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Stimulatory effect of muscimol on gastric acid secretion stimulated by secretagogues in vagotomized rats under anesthesia

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Abstract

The effect of intravenous administration of muscimol, a $GABA_A$ receptor agonist, on gastric acid secretion from perfused stomach was studied in vagotomized rats anesthetized with urethane. Muscimol did not stimulate acid secretion by itself. In contrast, muscimol dose dependently potentiated acid secretion induced by pentagastrin, bethanechol and direct vagal stimulation, but not histamine. Muscimol-potentiated acid secretion induced by pentagastrin and bethanechol was not influenced by pretreatment with atropine or cimetidine, respectively. Muscimol-potentiated acid secretion evoked by direct vagal stimulation was prevented by pretreatment with proglumide, a gastrin receptor antagonist. Muscimol-potentiated acid secretion evoked by bethanechol was dose dependently prevented by bicuculline methiodide, suggesting an involvement of peripheral $GABA_A$ receptors. These results suggest that muscimol stimulates acid secretion under certain conditions, and that two mechanisms are involved in this effect. The effects of muscimol on acid secretion may be mediated by increasing the release of histamine by pentagastrin, bethanechol and direct vagal stimulation. In addition, muscimol would also be effective if muscarinic agents were already occupying muscarinic acetylcholine receptors on parietal cells.

Keywords: Gastric acid secretion; Muscimol; $GABA_A$ receptor

1. Introduction

γ-Aminobutyric acid (GABA) (Yamasaki and Goto, 1989) and various GABAergic agents (Levine et al., 1981; Goto and Debas, 1983; Del Tacca et al., 1990) modulate gastric acid secretion in rats. Their effects are so far thought to be due to the central action of GABA, which is mediated by the vagal parasympathetic pathway.

In the stomach, the secretory cells of the gastric mucosa are known to accumulate GABA (Erdö and Wolff, 1988) and contain GABA-like immunoreactivity (Jessen et al., 1988). More recently, Davanger et al. (1994) showed that GABA colocalizes with gastrin in G cells in rat antral mucosa. The binding studies also suggest that $GABA_A$ receptors are present in all regions of the rat stomach (Erdö et al., 1989, Erdö et al., 1990). Moreover, pharmacological evidence suggests that $GABA_A$ receptors in the gastric mucosa may regulate the secretion of acetylcholine, gastrin (Harty and Franklin, 1986; Harty et al., 1991) and gastric acid (Tsai et al., 1987). These findings demonstrate that GABA may influence the gastric functions by both central and multiple gastric mechanisms.

The peripheral administration of the $GABA_B$ receptor agonist, baclofen, to vagotomized rats is associated with an increase in acid secretion, implying that the extravagal pathways are also involved in this stimulatory effect (Blandizzi et al., 1992). However, the mechanism of influence of parenteral muscimol, a $GABA_A$ receptor agonist, on acid secretion is still unknown.

In order to more accurately characterize the role of $GABA_A$ receptors in the peripheral regulation of gastric acid secretion, the effect of parenteral muscimol in vagotomized rats was investigated in this study.

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Table 1
Effect of muscimol on gastric acid secretion of perfused stomach in rats under urethane anethesia

Drug	Dose and route	Basal level [a]	Acid output (μEq/30 min)		
		(μEq/30 min)	0–30 (min)	30–60 (min)	60–90 (min)
Intact rats					
Muscimol	1 mg/kg i.v.	10.1 ± 1.6	7.6 ± 2.7	7.0 ± 2.4	8.8 ± 3.4
	2 mg/kg, i.v.	7.0 ± 1.7	8.2 ± 2.6	12.9 ± 2.9	13.8 ± 4.1
	4 mg/kg, i.v. [b]	9.5 ± 2.0	12.5 ± 3.1	14.5 ± 3.5	11.6 ± 3.1
	1 μg/rat, i.c.v.	10.5 ± 1.2	13.4 ± 3.8	43.0 ± 1.9 [d]	83.6 ± 13.8 [d]
Vagotomized rats					
Muscimol	1 mg/kg, i.v.	11.1 ± 1.4	6.9 ± 2.9	7.9 ± 2.4	8.2 ± 3.0
	2 mg/kg, i.v.	6.7 ± 1.7	5.6 ± 1.2	3.5 ± 1.4	2.0 ± 0.8
	4 mg/kg i.v. [c]	9.2 ± 2.0	8.7 ± 2.1	7.8 ± 1.7	6.0 ± 1.6
	1 μg/rat, i.c.v.	4.7 ± 2.6	1.6 ± 1.3	0	0

