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HISTAMINE H_2-RECEPTOR MEDIATED STIMULATION OF GASTRIC ACID SECRETION BY MERCAPTOMETHYLIMIDAZOLE

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Abstract—Intraperitoneal administration of mercaptomethylimidazole (methimazole), a potent antithyroid drug belonging to the thionamide group, caused a significant increase in gastric secretion both in control and pylorus-ligated mice. The drug also induced significant stimulation of gastric acid and pepsinogen secretion in both the animal systems studied. The dose–response curve indicated a nearly 10-fold increase in acid output by injection of 0.55 mg mercaptomethylimidazole per 25 g body weight. The duration profile of the drug response at the dose mentioned showed acid secretion almost at a linear rate up to 2.5 hr, after which the response decreased to some extent. Of the other antithyroid drugs of the same family, only thiourea activated acid secretion but the response was much smaller than mercaptomethylimidazole. Histamine, one of the physiological secretagogues of gastric acid secretion, was found to be less active than mercaptomethylimidazole. Mercaptomethylimidazole-induced stimulation of acid secretion could be effectively blocked by prior administration of cimetidine and completely by omeprazole and not by atropine. Verapamil and nifedipine had also some inhibitory effect. These observations indicate that mercaptomethylimidazole stimulates HCl secretion through the involvement of H_2-receptor and through the functioning of the H^+–K^+-ATPase of the parietal cells. The bulk movement of water during increased HCl secretion was partially sensitive to cimetidine and omeprazole and was also associated with an increased secretion of Na^+ and K^+ in the gastric juice. This indicates that mercaptomethylimidazole also induced water transport through a separate mechanism.

Gastric acid secretion is known to be stimulated by several physiological secretagogues such as histamine, acetylcholine and gastrin through the involvement of second messengers, cAMP, Ca^{2+} or inositol triphosphate [1–6]. These messengers activate various cellular protein kinase [7, 8] finally resulting in the stimulation of H^+–K^+-ATPase located in the apical membranes or endoplasmic tubulo-vesicles of the parietal cells [9–13]. This enzyme is now known as the electroneutral H^+/K^+ exchange pump involved in the terminal step of HCl secretion [9, 14]. A variety of compounds inhibits acid secretion working either at the basolateral membrane of the parietal cells such as histamine H_2-receptor antagonists [15] and anticholinergic agents [16] or interacting at the secretory membrane such as inhibitors of H^+–K^+-ATPase [17]. Of the compounds belonging to the second group, omeprazole, a substituted benzimidazole has received considerable attention in recent years as one of the most potent, clinically effective and long-acting gastric antisecretory agents [14, 18–23].

Mercaptomethylimidazole, a potent antithyroid drug is long known to inhibit thyroid hormone biosynthesis through inhibition of thyroid peroxidase [24]. Recently, we observed in the gastric gland proper, the presence of a peroxidase [25] modulated by adrenal glucocorticoids [26]. While studying the possible function of this enzyme in gastric physiology by using mercaptomethylimidazole, an inhibitor of this enzyme [27, 28], we observed that this drug causes a copious flow of gastric secretion containing an almost tenfold higher amount of HCl than normal. In this communication, we present evidence that mercaptomethylimidazole, unlike substituted benzimidazole, is a potent secretory drug which stimulates gastric acid secretion through the involvement of the H_2 receptor and the proton pumping H^+–K^+-ATPase of the parietal cells.

MATERIALS AND METHODS

Materials

Mercaptomethylimidazole (1-methyl-2-thiolimidazole), thiouracil, imidazole, histamine, nifedipine, verapamil, pepsin, albumin and cimetidine were obtained from Sigma (St. Louis, MO) and thiourea from E. Merck, (F.R.G.). Atropine was a product of Aldrich Wisconsin (WI), Omeprazole was a generous gift from Dr. W. Beil of Medizinische Hochschule Hanover, F.R.G.

