452 | 0.4052 | 0.3807 |
| Fistula pepsin (U/10 min) | | | | | | | |
| Mean | 142.1 | 203.9 | 373.6 | 298.6[c] | 317.0[c] | 384.4 | 379.9 |
| ± SE | 37.0 | 78.6 | 122.4 | 79.7 | 75.3 | 142.7 | 123.9 |
| Pouch $H^+$ (mequiv/10 min) | | | | | | | |
| Mean | 0.1787 | 0.3273[c] | 0.5969[d] | 0.6353[d] | 0.5937[d] | 0.5597[d] | 0.5543[d] |
| ± SE | 0.0148 | 0.0353 | 0.0531 | 0.0482 | 0.0494 | 0.0557 | 0.0727 |
| Pouch pepsin (U/10 min) | | | | | | | |
| Mean | 43.29 | 56.07 | 59.55 | 45.95 | 44.04 | 48.68 | 38.4 |
| ± SE | 8.89 | 14.5 | 11.09 | 7.67 | 9.04 | 14.47 | 7.92 |

[a] Seven experiments on seven dogs.
[b] Arrow indicates the start of ethanol infusion.
[c] Significant increase from basal ($P < 0.05$).
[d] Significant increase from basal ($P < 0.01$).

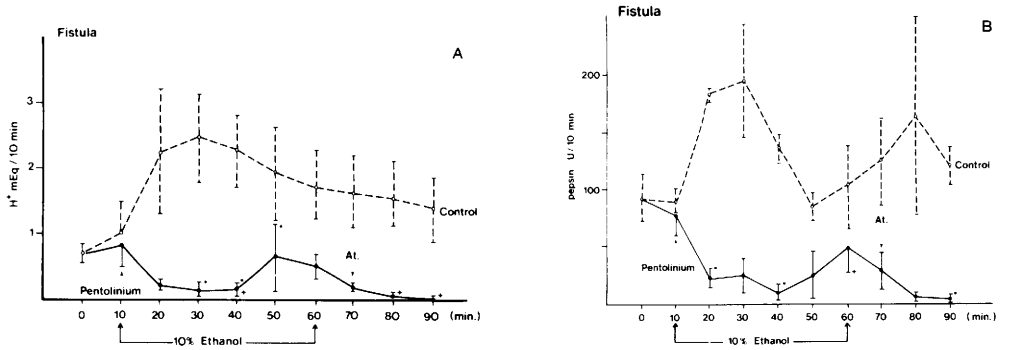


FIG. 1. The effect of intravenous ethanol on fistula acid secretion (A) and on pepsin secretion (B) with and without (control) ganglionic blockade and atropine (At.) in the same dogs. (*) Significantly different from control, $P < 0.05$; (+) significantly different from basal, $P < 0.05$ by paired $t$ test; $n = 4$.

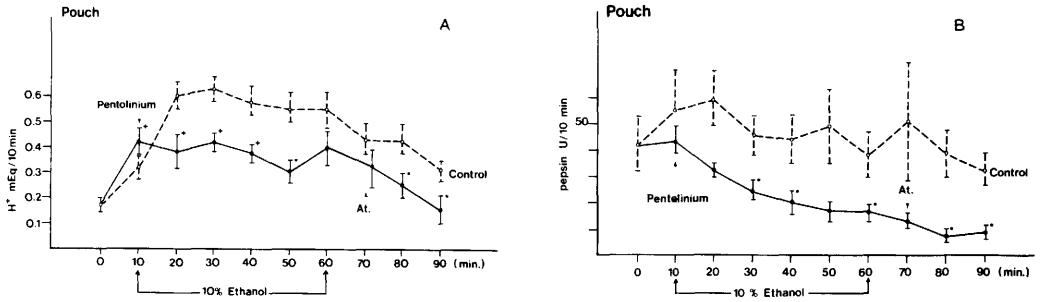


FIG. 2. The effect of intravenous ethanol on Heidenhain pouch acid (A) and pepsin (B) with and without (control) ganglionic blockade and atropine (At.) in the same dogs. (*) Significantly different from control, $P < 0.05$; (+) significantly different from basal, $P < 0.05$ by paired $t$ test; $n = 4$.

TABLE II. THE EFFECT (MEAN ± SE) OF CERVICAL VAGAL BLOCK ON ACID AND PEPSIN SECRETION.[a]

| | C.V.B. | Control |
|---|---|---|
| Fistula $H^+$ (mequiv/10 min) | 1.4779 ± 0.4205 | 0.7108 ± 0.1585 |
| Fistula pepsin (U/10 min) | 147.8 ± 91.6 | 145.1 ± 44.6 |
| Pouch $H^+$ (mequiv/10 min) | 0.3479 ± 0.0353 | 0.2548 ± 0.0316 |
| Pouch pepsin (U/10 min) | 16.95 ± 5.53 | 27.32 ± 5.49 |

[a] Paired comparison yielded no significant difference between vagal block and control.