[a] Basal level was 3 times the amount of 10 min before muscimol treatment. [b] Three/six rats were dead. [c] 2/6 of rats were dead. All values are means ± S.E. of six rats per group, except [b] and [c]. [d] $P < 0.001$ compared with the basal level by the paired t-test.

2. Materials and methods

Male Wistar rats weighing 220–270 g were used. The rats were fasted for 24 h before each experiment but were allowed to drink water.

The rats were anesthetized with urethane (1.35 g/kg, i.p.). A cannula was inserted into the trachea, and the esophagus was ligated. The abdomen was then opened, the pylorus ligated and a dual polyethylene gastric cannula was placed through a small incision in the forestomach. The lumen was perfused with saline solution and the perfusate was automatically titrated in the reservoir with 0.01 N NaOH using a pH stat as described previously (Watanabe et al., 1987). The femoral vein was cannulated for administration of drugs. After stabilization of basal acid secretion for usually 30–40 min after the initiation of the gastric lumen perfusion, performing drug or electrical vagal stimulation was given. The basal acid secretion during 10 min before the begining of experiments was about 0–4 μEq/10 min.

Experiments were performed in rats in which the vagus nerve was carefully separated from the carotid arteries and cut at the cervical level at the time of the

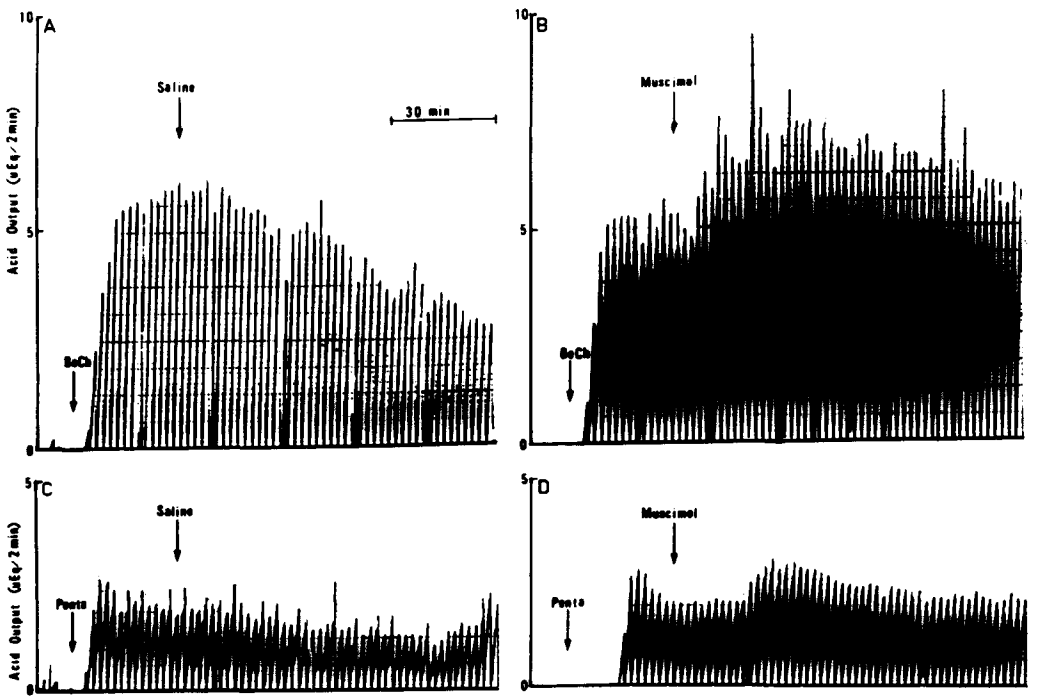

Fig. 1. Typical tracings of acid output measurement demonstrating the potentiating effect of muscimol on acid secretion induced by bethanechol (A and B) and by pentagastrin (C and D). Muscimol (1 mg/kg, i.v.) or saline (0.1 ml/100 g body weight) was administered 30 min after bethanechol (BeCh; 1 mg/kg, s.c.) or