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The Vagus Nerve and its Non-cholinergic Mechanism in the Modulation of Ethanol-induced Gastric Mucosal Damage in Rats

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Abstract—The role of the cholinergic pathway in the vagus nerve in modulating gastric lesion formation by ethanol was examined, using an ex-vivo stomach chamber preparation. Subdiaphragmatic vagotomy significantly increased the lesion areas but lowered acid secretion and gastric mucosal blood flow (GMBF). Atropine had no effect, whereas pirenzepine antagonized ethanol-induced mucosal damage. All three procedures showed similar potencies in depressing acid secretion, but only pirenzepine reversed the fall in the GMBF produced by ethanol. These differential effects of vagotomy, atropine and pirenzepine on gastric function suggest that the cholinergic component in the vagus nerve may not be important in the formation of ethanol-induced gastric damage. The persistent protective action as well as the restoration of ethanol-induced GMBF drop by pirenzepine in vagotomized animals further support this hypothesis. The worsening effect of vagotomy is probably modulated by a non-cholinergic mechanism, the abolition of which makes the gastric mucosa more susceptible to damage by ethanol. The acid-independent protective action of pirenzepine and its influence on the GMBF, which were not exhibited by atropine, are indeed unique and perhaps may be attributed to this non-cholinergic pathway.

Since the vagus nerve plays a dominant role in controlling acid secretion, suppression of its activity by pharmacological (e.g. antimuscarinic drugs) or surgical (e.g. vagotomy) methods has been employed in the treatment of gastric and duodenal ulcers (Hirschowitz 1982). However, in many clinical and experimental investigations, vagotomy has been shown to increase the size of the gastric mucosal lesions, in spite of its effectiveness in acid-suppression (Cho et al 1992; Mozsik et al 1992). Even in cases with successful healing, the high relapse rate as well as other unexpected severe side-effects (including mortality) after vagotomy suggest that it should not be recommended as a treatment of choice for gastric ulcers (Weinberg & McLenathen 1963; Stabile & Passaro 1983); antimuscarinic drugs have, therefore, been a more suitable alternative form of therapy. Atropine, an antimuscarinic drug, reduces the severity of gastric lesion formation (Foschi et al 1986; Cho & Ogle 1991). However, contrasting results have been reported in another study using intragastric treatment with antisecretory doses of atropine (Martinotti et al 1984). These inconsistent observations have raised the question of whether or not blocking the cholinergic component of the vagus nerve is responsible for the modulating action of antimuscarinic drugs, and whether this action is related to the antisecretory property of these agents.

The present study compares the actions of vagotomy, atropine (a muscarinic M_1- and M_2-receptor antagonist) and pirenzepine (a muscarinic M_1-receptor antagonist) on gastric mucosal lesion formation induced by ethanol, in an attempt to clarify the role of the cholinergic component of the vagus nerve in modifying ethanol-evoked gastric damage.

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Materials and Methods

Materials

Male Sprague-Dawley rats, 240–260 g, were housed in an air-conditioned room with constant temperature (22 ± 1°C) and humidity (65–70%). They were fed a standard diet of laboratory chow (Ralston Purina, USA) and had free access to tap water. The animals were starved in individual cages with wide wire mesh floors (to prevent coprophagy) 24 h before starting experiments, but allowed free access to tap water.

Pirenzepine (pirenzepine dihydrochloride; Sigma, St Louis, MO) or atropine (atropine sulphate; Sigma) was dissolved in a 0·9%w/v NaCl (saline) and injected intraperitoneally.

Ex-vivo stomach chamber preparation

The animals were anaesthetized with an intraperitoneal injection of sodium pentobarbitone (Abbott, USA, 60 mg kg^{-1}) and kept warm with heating lamps. Their tracheae were cannulated before a midline laparotomy was carried out. The vagi along the oesophagus were either cut subdiaphragmatically at 45 min before the start of experiments or left intact. An ex-vivo stomach chamber was then prepared (Mersereau & Hinchey 1973), without disturbing the major blood vessels and nerves.