Methods

Male Balb-c mice weighing around 25 g were fasted for 20 hr with water *ad libitum* prior to intraperitoneal drug administration. The animals were killed by cervical dislocation at the time stipulated, the abdomen was opened and a ligation was made at the pyloric and esophageal end to block the loss of gastric secretion during manipulation to dissect the stomach out. The gastric fluid was collected by flushing the stomach cavity with 2 ml of 0.9% saline through the pyloric end. It was centrifuged at 5000 *g* for 10 min in an RC 5B refrigerated Sorvall cen-

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Table 1. Effect of MMI on the volume of gastric juice secreted in control and pylorus ligated mice

System	Volume of gastric juice secreted (ml) Control	N	MMI-treated	N
Pylorus non-ligated	0.046 ± 0.006	12	0.31 ± 0.025*	15
Pylorus ligated	0.063 ± 0.014†	19	0.34 ± 0.038*†	24

Pylorus ligation was made as described under Materials and Methods: 0.55 mg MMI in 0.1 ml water was injected i.p. in to each of the pylorus non-ligated and pylorus-ligated animals while the control group received 0.1 ml of water as vehicle. The animals were killed after 2.5 hr to collect the gastric juice.

* $P < 0.001$ when MMI-treated data were compared with the respective control value.

† P not significant when data of pylorus ligated animals were compared with those of pylorus non-ligated animals.

trifuge and the clear supernatant was collected in a graduated test tube. The volume above 2 ml was recorded as the volume of the gastric juice secreted.

Pylorus ligation. The experiment was also carried out in pylorus ligated mice to block the loss of gastric fluid if any and also to prevent contamination from intestinal secretions. This was done in mice according to Shay *et al.* [29] with the following modification. The animals were anesthetised with intraperitoneal administration of 0.15 ml aqueous solution of hexabarbital (1.5 mg). Light ether anesthesia may be given during the operation, if necessary. The abdomen was opened, the pyloric end of the stomach was ligated and the abdomen was closed with the help of a few stitches. After 2.5 hr when the animals had overcome operational shock, the drug was injected intraperitoneally and after 2.5 hr the animals were killed by cervical dislocation and the gastric juice collected as described above.

Quantitation of HCl secreted. An aliquot (1 ml) of the clear supernatant obtained after Sorvall centrifugation was titrated with 1 mM NaOH to pH 6.5 using an automatic buret and pH stat from Radiometer Copenhagen to quantitate H^+ secreted in the gastric fluid. The result was expressed as the total mount of H^+ (μmoles) secreted in the gastric fluid. This value was divided by the weight of the stomach to calculate μmoles of H^+ secreted per g of stomach.

Assay of pepsin activity. The amount of pepsinogen secreted in the gastric fluid was assayed as pepsin activity. An aliquot (0.1 ml) of the clear supernatant was assayed according to the method of Anson and Mirsky [30] as modified by Schlamowitz and Peterson [31]. The result was expressed as units of pepsin acitvity using porcine pepsin as standard.

Assay of H^+–K^+-ATPase activity. Stomach was dissected out from a group of at least four animals injected (i.p.) with vehicle or mercaptomethylimidazole (0.55 mg) and killed after 2.5 hr. Mucosa was scraped from fundic region of the stomach after washing with normal saline and blotting the surface with filter paper. Microsomal preparation was made from the homogenate by subcellular fractionation and H^+–K^+-ATPase activity was assayed as described by Im *et al.* [21]. The difference of activity in presence or absence of K^+ was used as a measure of enzyme activity. The result was expressed as μmoles of phosphate liberated/hr per mg protein. Phosphate was determined according to the method of Taussky and Shorr [32] and protein by Lowry *et al.* [33].

Estimation of Na^+ and K^+. Gastric secretions from control and MMI-treated animals were collected with 2 ml of double-distilled water instead of normal saline and clarified by centrifugation at 5000 *g* for 10 min. To 1 ml of the clear supernatant, 0.5 ml of 50% H_2SO_4 was added and heated until it became dark. A few drops of nitric acid were then added and heated again until the solution became colourless. The volume was made up to 4 ml with double-distilled water and used for Na^+ and K^+ estimation by atomic absorption spectrometer after further 10-fold dilution.

Vehicle of the drugs. All the drugs used were in aqueous solution except omeprazole which was dissolved in normal saline containing 25% ethanol and nifedipine in absolute ethanol (to be protected from light). Usually the drugs were prepared in such a concentration that 0.1–0.2 ml of the solution containing the desired amount could be injected. In all cases the same volume of the vehicle was administered to the control animals.