pentagastrin (Penta; 2 mg/kg, s.c.). Ordinate scale: rate of acid secretion/2 min. The intragastric perfusate was titrated with 0.01 N NaOH. The titrated volume of the NaOH solution was recorded and expressed in terms of μEq/2 min. Abscissa scale: chart speed was 30 mm/30 min.

experiment. In a group of vagotomized rats, the distal end of the left vagus nerve was stimulated for 120 min with a pair of platinum electrodes at 5 V, 20 Hz and 2 ms.

Cannulation for intracerebroventricular injection: for injection of drugs into the whole cerebroventricles, a stainless steel cannula (outer diameter 0.35 mm) was stereotaxically implanted into the lateral cerebroventricle (with skull flat: 1.0 mm behind bregma; 1.5 mm lateral to the sagittal suture and 4.5 mm vertical), and fixed with dental cement. Each drug solution was applied in a volume of 10 μl over 2 min. At the end of experiments, pontamin sky blue solution was injected into the lateral ventricle to make sure that the solution diffused into the cerebral cavities.

The drugs used were muscimol, bethanechol, histamine, pentagastrin, bicuculline methiodide, atropine, cimetidine (Sigma, St. Louis, MO), and proglumide (Rotta, Italy). All drugs were dissolved in saline.

Except in Table 1, statistical analysis was performed by one-way analysis of variance (ANOVA) coupled with Dunnett's test. While statistically significant difference between the treatment and control was tested by a paired t-test in Table 1, a value of $P < 0.05$ was considered significant.

3. Results

3.1. Effect of muscimol on basal gastric acid secretion

As shown in Table 1, intravenous administration of muscimol (1–4 mg/kg) did not stimulate the basal gastric acid secretion in rats with intact vagus nerve or