General experimental protocol

After preparation of the ex-vivo stomach chamber, the gastric mucosa forming the base of the chamber was washed with two changes of distilled water. This was followed by a stabilization period of 30 min without further changes of the chamber fluid. The contents of the chamber were then discarded and replaced by 1·5 mL distilled water (0 min). This incubation solution in the chamber was carefully removed after 15 min and replaced with a similar volume of

incubating solution for a further 15 min. The volumes of collected solutions were then measured (inter-sample variation of measurements was 0·6%), and the samples stored at −20°C for subsequent determination of their acid content. The experiments of the core study comprised six sequential 15-min incubation periods; distilled water was used as the incubating fluid from 0 to 60 min, being replaced by 100% ethanol for the fifth and sixth incubation periods from 60 to 90 min. In the first group of animals, the vagi were cut subdiaphragmatically at 45 min before the gastric chamber was incubated with distilled water (first four 15-min incubation periods) and later with ethanol (last two 15-min incubation periods). For the other groups, pirenzepine or atropine (both given in doses of 1 or 2 mg kg^{-1}) or saline (1 mL kg^{-1}) was injected intraperitoneally into vagus-intact animals, 45 min before the start of experiments. A supplementary study on the action of pirenzepine on gastric damage and gastric mucosal blood flow in vagus-intact or vagotomized animals was carried out using a 60-min paradigm, with distilled water incubated during the first two 15-min intervals and 100% ethanol incubated during the last two 15-min intervals. Doses of pirenzepine (0·1, 0·5, 1·0 mg kg^{-1}) or saline (1 mL kg^{-1}) were injected at 0 min to the animals, with or without vagotomy, 45 min before injection.

Measurement of gastric mucosal blood flow

The gastric mucosal blood flow (GMBF) was measured by the laser Doppler technique (Shepherd & Riedel 1982), using a laser Doppler flowmeter (Periflux, Sweden). The same detector was placed 0·5 mm above and perpendicular to the gastric mucosal surface at three locations (anterior and posterior fundus, and antrum) subsequently. Each blood flow measurement was performed with a frequency of 4 Hz over a fixed period of 1·5 ms. The GMBF reading, expressed in arbitrary units, was taken at the end of each 15-min interval on the three designated positions immediately before collecting the incubation fluid. The final values of the GMBF were represented as the mean of the readings of the three locations at each time interval.

Measurement of gastric acid content

Half a millilitre of each collected sample was added to 9·5 mL distilled water; the acid present was measured by titration against 0·01 M NaOH to pH 7·4 using a PHM82 pH meter and a TTT80 autotitrator (Radiometer, Copenhagen, Denmark). Acid content was expressed as μmol H^+ ion secreted per 15 min per 100 mm^2 of glandular mucosal surface area.

Measurement of gastric lesions

Mucosal damage was evaluated immediately after the last measurement of blood flow and collection of gastric solution (at 90 or 60 min, respectively). Lesion severity was determined by measuring the area of the lesions, initially traced on a glass slide using a transparent grid (with 1-mm squares) placed on the slide. Lesion size was also expressed as a percentage of the total glandular mucosal area forming the base of the ex-vivo chamber.

Statistical analysis

The results were expressed as the means ± s.e.m., the differences were analysed for statistical significance using the unpaired Student's *t*-test.

Table 1. Comparison of the effects of vagotomy, atropine, pirenzepine and saline-injected control (vagotomized or given intraperitoneally 45 min beforehand) on gastric acid secretion. Values are means ± s.e.m. (n = 12 for control or vagotomized group, n = 10 for groups with drug pretreatment).