Statistical evaluation. All the data were presented as the mean ± SEM (standard error of mean). Significance was calculated from Student's *t*-test.

RESULTS

Mercaptomethylimidazole (MMI) has been found to be a potent secretory drug inducing a copious flow of gastric juice. The optimum dose of MMI (0.55 mg) caused a significant accumulation of gastric juice, the volume of which was more than sixfold higher than the control secretion in pylorus non-ligated unoperated animals (Table 1). Since the probability exists that some gastric juice may be lost through the pylorus and may be contaminated with other secretions, the effect of MMI on the volume of gastric juice secreted was also studied in pylorus-ligated mice (Table 1). The result shows that although the accumulation of gastric fluid in pylorus-ligated animals was slightly higher than in non-ligated controls, it was not statistically significant. Administration of MMI to the pylorus–ligated animals, also caused significant accumulation of the gastric fluid, the volume of which was more than fivefold higher than the

Table 2. Effect of MMI on gastric acid and pepsinogen secretion in control and pylorus ligated mice

System	μmoles of H^+ secreted				Units of pepsinogen secreted			
	Control	N	MMI-treated	N	Control	N	MMI-treated	N
Pylorus non-ligated	2.3 ± 0.15	118	20.52 ± 1.38*	40	38.6 ± 3.14	102	323.5 ± 20.3*	30
Pylorus ligated	3.05 ± 0.86†	13	17.10 ± 2.67*†	13	293.76 ± 22.67*	13	961.2 ± 83.5*	15

Experimental procedure was exactly the same as that described in the legend of Table 1.

* $P < 0.001$ when MMI-treated values were compared with the respective controls or when pepsinogen data of both control and MMI-treated groups of pylorus ligated mice were compared with those of pylorus non-ligated mice.

† P not significant when data on acid secretion of control and MMI treated groups of pylorus ligated mice were compared with those of pylorus non-ligated mice.

control value. However, no statistically significant difference in the volume of gastric juice between pylorus-ligated and non-ligated animals after MMI administration was noted. This clearly indicates that no significant loss of gastric fluid occurs in control and after MMI treatment in pylorus non-ligated animals if the fluid is collected within 2.5 hr after the drug administration. Table 2 indicates the effect of MMI on gastric acid and pepsinogen secretion in both control (pylorus non-ligated) and pylorus-ligated animals. The result shows that although the acid output in the control group was slightly increased in pylorus ligated animals compared to the non-ligated groups, the increase was not statistically significant. On the other hand, administration of MMI to both pylorus non-ligated and ligated animals caused six- to ninefold stimulation of HCl secretion. Furthermore, the amount of HCl secreted in pylorus ligated animals by MMI was not significantly different from the amount secreted from the pylorus non-ligated animals. However, pepsinogen secretion in pylorus ligated animals was found to be significantly increased (nearly eightfold) in comparison to the non-ligated control animals due to ligation of the pylorus. Although MMI significantly stimulated pepsinogen secretion in both the groups, the stimulation was ninefold higher than control in pylorus non-ligated animals while it was nearly 3.5-fold higher in pylorus ligated groups. Thus the response was much better in pylorus non-ligated animals in comparison to the ligated group although the absolute amount of pepsinogen secreted was higher in the ligated animals. However, apart from the pepsinogen secretion, it is evident from the data presented in Tables 1 and 2 that neither the volume of gastric juice nor the amount of HCl secreted in both control and MMI-treated mice were significantly altered when gastric juice was collected from pylorus non-ligated control animals than when it was collected from the pylorus ligated group. Although pylorus-ligated animals have the advantage of collection of all the gastric juice accumulated, it has the inherent disadvantage that gastric secretion may be altered due to anesthesia, vasovagal reflex, altered secretion of the gastrointestinal hormones due to manipulation of the gastrointestinal tract during operation and operational stress during pylorus ligation. On the other hand, pylorus non-ligated intact animals have the advantage that the gastric secretion is influenced only by the drug administered. This point has also been clarified recently by Wang *et al.* [34] in rats. As our results indicate that the volume of gastric juice as well as the amount of HCl secreted in control and MMI-treated mice in pylorus non-ligated unoperated animals were not significantly different from the pylorus ligated animals, at least during the time period studied, intact mice could be conveniently used for the rest of the experiments to avoid complications due to pylorus ligation mentioned above.