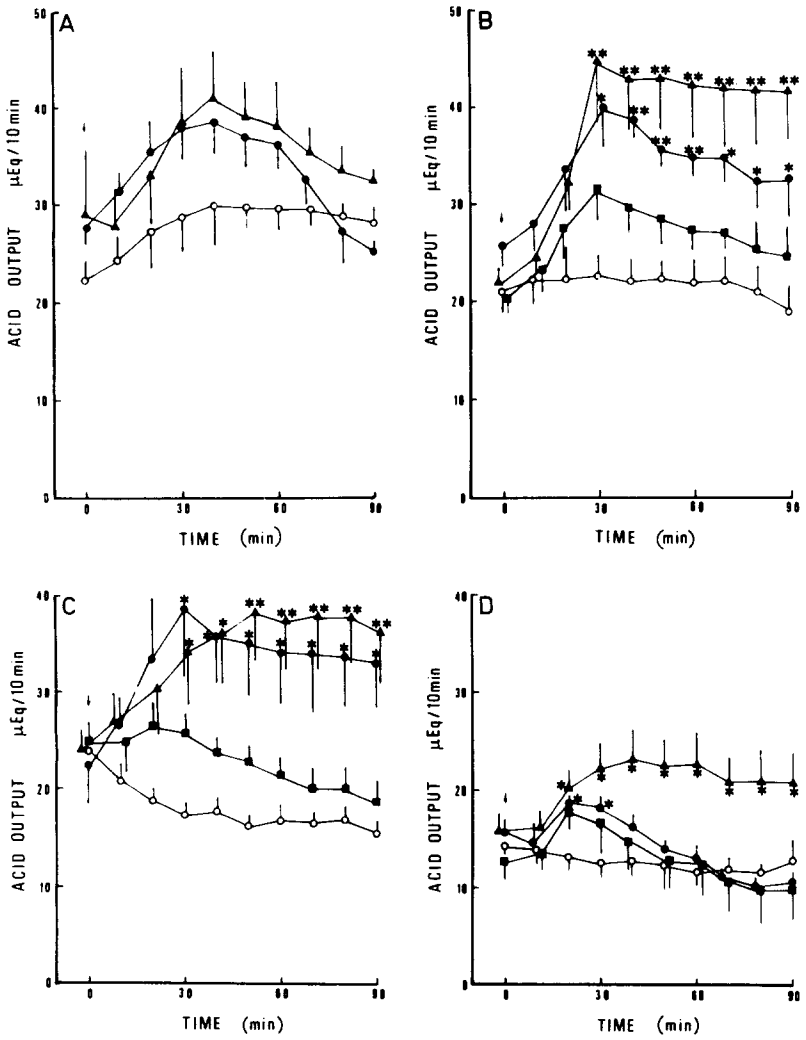

Fig. 2. Muscimol-potentiated acid secretion induced by (A) histamine (10mg/kg, s.c.) (B) vagal stimulation (C) bethanechol (1 mg/kg, s.c.) (D) pentagastrin (2 mg/kg, s.c.). Muscimol was administered i.v. 30 min after secretagogues or vagal stimulation. ○: Saline; ■: muscimol 0.25 mg/kg; ●: muscimol 1 mg/kg; ▲: muscimol 2 mg/kg. All values are means ± S.E. of eight rats. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with saline group in the same period.

Table 2
Effect of bicuculline methiodide (BCM), cimetidine, atropine or proglumide on acid secretion induced by bethanechol, pentagastrin or direct vagal stimulation

Drugs	Dose (mg/kg)	Route	Acid output (μEq/2h)	Control acid output [a] (μEq/10 min)
Bethanechol	1.0	s.c.		
+ Saline	–	s.c.	237.7 ± 1.0	22.8 ± 1.5
+ proglumide	800.0	i.p.	109.0 ± 20.3 [c]	9.8 ± 1.8 [c]
+ cimetidine	2.5	s.c.	91.9 ± 13.8 [c]	8.6 ± 1.2 [c]
+ BCM	1.0	s.c.	254.6 ± 36.3	22.0 ± 2.9
	5.0	s.c.	242.8 ± 27.6	21.0 ± 3.0
	10.0	s.c.	196.8 ± 19.3	17.8 ± 1.1
Pentagstrin	2.0	s.c.		
+ Saline	–	s.c.	174.3 ± 23.1	15.5 ± 1.7
+ Atropine	0.5	s.c.	148.4 ± 14.9	14.0 ± 1.1
+ BCM	10.0	s.c.	167.0 ± 15.1	16.2 ± 3.1
Direct vagal stimulation				
+ Saline	–	i.p.	201.3 ± 26.1	21.1 ± 2.4
+ proglumide	800.0	i.p.	93.9 ± 17.5 [c]	10.5 ± 1.5 [b]
+ cimetidine	2.5	s.c.	99.1 ± 15.1 [c]	8.5 ± 0.8 [c]
+ BCM	10.0	s.c.	208.7 ± 23.0	19.7 ± 0.6

Proglumide, cimetidine or BCM were simultaneously injected with bethanechol or direct vagal stimulation. Atropine or BCM was simultaneously given with pentagastrin. [a] Control acid output: the amount of gastric acid secretion at 20–30 min after secretagogue injection. All values were means ± S.E. of eight rats per group. [b] $P < 0.05$, [c] $P < 0.01$ compared with saline group.

in vagotomized rats. Death was observed when muscimol (4 mg/kg, i.v.) was given. Intracerebroventricular administration of muscimol (1 μg/rat) evoked gastric acid secretion in rats with intact vagus nerve, but not in vagotomized rats.

