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Elevation of histidine decarboxylase activity in the stomach of mice by ulcerogenic drugs

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Abstract

Histamine is involved in the development of gastric lesions. To examine the contribution of the histamine-forming enzyme, histidine decarboxylase, to drug-induced gastric lesions, we compared the effects of aspirin, indomethacin and dexamethasone on histidine decarboxylase activity in mice. Administration of these drugs, orally or intraperitoneally, elevated histidine decarboxylase activity in the stomach but not in the liver, lung or spleen, dexamethasone being the most potent. In contrast, acetaminophen (a non-ulcerogenic drug) was inactive. These results and our previously reported findings (elevation of histidine decarboxylase activity by lipopolysaccharide, interleukin-1 and tumour necrosis factor, and by different types of stress) suggest that an elevation of histidine decarboxylase activity in the stomach may be a common feature of the responses to ulcerogenic stimuli. The possible participation of histidine decarboxylase in gastric lesions is discussed on the basis of the known actions of histamine, our findings and the effect of histamine H_2 receptor antagonists on histidine decarboxylase activity.

Keywords: Histidine decarboxylase; Stomach; Aspirin; Indomethacin; Dexamethasone; Histamine H_2 receptor antagonist

1. Introduction

The generation of gastric ulcers is a complex area of research and, for the reasons given below, we recently focused on histidine decarboxylase (the histamine-forming enzyme) in the stomach as a possible common factor. Histamine is thought to be the final mediator in the pathway leading to the secretion of gastric acid (Code, 1965; Black et al., 1972) and to play a key role in the development of gastric lesions, because treatment with histamine H_2 receptor antagonists is an effective strategy against gastric lesions (Brunton, 1996). In addition, recent studies have identified two new actions of histamine. First, histamine releases interleukin-16 from $CD8^+$ T cells or epithelial cells: interleukin-16 may induce migration of $CD4^+$ cells such as monocytes, eosinophils and T cells (Center et al., 1996), while eosinophils have a possible role in gastric ulcer formation (Otani et al., 1997; Ohmiya et al., 1997; Hunyady et al., 1996; Niemela et al., 1995). Second, histamine induces Th1-suppressed–Th2-promoted responses (Elenkov et al., 1998; Van Der Pouw Kraan et al., 1998), thus facilitating the development or prolongation of *Helicobacter pylori* infection (Karttunen et al., 1997).

The primary storage site for histamine in the stomach has been shown to be the enterochromaffin-like cells (Håkanson et al., 1986; Nissinenn et al., 1992). Feeding not only stimulates the release of histamine from enterochromaffin-like cells but also increases its synthesis by elevating histidine decarboxylase activity (Kahlson et al., 1964; Kahlson and Rosengren, 1968; Rosengren and Sevensson, 1969). The release and formation of histamine following feeding has been shown to be mediated by gastrin, which in turn stimulates the formation of histidine decarboxylase-mRNA (Kahlson et al., 1964; Håkanson et al., 1974; Dimaline et al., 1993).

Interestingly, some ulcerogenic stimuli, such as stress, non-steroidal anti-inflammatory drugs and steroids, have also been reported to induce histidine decarboxylase in the stomach of rats (Schwartz et al., 1966; Bouclier et al., 1983c; Araki et al., 1991). We recently found that some types of stress elevate histidine decarboxylase activity selectively in the stomach of mice, too (Ayada et al., 2000).

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Surprisingly, anti-secretagogues (histamine H_2 receptor antagonists and proton-pump inhibitors) and $NaHCO_3$ (an antacid) also elevate gastric histidine decarboxylase activity in rats (Maudsley et al., 1973, 1974; Bouclier et al., 1983a; Ryberg et al., 1989; Ding et al., 1996). Moreover, careless or sudden withdrawal of these drugs often brings about a recurrence of ulceration (Douglas, 1980).

H. pylori (or its lipopolysaccharide), and its promotion of interleukin-1 or tumour necrosis factor production, may be involved in the generation of gastric lesions (Crabtree et al., 1991; Padol et al., 2001). We previously found that in mice, injection of lipopolysaccharide, interleukin-1 or tumour necrosis factor not only retarded gastric emptying but also elevated gastric histidine decarboxylase activity (Endo and Kumagai, 1998). However, these inflammatory stimuli induce histidine decarboxylase in other tissues, too, such as liver, lung, spleen and bone marrow (Endo et al., 1992a). The induction of histidine decarboxylase activity by these stimulators occurs via the formation of new histidine decarboxylase-mRNA (Kikuchi et al., 1997).