The effect of MMI on the Na^+ and K^+ content of the gastric secretion was also investigated in order to determine whether MMI specifically stimulates H^+ transport from the parietal cells or not. Table 3 shows the effect of MMI on Na^+ and K^+ content of the gastric secretion. The result indicates that MMI also stimulates Na^+ secretion by more than twofold and K^+ secretion by fourfold. This increase in cation transport is not due to any damage of the gastric mucosa as no necrosis was observed after MMI administration. Furthermore, absence of DNA in the gastric secretion indicates that MMI does not cause any damage to the mucosal cells.

Gastric HCl secretion was found to be dependent on the dose of MMI administered as shown in Fig. 1. MMI caused dose-dependent stimulation of gastric acid output at least up to the dose of 0.55 mg above which no further increase in acid secretion occurred. At the optimum dose of 0.55 mg, total acid output was increased by ninefold. Almost similar stimulation was also observed when the acid output was expressed as total H^+ per g of stomach. Duration profile of acid secretion with 0.55 mg MMI indicates that total acid output increased almost linearly with time at least up to 2.5 hr after which it decreased to some extent. At 4 hr after MMI administration, the acid output decreased by 25.3% of the maximum secretion at 2.5 hr. Since MMI is widely used as an antithyroid drug, it was thought interesting to investigate the effect of other antithyroid drugs of the thionamide group on gastric acid secretion. Table 4 shows the relative efficiency of the various antithyroid drugs on gastric acid secretion. Of the three drugs tested, MMI was found to be most potent in acid secretion. Thiourea caused a small but significant increase in acid output while thiouracil had no significant effect. As the acid output by thiourea was much lower than that of MMI, the fluid accumulation was too small to be detected. Unlike MMI, imidazole which is, however, not an antithyroid drug, had no effect on gastric acid secretion.

Table 3. Effect of MMI on gastric Na^+ and K^+ secretion

	Na^+ content (nmol)	N	K^+ content (nmol)	N
Control	180.68 ± 13.15	7	17.6 ± 4.3	4
MMI treated	423.26 ± 44*	13	70.1 ± 12.24†	8

Gastric secretion was collected from control and MMI-treated (0.55 mg MMI in 0.1 ml water injected i.p.) mice and processed for atomic absorption spectrometric determination for Na^+ and K^+ concentration as described under Materials and Methods.
* $P < 0.001$.
† $P < 0.01$.

Table 4. Effect of various antithyroid drugs on gastric acid secretion

	HCl secretion		
	μmoles H^+/g	Total H^+ (μmol)	N
Control	12.0 ± 0.76	2.30 ± 0.15	118
+MMI	97.2 ± 6.25*	20.52 ± 1.38*	40
+Thiourea	24.64 ± 3.67†	5.66 ± 0.92†	13
+Thiouracil	10.67 ± 2.32‡	2.26 ± 0.51‡	14
+Imidazole	10.05 ± 3.25‡	2.0 ± 0.57‡	12

Gastric secretion was collected at 2.5 hr after intraperitoneal administration of 0.1 ml (0.55 mg) of the compound indicated. The control animals received the same amount of water as vehicle.
* $P < 0.001$.
† $P < 0.01$.
‡ P not significant.

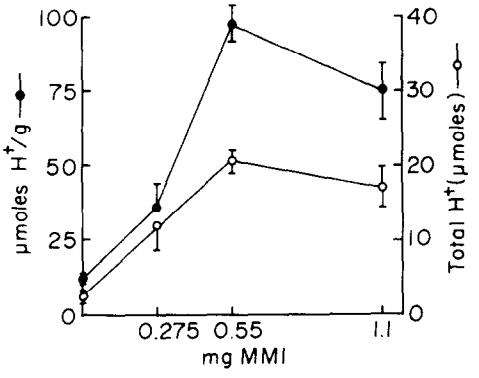

Fig. 1. Dose–response profile of gastric acid secretion after administration of MMI. The animals were injected (i.p.) with 0.1 ml of aqueous solution of MMI containing the amount as indicated. The animals were killed at 2.5 hr to collect the gastric secretion. N = 12–40.