	Gastric acid secretion (H^+ μmol/15 min/100 mm^2)					
Pretreatment	15 min	30 min	45 min	60 min	75 min	90 min
Saline 1 mL kg^{-1}	9·84 ± 0·43	8·09 ± 0·37	7·14 ± 0·50	6·48 ± 0·61	0·22 ± 0·03	0·15 ± 0·02
Vagotomy	1·64 ± 0·31**	0·64 ± 0·13**	0·32 ± 0·06**	0·28 ± 0·05**	0·06 ± 0·03**	0·03 ± 0·01**
Atropine 1 mg kg^{-1}	0·92 ± 0·20**	0·24 ± 0·05**†	0·12 ± 0·02**††	0·13 ± 0·01**††	0·05 ± 0·03**	0·04 ± 0·02**
2 mg kg^{-1}	0·23 ± 0·07**†††	0·12 ± 0·01**†††	0·12 ± 0·02**†††	0·08 ± 0·01**†††	0·03 ± 0·01**	0·03 ± 0·01**
Pirenzepine 1 mg kg^{-1}	0·53 ± 0·19**††	0·24 ± 0·07**††	0·16 ± 0·03**†	0·11 ± 0·01**††	0·09 ± 0·03*	0·02 ± 0·01**
2 mg kg^{-1}	0·32 ± 0·10**††	0·19 ± 0·05**††	0·13 ± 0·02**†††	0·10 ± 0·01**††	0·03 ± 0·01**	0·03 ± 0·01**

*$P < 0·01$, **$P < 0·001$ compared with the saline-injected non-vagotomized control. †$P < 0·02$, ††$P < 0·01$, †††$P < 0·001$ compared with the vagotomized group. Note: distilled water incubation between 0 and 60 min, 100% ethanol incubation between 60 and 90 min.

Table 2. Comparison of the effects of vagotomy, atropine, pirenzepine and saline-injected control (vagotomized or given intraperitoneally 45 min beforehand) on gastric mucosal blood flow. Values are means ± s.e.m. (n = 12 for control or vagotomized group, n = 10 for groups with drug pretreatment).

	Gastric mucosal blood flow (arbitrary units)					
Pretreatment	15 min	30 min	45 min	60 min	75 min	90 min
Saline 1 mL kg^{-1}	33·8 ± 0·7	34·0 ± 0·7	34·2 ± 0·8	34·2 ± 0·8	32·8 ± 0·9	25·9 ± 0·8
Vagotomy	29·7 ± 0·7****	29·1 ± 0·8****	29·2 ± 0·7****	28·7 ± 0·7****	28·4 ± 0·8***	21·8 ± 0·8***
Atropine 1 mg kg^{-1}	32·8 ± 0·5†††	32·9 ± 0·4†††	32·6 ± 0·7†††	32·0 ± 0·8†††	30·8 ± 0·6†	25·0 ± 0·8††
2 mg kg^{-1}	33·2 ± 0·9†††	32·9 ± 0·8†††	32·4 ± 0·8†††	32·6 ± 0·9†††	31·3 ± 0·7††	26·1 ± 0·8†††
Pirenzepine 1 mg kg^{-1}	33·4 ± 0·5††††	33·1 ± 0·7†††	32·8 ± 0·7†††	32·7 ± 0·8†††	32·6 ± 0·9†††	28·7 ± 1·0*††††
2 mg kg^{-1}	32·3 ± 0·8††	32·6 ± 0·9†††	32·5 ± 0·9†††	32·6 ± 0·8†††	32·4 ± 0·8†††	28·8 ± 0·8**††††

*$P < 0·05$, **$P < 0·02$, ***$P < 0·01$, ****$P < 0·001$ compared with the non-vagotomized saline-injected control. †$P < 0·05$, ††$P < 0·02$, †††$P < 0·01$, ††††$P < 0·001$ compared with the vagotomized group. Note: distilled water incubation between 0 and 60 min, 100% ethanol incubation between 60 and 90 min.