3.2. Effect of muscimol on gastric acid secretion induced by secretagogues or direct vagal stimulation

Preliminary studies were conducted to establish the effect of secretagogues and vagal stimulation on gastric

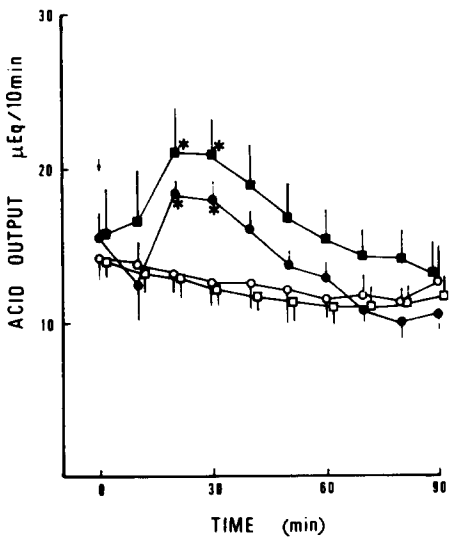

Fig. 3. Effect of atropine on muscimol-potentiated acid secretion induced by pentagstrin. Muscimol (1 mg/kg) was administered i.v. 30 min after pentagastrin (2 mg/kg), and atropine (0.5 mg/kg, s.c.) was injected simultaneously with pentagastrin. □: Atropine + saline; ■: atropine + muscimol; ○: saline + saline; ●: saline + muscimol. All values are means ± S.E. of eight rats. $^{*}P < 0.05$ compared with saline group in the same period.

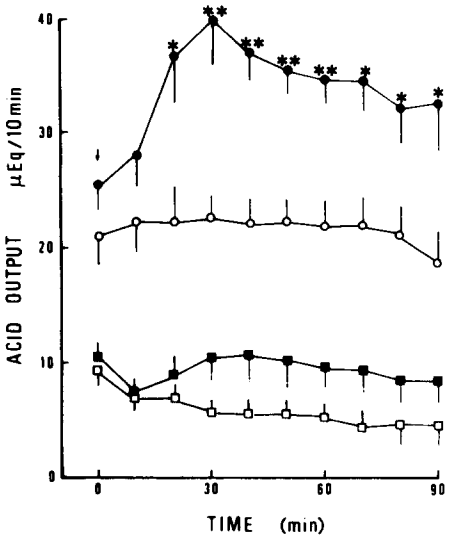

Fig. 4. Effect of proglumide on muscimol-potentiated acid secretion induced by electrical vagal stimulation. Muscimol (1 mg/kg) was administered i.v. 30 min after electrical vagal stimulation, and proglumide (800 mg/kg, i.p.) was injected simultaneously with electrical vagal stimulation. □: Proglumide + saline; ■: proglumide + muscimol; ○: saline + saline; ●: saline + muscimol. All values are means ± S.E. of eight rats. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with saline group in the same period.

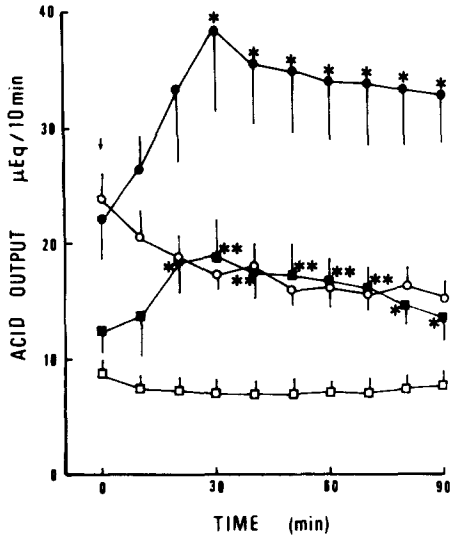

Fig. 5. Effect of cimetidine on muscimol-potentiated acid secretion induced by bethanechol. Muscimol (1 mg/kg) was administered i.v. 30 min after bethanechol (1 mg/kg), and cimetidine (2.5 mg/kg, s.c.) was injected simultaneously with bethanechol. □: Cimetidine + saline; ■: cimetidine + muscimol; ○: saline + saline; ●: saline + muscimol. All values are means ± S.E of eight rats. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with saline group in the same period.