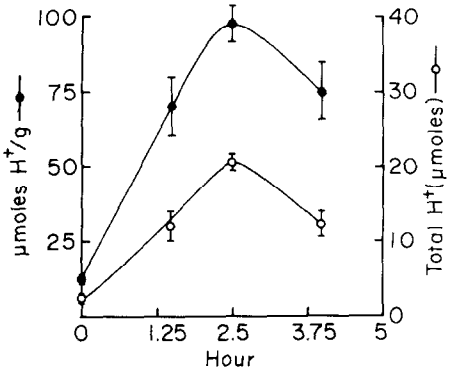

Fig. 2. Duration profile of gastric acid secretion after administration of MMI. The procedure was same as described in the legend of Fig. 1 except that the animals were killed at various time periods as indicated to collect the gastric secretion after administration of 0.55 mg MMI. N = 12–40.

The potency of MMI in inducing gastric acid secretion was compared with a known secretory compound such as histamine. Table 5 shows that MMI was more effective than histamine when HCl secretion was compared under identical conditions. The result shows that MMI was at least five times more active than histamine. However, histamine effect on acid secretion was found to be improved when acid output was measured at 30 min after subcutaneous injection of 1.1 mg histamine. Under this condition, too, histamine was still less potent than MMI.

The mechanism of action of MMI on the stimulation of gastric acid secretion was studied by prior administration of cimetidine, a histamine H_2-receptor antagonist or atropine, the anticholinergic agent known to block HCl secretion induced by physiological secretagogues such as histamine, gastrin and acetylcholine. Table 6 shows that MMI-induced acid secretion was inhibited by 75% by prior administration of cimetidine. Cimetidine, however, had no significant effect on control secretion. Atropine was ineffective in blocking the MMI effect. These data indicate that MMI stimulates acid secretion through the involvement of H_2-receptors of the parietal cells possibly through the liberation of histamine and not through acetylcholine. However, involvement of gastrin working through the H_2-receptor cannot be excluded. The bulk flow of water accompanying increased HCl secretion was also partially blocked with cimetidine but not with atropine. Omeprazole which is known to block the acid secretion through the inhibition of H^+–K^+-ATPase activity of the parietal cells, was found to be most effective as it completely blocked the MMI-induced acid secretion. Omeprazole also caused a significant decrease (~60%) in the volume of the gastric fluid while there was a complete block of acid secretion. The effect of some Ca^{2+} antagonists such as verapamil and

Table 5. Potency of MMI in comparison to histamine in stimulating gastric acid secretion

	Dose (mg)	Route	Duration (hr)	HCl secretion μmoles of H^+/g	HCl secretion Total H^+ (μmol)	N
Control				12.0 ± 0.76	2.3 ± 0.15	118
+Histamine	0.55	i.p.	2.5	18.8 ± 2.12†	3.9 ± 0.71†	12
+MMI	0.55	i.p.	2.5	97.2 ± 6.25*	20.52 ± 1.38*	40
+Histamine	1.1	sc.	0.5	20.2 ± 4.0†	4.6 ± 1.0†	12
+MMI	1.1	sc.	0.5	76.32 ± 12.29*	18.35 ± 3.07*	12

Gastric secretion was collected after administration (0.1 ml) of the compound indicated. The control animals received same amount of water as vehicle.

* $P < 0.001$ when MMI data were compared against control or against histamine.

† $P < 0.05$ when histamine data were compared against control.