Collectively, the above results led us to the idea that an elevation of gastric histidine decarboxylase activity might be a common feature of the responses to ulcerogenic drugs. However, we felt that to test this hypothesis, more data from experiments using other ulcerogenic agents and other species were needed, thus enabling us to compare their effects. In the present study with mice, therefore, we compared the effects on histidine decarboxylase activity of five drugs: two typical non-steroidal anti-inflammatory drugs currently in common use (aspirin and indomethacin), a typical synthetic glucocorticoid (dexamethasone) and two histamine H_2 receptor antagonists currently in clinical use (cimetidine and ranitidine). We also examined the effect of acetaminophen, because this drug is not ulcerogenic, although it shares some actions with aspirin (it is antipyretic and analgesic) (Insel, 1996). Surprisingly, we could find no documentation on the effects of aspirin, indomethacin or acetaminophen on gastric histidine decarboxylase activity. Moreover, the effects of the above drugs in laboratory animals have been mostly observed after their intraperitoneal or subcutaneous injection. Consequently, in the present study, we examined the effect of oral drug administration, too.

2. Materials and methods

2.1. Animals

Male BALB/c mice (6–7 weeks old) were obtained from our university facility for experimental animals. They were kept under a conditioned light (7 a.m. to 7 p.m.)/dark cycle and given food and water ad libitum until the morning of the experiment. All procedures conformed to the *Guidelines for Care and Use of Laboratory Animals* of Tohoku University. At 0830 h on the day of the experiments, all mice were moved to cages (five to six mice per cage) with new wood-chip bedding and were kept there for 5 h without food but with free access to water. Experiments were started at between 1330 and 1430 h. During the experiment itself, the mice were deprived of both food and water.

2.2. Materials

Aspirin, indomethacin, acetaminophen, dexamethasone 21-phosphate (disodium salt), cimetidine and ranitidine were purchased from Sigma (St. Louis, MO, USA). For intraperitoneal injection, they were each dissolved in sterile saline, the pH of each solution being adjusted to 6.5–7.5 with NaOH or HCl solution, and they were injected at 0.1 ml per 10 g body weight. For oral administration, they were dissolved or suspended in saline and administered at 0.1 ml per 10 g body weight.

2.3. Assay of histidine decarboxylase activity

Histidine decarboxylase activity was assayed using our previously described method (Endo, 1983) with a slight modification (Endo et al., 1998). Briefly, mice were decapitated and the tissues (whole stomach, liver, lungs and spleen) were then rapidly removed and stored at −80 °C. Each stomach, having been cut open with scissors, was washed in ice-cold saline, blotted on a filter paper and stored at −80 °C. Each tissue sample (less than 250 mg) was put into a cooled Teflon tube with phosphorylated cellulose and 2.5 ml of ice-cold 0.02 M phosphate buffer (pH 6.2) containing pyridoxal 5′ -phosphate and dithiothreitol, and then homogenised. The supernatant obtained after centrifugation of the homogenate was used as the enzyme solution. Reaction mixture (1 ml) containing the enzyme solution was incubated at 37 °C for 4 h with histidine. After the enzyme reaction had been terminated by adding $HClO_4$, the histamine formed during the incubation was separated by chromatography on a small phosphorylated cellulose column, then quantified fluorometrically as previously described (Endo, 1983). Histidine decarboxylase activity was expressed as nanomoles of hista-

Table 1
Dose-dependent elevation of histidine decarboxylase (HDC) activity induced by intraperitoneal or oral administration of aspirin and indomethacin

Reagents	Dose (mg/kg)	HDC activity (nmol/h/g)	
		Intraperitoneal	Oral
Saline		4.9 ± 1.5 (0/4)[a]	4.5 ± 1.0 (0/4)[a]
Aspirin	50	7.9 ± 2.3 (0/4)	
	100	9.0 ± 0.4[b] (0/4)	5.5 ± 1.2 (0/4)
	200	11.8 ± 3.3[b] (0/4)	7.7 ± 2.0[b] (0/4)
Indomethacin	5	10.6 ± 2.7[b] (0/4)	
	10	13.5 ± 3.4[b] (0/4)	8.5 ± 1.3[b] (0/4)
	20	18.2 ± 3.4[b] (0/4)	12.9 ± 2.3[b] (3/4)

Stomachs were removed 4 h after the administration of aspirin, indomethacin or saline. The values are means ± S.D. from four mice.