acid secretion. After subcutaneous administration of histamine (10 mg/kg), bethanechol (1 mg/kg) and pentagastrin (2 mg/kg), the gastric acid secretion gradually increased and reached a steady level within 30 min; furthermore, this steady level was maintained for at least 90 min. The same result was obtained when the vagus nerve was continuously stimulated. The acid secretion induced by direct vagal stimulation was completely blocked by atropine (1 mg/kg) when it was i.v. injected at 30 min after electrical stimulation. The amounts of acid output at 20–30 min after histamine, bethanechol, pentagastrin or vagal stimulation were 22.4 ± 2.0 μEq/10 min, 23.9 ± 2.7 μEq/10 min, 14.3 ± 1.6 μEq/10 min or 22.1 ± 2.0 μEq/10 min, respectively.

Muscimol (0.25, 1 and 2 mg/kg) was injected i.v. at 30 min after secretagogue injection or direct vagal stimulation. The secretion stimulated by pentagastrin, direct vagal stimulation or bethanechol, but not histamine, was definitely augmented by muscimol (Figs. 1 and 2). The stimulatory effect of muscimol began about 10 min after the administration, and the maximal effect was observed about 20–30 min after administration.

3.3. Effect of bicuculline methiodide, cimetidine, atropine and proglumide on the effect of muscimol

As shown in Table 2, acid secretion induced by pentagastrin (2 mg/kg, s.c.) was not affected when it was simultaneously administered with atropine (0.5 mg/kg, s.c.). In contrast, acid secretion provoked by direct vagal stimulation or bethanechol (1 mg/kg, s.c.) was partially depressed when it was simultaneously administered with proglumide (800 mg/kg, i.p.) or cimetidine (2.5 mg/kg, s.c.). Acid secretion induced by bethanechol (1 mg/kg, s.c.), pentagastrin (2 mg/kg, s.c.) and direct vagal stimulation were not influenced by bicuculline methiodide which was simultaneously administered with secretagogues or vagal stimulation. The amount of gastric acid secretion at 20–30 min after secretagogues (which were simultaneously administered with the antisecretory agent) was also shown in

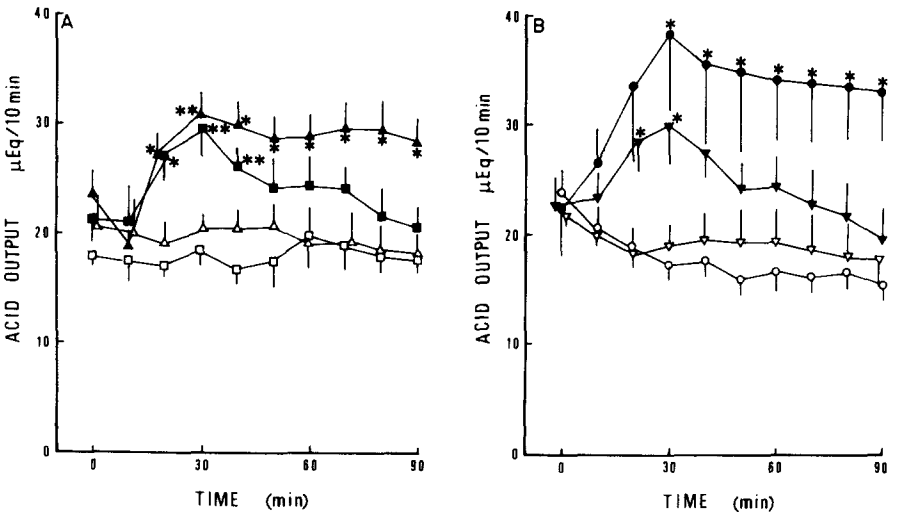

Fig. 6. Effect of bicuculline methiodide (BCM) on muscimol-potentiated acid secretion induced by bethanechol. Muscimol (1 mg/kg) was administered i.v. 30 min after bethanechol (1 mg/kg, s.c.)), and BCM was s.c. injected simultaneously with bethanechol. △: BCM 1 mg/kg + saline; ▲: BCM 1 mg/kg + muscimol; □: BCM 5 mg/kg + saline; ■: BCM 5 mg/kg + muscimol; ▽: BCM 10 mg/kg + saline; ▼: BCM 10 mg/kg + muscimol; ○: saline + saline; ●: saline + muscimol. All values are means ± S.E. of eight rats. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with saline group in the same period.