Table 6. Effect of various antisecretory agents on MMI-induced gastric acid secretion

	HCl secretion μmoles H^+/g	HCl secretion Total H^+ (μmol)	N
Control	12.0 ± 0.76	2.3 ± 0.05	118
+MMI	97.2 ± 6.25*	20.52 ± 1.38*	40
+Cimetidine + MMI	25.66 ± 5.45*	5.74 ± 1.22*	12
+Atropine + MMI	106.5 ± 7.4†	26.8 ± 2.28†	12
+Omeprazole + MMI	10.83 ± 2.02*	2.75 ± 0.51*	18
+Verapamil + MMI	39.10 ± 6.55*	8.34 ± 1.14*	19
+Nifedipine + MMI	64.80 ± 8.96‡	12.61 ± 1.76‡	16

0.1 ml of a solution of cimetidine (2 mg), atropine (10 μg) or omeprazole (1 mg) was injected (i.p.) into each animal of the respective group 1 hr before the administration of 0.1 ml (0.55 mg) MMI (i.p.) while verapamil or nifedipine (200 μg) was injected (i.p.) 30 min before MMI administration. Animals were killed 2.5 hr after MMI injection to collect the gastric secretion.

* $P < 0.001$ when compared with the respective groups.

† P not significant.

‡ $P < 0.05$ when compared with the respective group.

Table 7. Effect of MMI on H^+–K^+-ATPase activity

	H^+–K^+-ATPase activity (μmol/P_i/hr/mg)	N
Control	5.76 ± 1.38	3
MMI treated (*in vivo*)	4.38 ± 1.56*	3
+MMI 1 mM (*in vitro*)	5.10 ± 1.0*	3

H^+–K^+-ATPase activity was assayed as described under Materials and Methods.

* P not significant.

nifedipine on MMI-induced acid secretion has also been investigated. Verapamil caused 60% inhibition while nifedipine caused around 35% inhibition of MMI-induced acid secretion. As MMI's effect on acid secretion is sensitive to omeprazole, the effect of MMI on H^+–K^+-ATPase activity was studied both in *in vitro* and in *in vivo* experiments. Table 7 indicates that MMI had no significant effect on H^+–K^+-ATPase activity *in vivo*, nor did it alter the activity in *in vitro* experiments.

DISCUSSION

Various secretory and antisecretory compounds are known to alter acid secretion by interaction either with the receptor at the basolateral membrane or with the H^+–K^+-ATPase system at the apical membrane of the parietal cells. Our results indicate that MMI is a potent secretory drug stimulating both acid and pepsinogen secretion along with the bulk movement of water constituting the significant accumulation of gastric fluid both in pylorus ligated and non-ligated animals. Of the antithyroid drugs of the thionamide group, MMI is most effective in inducing both H^+ and water transport and it appears to be more potent than the most common secretory agents such as histamine. It is possible that MMI may have a primary effect of increasing water per-

meability resulting in the accumulation of gastric fluid and distension of the stomach which induces HCl secretion through vagal stimulation. Alternatively, MMI may directly stimulate acetylcholine release and induce HCl secretion. However, prior administration of atropine, the anticholinergic drug, could neither block water transport nor HCl secretion, indicating the absence of the cholinergic involvement in either of the processes. The most interesting observation of the present study is the sensitivity of MMI-induced acid secretion to cimetidine and omeprazole. Cimetidine effectively blocks MMI-induced H^+ secretion (with partial inhibition of water transport) indicating that increased H^+ transport by MMI may be mediated through the interaction of the H_2-receptor of the parietal cells. However, an almost complete block of MMI-induced acid secretion by omeprazole clearly indicates that increased H^+ transport is mediated entirely through the operation of the proton pumping H^+–K^+-ATPase of the parietal cells. A significant decrease (about 60%) in the volume of gastric fluid resulting from the block of acid secretion by omprazole indicates that a major part of water transport induced by MMI is associated with increased HCl secretion to maintain the osmotic balance. The remaining 40% of the water content of the gastric fluid may be due to an independent effect of MMI on the water transport mechanism not sensitive to omeprazole and the accompanying increased secretion of Na^+ in the gastric fluid may be necessary to maintain the osmolarity of the gastric secretion. Alternatively, the increased Na^+ content of the gastric fluid may arise from some back-diffusion of H^+ in exchange with Na^+ while the increased K^+ content may result from increased KCl permeability during stimulated H^+ transport by MMI. However, this is a conjecture and remains to be investigated.