[a] Incidence of haemorrhage in the stomach.

[b] $P < 0.01$ vs. saline group.

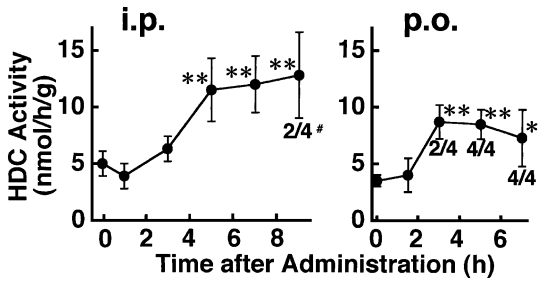

Fig. 1. Time course of the elevation of histidine decarboxylase (HDC) activity in the stomach following intraperitoneal (left) or oral (right) administration of indomethacin (20 mg/kg) to mice. Mice were killed at the indicated times. The values are means ± S.D. from four mice. Note different scales in the two panels. *$P<0.05$ or **$P<0.01$ vs. time 0. #Incidence of haemorrhage in the stomach.

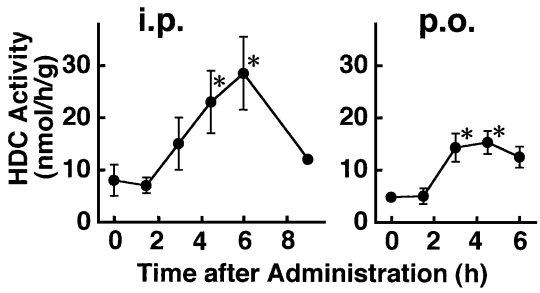

Fig. 2. Time course of the elevation of histidine decarboxylase (HDC) activity in the stomach following intraperitoneal (left) or oral (right) administration of dexamethasone (1 mg/kg) to mice. Mice were killed at the times indicated. The values are means ± S.D. from four mice. Note different scales in the two panels. **$P<0.01$ vs. time 0.

mine formed during 1 h of incubation by the enzyme contained in 1 g (wet weight) of each tissue (nmol/h/g). Histidine decarboxylase activity in bone marrow is expressed as the activity in 1 g (wet weight) of tibia plus femur, because these tissues were subjected to the assay without separating the bone marrow (Endo et al., 1992b).

2.4. Observation of gastric injury

Methods do exist for quantifying gastric lesions in rats, including measurement of the necrotic area after fixation in formalin solution. However, we could not use this method, because formalin denatures enzyme proteins and because we needed to freeze the stomach rapidly after its removal for the assay of histidine decarboxylase activity. Therefore, we counted the number of red spots on the gastric mucosa (Bouclier et al., 1983c) through a magnifying glass when each stomach was put into a glass tube to be washed with cold saline (see the above section). Any haemorrhagic gastric lesion present was quantified as follows: none (0 red spots), slight (1–3 red spots), medium (4–6 red spots) or strong (>7 red spots).

2.5. Data analysis

Experimental values are given as means ± standard deviation (S.D.). The statistical significance of differences was analysed by an unpaired *t* test after an analysis of variance: *P* values less than .05 were considered to indicate significance.

3. Results

3.1. Effects of aspirin, indomethacin and acetaminophen

The intraperitoneal or oral administration of aspirin or indomethacin elevated histidine decarboxylase activity in the stomach in a dose-dependent manner at 4 h after the injection (Table 1). Indomethacin enhanced histidine decarboxylase activity in the stomach at lower doses than did aspirin. In addition, oral administration of indomethacin, but not aspirin, produced haemorrhage (slight to moderate) in the stomach at 20 mg/kg. The time course of the histidine decarboxylase elevation in the stomach induced by intraperitoneal or oral administration of indomethacin is shown in Fig. 1. An intraperitoneal injection of indomethacin at 20 mg/kg produced no detectable gastric lesion at 1 to 7 h, although it caused haemorrhage (slight to moderate) in two out of four mice at 9 h after the injection (Fig. 1A). Oral administration of indomethacin at the same dose produced haemorrhage (slight to moderate) in the stomach in all four mice within 5 h (Fig. 1B). Neither aspirin nor indomethacin produced a significant elevation of histidine decarboxylase activity in the liver, lung or spleen (data not shown). There