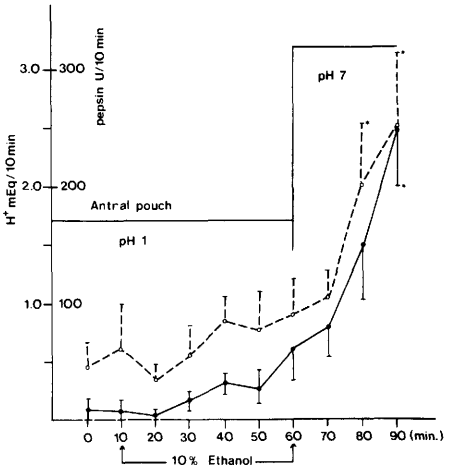


FIG. 3. The effect of intravenous ethanol on fistula pepsin (interrupted line) and acid secretion (continuous line) during antral acidification (pH 1) and subsequent neutralization (pH 7). $n = 4$.

increases in gastric secretion seen after 50 min of ethanol infusion were not significantly greater than the pre-ethanol basal secretion. After the pH in the antral pouch was changed to pH 7, a steep increase in acid and pepsin secretion was observed (Fig. 3).

In one dog, acidification of the antral pouch did not bring about a reduction in basal acid or pepsin secretion (3.541 mequiv/10 min and 589.6 U/10 min, respectively). The data from this dog were eliminated from all the calculations.

*Discussion.* Becker *et al.* (4) have shown that intravenous ethanol raises gastrin levels in blood draining the pyloric antrum in dogs. They did not report an elevation in peripheral blood despite an obvious increase in gastric secretion. Peripheral blood gastrin levels are notoriously poor predictors of gastric secretory activity and by themselves, at the present state of our understanding, offer no firm mechanistic explanation for alteration in gastric secretory activity; e.g., atropine, β-adrenergics, and many other factors raise serum gastrin and depress gastrin stimulated secretion (6, 7). We believe that our data add considerable probability to the idea that intravenous ethanol liberates gastrin which in turn stimulates secretion.

The ethanol-stimulated juice from the gastric pouch in our experiments, like that of gastrin, is low in pepsin when compared with cholinergically stimulated juice and, moreover, ethanol, while it increased Heidenhain pouch acid, did not raise pepsin at all. This is unique to gastrin and pentagastrin stimulation (8).

Acidification of an antral pouch during G-cell stimulation is well known to depress gastrin release as judged by secretion from

a denervated pouch or by serum gastrin levels (9). In our experiments acidification of an antral pouch was found to prevent the secretory response to intravenous ethanol almost totally. That the pouch was still responsive is shown by the 25-fold increase in secretion from the gastric fistula when the antral pH was adjusted to 7.

It has been both proposed and denied by several that ethanol acts centrally via the vagi to stimulate gastric secretion (3, 11, 9). This might occur via vagal stimulation of gastrin release in view of the evidence presented above. If it does, bilateral vagal block in the neck should abolish the effect. Since in our experiments bilateral vagal block was without effect on ethanol-stimulated secretion, a central vagally mediated mechanism seemed unlikely.

The depression of ethanol stimulation by atropine and ganglionic blockade is consonant with the idea of gastrin mediation since atropine depresses the peripheral action of gastrin and ganglionic block impedes its release. The increase in acid secretion, albeit a much reduced one, from the Heidenhain pouch after ganglionic blockade, was unexpected. It may be explained by the failure of pentolinium to block gastrin release completely plus the previously described augmentation of gastrin-stimulated secretion of acid from Heidenhain pouches following ganglionic blockade (11).

Irvine *et al.* (10) have reported that antrectomy had no effect on ethanol-stimulated gastric secretion and Daves *et al.* (2) have actually observed that acidification of the antrum augmented ethanol-stimulated gastric secretion. The absence of gastric fistulae in the animals of these two groups makes interpretation difficult. Woodward *et al.* (12) found that ethanol was still a good gastric-secretory stimulant after antrectomy and small bowel resection. Their experiments were, however, complicated by parental alimentation throughout.

*Summary.* In conscious dogs, intravenous infusion of ethanol stimulated gastric acid secretion both from the gastric fistula and from the Heidenhain pouch and stimulated pepsin secretion from the fistula but not from the pouch. Acute cervical vagal block with infiltration anesthesia had no effect on ethanol-stimulated gastric secretion. After ganglionic blockade (pentolinium tartrate) ethanol stimulated neither acid nor pepsin secretion from the fistula. Ethanol did not stimulate gastric secretion when the antrum was acidified with 0.1 *N* HCl. From these experiments, it was concluded that intravenous ethanol stimulated gastric secretion in the main by liberating antral gastrin.

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