Table 2. Cimetidine and proglumide significantly depressed the acid output induced by bethanechol and vagal stimulation.

The effect of muscimol (1 mg/kg, i.v.) potentiating the acid secretion evoked by pentagastrin (2 mg/kg, s.c.) was not influenced by pretreatment with atropine (Fig. 3). The effect of muscimol (1 mg/kg, i.v.) augmenting the acid secretion induced by direct vagal stimulation was prevented by pretreatment with proglumide (800 mg/kg, i.p.) (Fig. 4). Pretreatment with cimetidine (2.5 mg/kg, s.c.) did not modify the potentiating effect produced by muscimol (1 mg/kg, i.v.) on acid secretion caused by bethanechol (1 mg/kg, s.c.) (Fig. 5). Pretreatment with bicuculline methiodide (1, 5 and 10 mg/kg, s.c.) dose dependently inhibited the potentiating effect produced by muscimol (1 mg/kg, i.v.) on acid secretion caused by bethanechol (1 mg/kg) (Fig. 6).

4. Discussion

Our findings indicate that muscimol, a $GABA_A$ receptor agonist, potently stimulates acid secretion by pentagastrin, bethanechol and direct vagal stimulation, but not histamine. These results suggest that muscimol may enhance the release of histamine by bethanechol, pentagastrin and direct vagal stimulation.

Central $GABA_A$ receptors are known to play a major role in the regulation of gastric acid secretion (Levine et al., 1981; Del Tacca et al., 1990). The present studies also showed that intracerebroventricular administration of muscimol caused a gastric acid secretion in rats with intact vagus nerve, but not in vagotomized rats. However, Blandizzi et al. (1988) reported that subcutaneous administration of muscimol increased gastric acid secretion, this effect being prevented by i.c.v. bicuculline. These results further support the hypothesis that the acid hypersecretion of muscimol is of central origin. Our studies showed that parenteral muscimol did not stimulate acid secretion in rats with intact vagus nerve or in vagotomized rats. We do not know the reason for the different results obtained by us and Blandizzi et al. (1988). Also, several in vitro studies (Harty and Franklin, 1986; Tsai et al., 1987; Harty et al., 1991) reported that the peripheral $GABA_A$ receptors mediate a stimulatory effect on acid secretion. In the present studies, we further showed that intravenous administration of muscimol was capable of stimulating acid secretion induced by bethanechol, pentagastrin and direct vagal stimulation, but not histamine, in vagotomized rats. Therefore, these results provide evidence of the stimulatory role of peripheral $GABA_A$ receptor in the regulation of acid secretion.

According to the 'transmission hypothesis' for acid secretion, the nervous and hormonal mechanisms in the regulation of acid secretion are mediated by the release of histamine from enterochromaffin-like cells and the subsequent activation of the histamine H_2 receptor of the parietal cell (Black and Shankley, 1987; Marks et al., 1992). In vagotomized rats, muscimol did not affect the acid secretion induced by histamine, suggesting that gastric acid secretion potentiated by muscimol was unrelated to the direct activation of the histamine H_2 receptor on parietal cells.

Gastrin is a potent stimulant of acid secretion. Recently, Waldum et al. (1991) showed that the stimulation of acid secretion by gastrin may be completely explained by the stimulation of histamine release. Experimental results in this study also confirm that acid secretion induced by pentagastrin, a synthesis analogue of gastrin, was markedly inhibited by both proglumide, a gastrin receptor antagonist (data are not shown), and cimetidine. In accordance with this view, the augmentative effect of muscimol on pentagastrin would suggest that muscimol increased the histamine release caused by pentagastrin. Atropine, a muscarinic acetylcholine receptor blocker, can markedly inhibit the acid secretion by bethanechol, a stable choline ester (data are not shown). In the presence of atropine, acid secretion induced by pentagastrin was still augmented by muscimol, indicating that a direct activation by muscimol of muscarinic acetylcholine receptors on parietal cells seems to be excluded.