Table 2
Dose-dependent elevation of histidine decarboxylase (HDC) activity in the stomach induced by intraperitoneal or oral administration of dexamethasone

Dose of dexamethasone (mg/kg)	HDC activity (nmol/h/g)	
	Intraperitoneal	Oral
Saline	3.6 ± 1.8	2.3 ± 1.5
0.04	6.9 ± 3.9	
0.2	8.6 ± 2.7[a]	5.4 ± 2.0[a]
1.0	15.4 ± 3.0[a]	7.9 ± 2.0[a]
5.0		9.5 ± 0.7[a]

Mice were killed 4 h after the administration of dexamethasone or saline. The values are means ± S.D. from four mice.
[a] $P<0.01$ vs. saline group.

Table 3
Effect of intraperitoneal administration of cimetidine on histidine decarboxylase (HDC) activity in mouse tissues

	HDC activity (nmol/h/g)	
	Saline	Cimetidine
Stomach	3.6 ± 1.1	9.0 ± 0.5[a]
Liver	<0.2	<0.2
Lung	<0.5	<0.5
Spleen	<1	<1

Tissues were removed 3 h after intraperitoneal injection of cimetidine (50 mg/kg) or saline. The values are means ± S.D. from four mice.
[a] $P<0.01$ vs. saline-injected control.

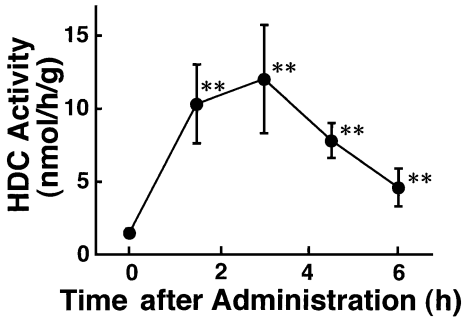

Fig. 3. Time course of the elevation of histidine decarboxylase (HDC) activity in the stomach following oral administration of ranitidine (50 mg/kg) to mice. Mice were killed at the times indicated. The values are means ± S.D. from four mice. $^{**}P<0.01$ vs. time 0.

was no significant elevation of gastric histidine decarboxylase activity and no gastric haemorrhage at 4 h after oral administration of acetaminophen (100 and 200 mg/kg) (data not shown).

3.2. Effect of dexamethasone

Intraperitoneal or oral administration of dexamethasone also elevated histidine decarboxylase activity in the stomach (Table 2), with even 0.2 mg/kg of this agent producing a significant elevation. Like indomethacin, dexamethasone produced a significant elevation of histidine decarboxylase activity 3–6 h after its intraperitoneal or oral administration (Fig. 2). However, unlike indomethacin, dexamethasone did not produce haemorrhage in the stomach. Like aspirin and indomethacin, dexamethasone did not elevate histidine decarboxylase activity in the liver, lung or spleen (data not shown).

3.3. Effect of the histamine H2 receptor antagonists, cimetidine and ranitidine

Intraperitoneal administration of cimetidine also elevated histidine decarboxylase activity in the stomach within 3 h of its injection (Table 3). This H_2 blocker (like aspirin, indomethacin and dexamethasone) failed to elevate histidine decarboxylase activity in the liver, lung or spleen. Oral administration of ranitidine also elevated gastric histidine decarboxylase activity (Fig. 3) and this elevation was more rapid than that induced by indomethacin (Fig. 1) or dexamethasone (Fig. 2), a near-maximum histidine decarboxylase elevation being seen 1.5 h after oral administration of ranitidine. In the present study, neither of these H_2 receptor antagonists produced haemorrhage in the stomach.

4. Discussion

In the present study, we found that when aspirin, indomethacin, dexamethasone, cimetidine or ranitidine were given intraperitoneally or orally, they all increased gastric histidine decarboxylase activity in mice. In terms of their effects on histidine decarboxylase activity, these drugs were all selective for the stomach. Acetaminophen, a non-ulcerogenic drug, was inactive in elevating gastric histidine decarboxylase activity. These results suggest that an elevation of histidine decarboxylase activity in the stomach may be a common effect of ulcerogenic drugs. In the following sections, we discuss both the possible mechanisms underlying the elevation of gastric histidine decarboxylase activity induced by these drugs and the possible implications of our findings.