Results

The effects of vagotomy, atropine or pirenzepine on gastric secretion

Vagotomy or drug treatment produced the same reductions in volume of gastric collection during the distilled water-incubating periods. Gastric acid secretion was also lowered significantly by vagotomy and by all doses of atropine and pirenzepine; the reduction was greater in the drug-treated groups (Table 1). Inhibition of acid secretion was seen during both the distilled water- and ethanol-incubating periods, with further acid reduction after ethanol administration in all groups.

The effects of vagotomy, atropine or pirenzepine on gastric mucosal blood flow

There was a time-dependent fall in the GMBF after ethanol administration (Table 2). Vagotomy significantly reduced the GMBF throughout the whole experimental period, with no influence on the ethanol-induced GMBF decrease. Atropine neither affected the basal GMBF nor the effect of ethanol on GMBF. Pirenzepine significantly reversed the ethanol-induced fall in GMBF seen during the ethanol-incubation periods, but it did not affect the basal value. Furthermore, this restoration of GMBF was not dose-dependent.

The effects of vagotomy, atropine or pirenzepine on gastric mucosal lesion formation

In ethanol-treated groups, the percentage and total mean lesion areas were significantly increased by vagotomy (Fig. 1). Atropine had no effect, but pirenzepine significantly reduced both parameters.

The comparison of gastric effects of pirenzepine in vagus-intact and vagotomized rats

The protective action and restoration of reduced GMBF after ethanol administration by pirenzepine in vagus-intact animals were consistent with the findings in Fig. 1 and Table 2. A general fall in basal GMBF in all vagotomized groups, either pretreated with saline or pirenzepine was observed when compared with the corresponding vagus-intact groups (Table 3). Nevertheless, the restoration of the ethanol-induced GMBF decrease by pirenzepine was still shown in vagotomized animals by the two higher doses. This effect is possibly related to the persistent gastric mucosal protection against ethanol damage, seen with the same doses of the drug in vagotomized animals.

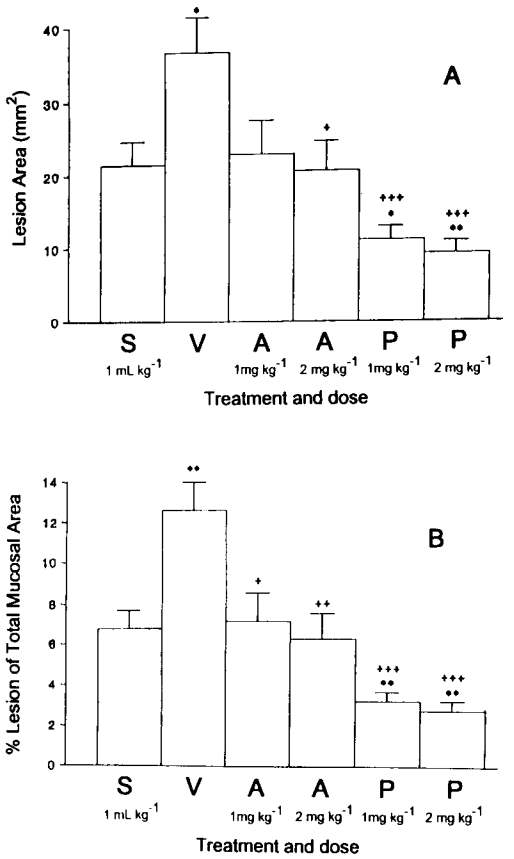

FIG. 1. Comparison of the effects of vagotomy (V) with saline (S), atropine (A) or pirenzepine (P) pretreatment (vagotomy or intraperitoneal injection was carried out 105 min before ethanol administration) on 100% ethanol-induced gastric mucosal damage. A. Lesion area. B. Lesion area as a % of the total glandular mucosal area. Column heights represent the mean value of 12 (controls or vagotomized) or 10 (drug-treated) animals and vertical lines indicate the s.e.m. $*P<0.02$, $**P<0.01$ compared with the saline-injected non-vagotomized control. $\dagger P<0.05$, $\dagger\dagger P<0.01$, $\dagger\dagger\dagger P<0.001$ compared with the vagotomized group.