Although secretagogues are known to work through the involvement of cAMP and/or Ca^{2+} which may activate protein kinases [1–8], the precise intracellular mechanism leading to the activation of H^+–K^+-ATPase is not clear yet. Since the MMI effect on acid secretion is sensitive to cimetidine, it appears that MMI is working through the H_2-receptor either directly as H_2-receptor agonist or indirectly through histamine or gastrin liberation. Chemically, MMI looks an unlikely candidate as a direct H_2-receptor agonist. It is therefore more likely that MMI may work through the liberation of histamine or gastrin. Although secretagogues are reported to stimulate HCl secretion at least partially through extracellular Ca^{2+}-entry mechanisms sensitive to calcium antagonists such as verapamil, nifedipine, nicardine and lanthenum [4, 5, 25–37], Chew [38] and Chew and Brown [6] have recently shown that calcium antagonists may inhibit acid secretion nonspecifically and the parietal cells respond to the secretagogues through the increase in the intracellular Ca^{2+} released from some intracellular source. Our studies indicate that MMI-induced acid secretion is more sensitive to verapamil than nifedipine. However, nifedipine is known to be more potent than verapamil with respect to calcium channel antagonism in excitable tissues as well as having no nonspecific effect like verapamil as discussed by Chew [38]. Thus low sensitivity of MMI-induced acid secretion to nifedipine indicates that either the parietal cell calcium channel has a different molecular configuration from that of the excitable cells, as suggested by Chew [38], or, if a Ca^{2+} entry mechanism is involved in MMI-induced acid secretion, it is not playing a major role in the process. Furthermore, increased sensitivity to verapamil may be due to its inhibitory effect on H^+–K^+-APTase through its interaction at the terminal K^+ binding site of the enzyme as shown by Im *et al.* [39]. However, Aadland and Berstad [40] observed no significant effect of verapamil on human gastric secretion *in vivo*. Thus, if the MMI effect is mediated through the liberation of histamine or gastrin, involvement of cAMP and/or Ca^{2+} as intracellular messengers may be anticipated. In that case, an increase in intracellular Ca^{2+} through the release from an intracellular source may play a more major role than a Ca^{2+} entry mechanism. Furthermore, it has been reported that secretagogues may not necessarily stimulate the H^+–K^+-ATPase activity but may bring about changes in the environment of the H^+–K^+-ATPase by transforming light membrane to heavy membrane containing a K^+-dependent H^+ pump and inducing KCl permeability to the latter [13, 41, 42]. Although MMI has no direct effect on H^+–K^+-ATPase activity, the possible role of MMI in membrane transformation resulting in increased KCl permeability and H^+ transport remains to be investigated.

Numerous early reports indicate an association of hyperthyroidism with hypoacidity and achlorohydria although the work is conflicting as both decreased secretion and normal secretion have also subsequently been reported [43]. As the present study indicates that antithyroid drugs like MMI and thiourea have significant effects in stimulating gastric acid secretion, these drugs, if used, may be cautiously applied in hyperthyroid patients with normal secretion or in patients with peptic ulcer. Since our studies indicate that MMI-induced acid secretion could be effectively blocked by well-known antisecretory agents such as cimetidine and omeprazole, this system of producing experimental hyperacidity by MMI may be used as a suitable animal model to find out the antisecretory effect of unknown compound.

The parietal cells of the fundic mucosa have been shown to contain peroxidase [25, 47], the physiological function of which is not clear yet. Mercaptomethylimidazole [27, 28], glucocorticoids [26] as well as indomethacine and acetylsalicylic acid [45] inhibit gastric peroxidase activity and they may stimulate acid secretion either through activation of the H_2-receptor (this study) or through inhibition of prostaglandin biosynthesis [46, 47]. It is tempting to speculate that peroxidase may have some role in the control of gastric acid secretion. We are currently investigating the possible function of the enzyme in parietal cell physiology. However, from the present study, we suggest that mercaptomethylimidazole, one of the most potent gastric secretory agents, stimulates acid secretion either by releasing endogenous histamine or by stimulating the histamine H_2 receptor on the parietal cells. Since both acid

and pepsinogen secretion are stimulated by mercaptomethylimidazole and as gastrin is involved in both the processes, the gastrin-releasing action of mercaptomethylimidazole is also a possibility. Further studies are in progress in this direction.

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