A unique defence system has developed in the stomach, its role being to guard against the undesirable effects of foreign materials, including bacteria, which often enter the stomach together with food. The secretion of HCl, a strong acid, is an effective strategy against such foreign materials. However, because HCl attacks the gastric mucosa itself, a specific protective system is needed within the stomach. This system includes the prostaglandins (Brunton, 1996), of which prostaglandin I_2 and prostaglandin E_2 serve as cytoprotective factors in the gastric mucosa. They inhibit acid secretion, enhance mucosal blood flow via dilatation of fine blood vessels and promote the secretion of cytoprotective mucus (Insel, 1996). Hence, the pathophysiology of gastric lesions is believed to involve an imbalance between aggressive factors (HCl and/or pepsin) and local mucosal defence systems, including prostaglandins (Brunton, 1996). Stress, substances such as non-steroidal anti-inflammatory drugs, infection by *H. pylori*, overeating, alcohol and smoking may all disturb this balance.

In our recent study, we found that some types of stress elevated histidine decarboxylase activity selectively in the stomach (Ayada et al., 2000). Glucocorticoids are known to be vitally important for homeostasis, and their secretion is regulated by negative feedback mechanisms involving the hypothalamic–pituitary–adrenal axis (Schimmer and Parker, 1996). However, stressful stimuli can override these control mechanisms, leading to a marked increase in the plasma concentration of glucocorticoids (Munck et al., 1984). In the present study, we found that as little as 0.2 mg/kg (by intraperitoneal or even oral administration) of dexamethasone, a synthetic glucocorticoid, produced a significant elevation of gastric histidine decarboxylase activity (Table 2). Therefore, the stress-induced elevation of gastric histidine decarboxylase activity may be attributable to an increased release of glucocorticoids.

Glucocorticoids are strong inhibitors of prostaglandin synthesis (Haynes, 1990). Although dexamethasone has been reported not to reduce the gastric level of 6-keto-prostaglandin F1α in unstimulated rats (Wallace, 1987), prednisolone has been found strongly to inhibit prostaglandin E_2 synthesis by NaCl-stimulated gastric mucosa in the rat (Nobuhara et al., 1985). Hence, it is likely that the elevation of gastric histidine decarboxylase activity induced by non-steroidal anti-inflammatory drugs, stress of various

types and dexamethasone occurs when the synthesis of prostaglandins is impaired. If this is true, the increased histidine decarboxylase activity is likely to occur in enterochromaffin-like cells, because histidine decarboxylase and its mRNA have been detected in enterochromaffin-like cells in rats following water-immersion stress (Asahara et al., 1996). Conceivably, gastric histidine decarboxylase activity in enterochromaffin-like cells might be controlled by a kind of "sensor" that can somehow recognize a decrease in the local synthesis (or local levels) of prostaglandins, and this may be the reason why non-steroidal anti-inflammatory drugs, stress and dexamethasone induce histidine decarboxylase in the stomach alone.

In addition to its effect on acid secretion, histamine has the ability both to dilate precapillary arterioles and to increase capillary permeability (Garrison, 1990; Babe and Serafin, 1996). Such dilatation and enhanced permeability would seem to be indispensable for enhancing both the supply of nutrients and O_2 and the removal of CO_2 and waste, and for maintaining the integrity of the gastric mucosa both in the face of attack by acid, etc., and during inflammatory responses. These physiological vascular responses are also important for the infiltration of immune cells (granulocytes and macrophages) into the site of inflammation. As mentioned above, prostaglandins (prostaglandin E_2 and I_2) play important roles in maintaining the integrity of the gastric mucosa: they can also enhance mucosal blood flow by dilating fine blood vessels. Hence, the elevation of histidine decarboxylase activity (i.e. production of histamine), resulting from an impaired synthesis of prostaglandins, might be a compensatory reaction serving to maintain or increase blood flow through the gastric mucosa.

Local irritation by orally administered non-steroidal anti-inflammatory drugs, inhibitors of prostaglandin synthesis, allows back-diffusion of acid into the gastric mucosa and subsequent tissue damage. Likewise, parenteral administration of these drugs has been reported to cause tissue damage and bleeding (as observed in this study, too), supporting the idea that an inhibition of prostaglandin synthesis may be a cause of gastric damage (Insel, 1996). The fact that acetaminophen, which is a weak inhibitor of (or does not inhibit) prostaglandin synthesis, has been found not to produce gastric lesions (Insel, 1996) may also support this idea.