Table 3. Effect of pirenzepine pretreatment (given intraperitoneally at 0 min) on gastric mucosal blood flow and lesion formation in vagus-intact or vagotomized rats. Values are means ± s.e.m. (n = 10).

	Gastric mucosal blood flow (arbitrary units)				Lesion area (mm^2)	% Lesion of total mucosal area
Pretreatment	15 min	30 min	45 min	60 min		
A. Vagus-intact animals						
Saline 1 mL kg^{-1}	33·2 ± 0·8	33·1 ± 0·9	31·0 ± 0·9	24·8 ± 0·8	18·50 ± 2·00	5·67 ± 0·57
Pirenzepine 0·1 mg kg^{-1}	33·7 ± 0·9	33·4 ± 0·8	31·3 ± 0·8	26·0 ± 0·8	11·50 ± 1·44**	3·46 ± 0·44***
0·5 mg kg^{-1}	33·0 ± 0·6	34·0 ± 0·6	32·7 ± 0·6	28·2 ± 0·8***	9·10 ± 1·29****	2·97 ± 0·46***
1·0 mg kg^{-1}	34·0 ± 0·9	34·0 ± 0·9	34·5 ± 0·9**	28·6 ± 0·8***	8·80 ± 1·98****	2·80 ± 0·64***
B. Vagotomized animals						
Saline 1 mL kg^{-1}	27·8 ± 1·0††††	28·2 ± 1·0†††	27·1 ± 1·0†††	21·9 ± 1·0†	28·90 ± 3·82†	8·95 ± 1·25†
Pirenzepine 0·1 mg kg^{-1}	27·8 ± 0·8††††	27·8 ± 0·9††††	27·0 ± 0·9†††	23·1 ± 0·8††	20·60 ± 3·69†	6·34 ± 1·13†
0·5 mg kg^{-1}	29·2 ± 0·9†††	28·7 ± 1·0††††	29·5 ± 0·9†††	25·8 ± 1·0*	18·10 ± 1·88***†††	5·56 ± 0·62***††††
1·0 mg kg^{-1}	29·3 ± 1·0†††	28·3 ± 1·1††††	29·5 ± 1·3†††	25·6 ± 1·2*	18·00 ± 2·18***†††	5·62 ± 0·70***†††

$*P<0.05$, $**P<0.02$, $***P<0.01$, $****P<0.001$ compared with the saline-injected control in A or B, respectively. $\dagger P<0.05$, $\dagger\dagger P<0.02$, $\dagger\dagger\dagger P<0.01$, $\dagger\dagger\dagger\dagger P<0.001$ compared with the corresponding group of vagus-intact animals in A. Note: distilled water incubation between 0 and 30 min, 100% ethanol incubation between 30 and 60 min.

Discussion

The role of the autonomic nervous system in the protective mechanism of the gastric mucosa against noxious agents is not fully understood. The vagus nerve consists of 90% afferent and 10% efferent fibres, including cholinergic and peptidergic fibres (Hirschowitz 1982). Surgical vagotomy not only terminates the ulcerogenic vagal drive of the cholinergic component, but may also block an unknown protective reflex in this nerve (Holzer & Sametz 1986). This latter property is demonstrated in the present study; vagotomized animals showed an increase in ethanol-induced gastric mucosal damage.

Experimental evidence indicates that the anti-ulcerogenic action of some antimuscarinic agents on different types of gastric mucosal lesions induced by necrotizing agents depends on their antisecretory action, rather than on cytoprotection (Kitagawa et al 1986). On the contrary, the present study demonstrates that both atropine and pirenzepine significantly lower gastric acid secretion, even to a greater extent than vagotomy, but only pirenzepine reduces gastric mucosal damage. These results also suggest that the cholinergic component of the vagus nerve may play an insignificant role in ethanol-induced gastric damage. Furthermore, it is unlikely that the antilesion action of pirenzepine (a specific M_1-receptor blocker) is mediated through cholinergic M_1 receptors, because nonspecific M_1- and M_2-receptor blockade by atropine had no protective action (Fig. 1). These findings suggest that a non-cholinergic mechanism participates in modulating the ulcerogenic action of ethanol.