The acid secretion induced by direct vagal stimulation was considered to totally depend on the release of acetylcholine from vagal cholinergic axon terminals, because of the complete blocking by atropine. Direct vagal stimulation is known to elevate plasma gastrin release from G cells of antrum (Smith et al., 1975; Schubert et al., 1982). In turn gastrin acts mainly by mobilizing histamine (Waldum et al., 1991). This view was also demonstrated by our findings that acid secretion induced by direct vagal stimulation was depressed by both proglumide and cimetidine. In vitro studies (Angus and Black, 1982; Sandvik et al., 1988) showed that electrical vagal stimulation apparently acts on the mucosal histamine-storing enterochromaffin cell via a muscarinic acetylcholine receptor to stimulate gastric acid secretion. Experimental results in this study showed that muscimol markedly potentiated the acid secretion induced by direct vagal stimulation, suggesting that muscimol increased the histamine release caused by acetylcholine and gastrin. In the presence of proglumide, muscimol-potentiated acid secretion induced by vagal stimulation was abolished. This result does not allow specific conclusions, since proglumide was able to counteract the hypersecretory effect evoked by vagal stimulation.

Bethanechol is considered to activate the parietal cells directly (Angus and Black, 1982; Marks et al., 1992), or in part through the release of histamine

(Angus and Black, 1982; Pagani et al., 1985). Various studies (Pagani et al., 1985; Watanabe et al., 1993), including ours, have shown that the portion of secretion induced by bethanechol sensitive to cimetidine may be attributed to the release of histamine. Our results also showed that bethanechol-induced acid secretion was depressed by proglumide, indicating that a stimulation of gastrin release was also involved in the action of bethanechol. Acid secretion induced by bethanechol was augmented by muscimol, suggesting that it increased the release of histamine caused by bethanechol. It appears suprising that muscimol still markedly augmented the acid secretion induced by bethanechol in the presence of cimetidine, while the histamine H_2 receptors were blocked and the hypersecretory effect evoked by bethanechol was depressed. This phenomenon may be explained by the other action of bethanechol, thus it can act directly on parietal cells to stimulate acid secretion. It seems possible that muscimol acted effectively when the muscarinic acetylcholine receptors of parietal cells were occupied by muscarinic agents.

Moreover, a binding study showed that gland cells of the gastric mucosa possess a $GABA_A$ receptor (Erdö et al., 1990), and that gastric mucosa accumulates GABA (Erdö and Wolff, 1988). These findings led us to consider the possibility of endogenous GABA being involved in the acid secretion. Bicuculline methiodide, a $GABA_A$ receptor antagonist, is a quaternary compound; thus, it is considered to act peripherally. Our results showed that s.c. bicuculline methiodide did not influence the acid secretion induced by bethanechol, pentagastrin and vagal stimulation, indicating that endogenous GABA levels were not involved in the excitatory effect of bethanechol, pentagastrin and vagal stimulation. Thirlby and Pleis (1991) also showed that peripheral administration of aminooxyacetic acid, a drug which increases GABA levels, and flumazenil, a drug which decreases GABAergic neurotransmission, did not affect the gastric acid secretion induced by bethanechol in vagotomized rats. However, we observed that bicuculline methiodide dose dependently prevented the potentiating effect of muscimol on bethanechol-induced acid secretion, indicating that $GABA_A$ receptors were involved in the action of muscimol on bethanechol.

In summary, since muscimol failed to potentiate acid hypersecretion evoked by histamine, the enhancing effects exerted by muscimol in the presence of bethanechol, pentagastrin or electrical stimulation could be interpreted in terms of potentiation of endogenous histamine release. Furthermore, muscimol was also effective if bethanechol previously occupied muscarinic acetylcholine receptors on parietal cells, and finally, the effect of muscimol was also related to the $GABA_A$ receptor.

Acknowledgements

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