It has been shown that increased blood flow can render the gastric mucosa more resistant to noxious agents (Robert 1984). In the present study, vagotomy markedly decreased the GMBF and this effect was not seen with atropine and pirenzepine, indicating that a non-cholinergic component of the vagus nerve could play a role in controlling the blood flow in the stomach. Elimination of this factor by vagotomy reduced the GMBF and aggravated ethanol-induced gastric damage (Table 2, Fig. 1). Although it has been reported that the gastric acid level does have some correlation with the GMBF (Holzer et al 1991), this may not be true in all cases. In the present study, antisecretory doses of atropine and pirenzepine did not alter the basal GMBF, although there was reduction in both parameters by vagotomy (Tables 1, 2). The same result was also obtained in another study where no reduction of the GMBF was seen after the administration of three acid inhibitors (Cho et al 1992). Guth et al (1984) found that both gross and histologic injury occurred at 1 min after intragastric alcohol administration, with almost total stasis of blood flow in the injured area. On the contrary, the current study indicates that a significant fall in GMBF occurs only 30 min after ethanol administration (Tables 2, 3). Since the GMBF measurements represent the mean of the readings at three designated positions on the gastric mucosa, the results are more likely to reflect the general haemodynamic changes in the mucosa, instead of only at the lesion sites. Thus, a progressive drop in GMBF was observed in the present study.

Henagan et al (1984) reported that truncal vagotomy reversed the cytoprotective actions of mild irritants and of a prostaglandin E_2 analogue against ethanol-induced gastric damage. However, other investigations have shown that endogenous prostaglandins do not contribute to the protective action of pirenzepine; this has been demonstrated by the inability of indomethacin to block its action (Takeda et al 1985). Also, no change in the mucosal generation of prostaglandins has been observed with such cytoprotection (Konturek et al 1982). Therefore, the requirement of intact vagus nerves in the cytoprotective action of prostaglandins does not apply to the antilesion action of pirenzepine, and this has been shown in the current study (Table 3).

Pirenzepine prevented the fall in GMBF induced by ethanol in both vagus-intact and vagotomized animals (Table 3). This restoration of normal blood flow may have resulted from protection against damage to the vascular bed or the epithelial layer. In a study on gastric mucosal integrity, pirenzepine has been shown to antagonize the reduction of mucosal potential difference and the altered Na^+ ion concentration caused by ethanol (Varin et al 1984). This phenomenon has also been demonstrated in our laboratory (unpublished findings).

A recent report by Holzer et al (1991) has indicated that the capsaicin-sensitive sensory neurons are responsible for signalling the defensive mechanism by improving the mucosal blood flow in the submucosal arterioles, so that deep mucosal injury is prevented. In addition, bilateral cervical vagotomy can significantly reduce the secretory response to gastric distention to the same extent as capsaicin treatment (Raybould & Tache 1989). Thus, taking into account these phenomena, it is possible that vagotomy, by cutting the signal transmission of the capsaicin-sensitive afferent fibres, may influence the defensive mechanism of the gastric mucosa against ethanol-evoked damage.

To conclude, the findings indicate that vagotomy increases gastric damage caused by ethanol. It is unlikely that the cholinergic component of the vagus nerve plays a significant role in the pathogenesis of ethanol-induced gastric mucosal damage. Instead, it is probable that the lesion-aggravating effect of vagotomy is due to disturbance of the GMBF, whereas the protective action of pirenzepine may involve the maintenance of gastric mucosal integrity; both effects are mediated via a non-cholinergic mechanism.

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