Although there is considerable debate about the possible association between peptic ulcers and glucocorticoid therapy (Piper et al., 1991; Schimmer and Parker, 1996), there is no doubt that repeated administration of glucocorticoids to rats produces gastric lesions (Robert and Nezamis, 1958; Nobuhara et al., 1985; Wallace 1987). It has been suggested that glucocorticoid therapy may trigger the onset of haemorrhage and perforation in peptic ulcers, an effect that may begin insidiously (Schimmer and Parker, 1996), especially when they are administered concomitantly with non-steroidal anti-inflammatory drugs (Piper et al., 1991). However, there is also a report that dexamethasone suppresses indomethacin-induced gastric damage in rats (Appleyard et al.,1996). In the present study, in spite of its potent ability to elevate gastric histidine decarboxylase activity, dexamethasone itself (single injection) did not produce gastric lesions in the stomach. However, repeated injections of dexamethasone, as well as of prednisolone, have been shown to produce gastric lesions in rats. We think that after a single injection of dexamethasone, its anabolic effects may protect the gastric mucosa against its ulcerogenic action. Indeed, Filaretova et al. (1998) suggested that the effects of glucocorticoids at concentrations within the physiological range may be different from the effects induced by pharmacological amounts, and that glucocorticoids should be considered as having a dual action. Histamine also exhibits a dual action: gastroprotective at low doses but toxic at high doses (Sergeev and Levkovets, 1991; Takeuchi et al., 1988). Thus, when taken repeatedly (by, for example, patients with chronic gastritis, ulcers, prolonged stress or infection with *H. pylori*), dexamethasone may, alongside its immunosuppressive effect, induce a large and/or prolonged elevation of histidine decarboxylase activity, and this may contribute to the production of gastric lesions.

A decrease in the amount of histamine in store (possibly, in enterochromaffin-like cells) leads to an enhancement of histidine decarboxylase activity, while an increase lowers it (Kahlson et al., 1964). Blockade of H_2 receptors may be recognized by this negative feedback system as a decrease in the histamine level and thus lead to an induction of histidine decarboxylase (Maslinski and Sewing, 1977). However, it has also been shown that the gastrin released in response to inhibition of gastric acid secretion by antisecretagogues (H_2 blockers and proton pump inhibitors) or following pH neutralization ($NaHCO_3$) can increase histidine decarboxylase activity (Ryberg et al., 1989; Ding et al., 1996). Whatever the mechanism, it should be noted that the drugs used widely to treat gastric diseases have the ability to induce histidine decarboxylase.

It is a fact that H_2 blockers are clinically effective at suppressing gastric lesions. However, it has also been noted that sudden and/or careless withdrawal of H_2 blockers from patients often results in a recurrence of ulceration (Douglas, 1980). A possible, albeit speculative, explanation for this recurrence is as follows: (i) sudden or careless withdrawal of H_2 blockers could produce a state in which H_2 receptors are once again exposed to histamine; (ii) at the same time, there is still an enhanced production of histamine due to the elevated gastric histidine decarboxylase activity induced by the H_2 blocker itself; (iii) this state may lead to an unexpected and powerful secretion of HCl, leading to (or participating in) rapid damage to the gastric mucosa.

Bouclier et al. (1983a–c) showed that administration of a histidine decarboxylase inhibitor (i) shortens the duration of gastrin-induced acid secretion, (ii) prolongs the anti-secretory action of cimetidine and (iii) decreases the incidence of gastric lesions induced in rats by restraint-stress combined

with cold (to the same extent as cimetidine). Histidine decarboxylase inhibition has also been shown to decrease the incidence of gastric lesions induced by excessive production of histamine in *Mastomys natalensis* (an African rodent of a size between mice and rats) (Hosoda et al., 1985). These observations support the causal involvement of increased gastric histidine decarboxylase activity in gastric damage.

Finally, as described above, histidine decarboxylase activity in the stomach is enhanced in response not only to various types of ulcerogenic stimuli but also to various types of drugs used to treat gastric lesions. Hypertonic saline also elevates gastric histidine decarboxylase activity (Ding et al., 1996). As shown in the present study, the elevation of histidine decarboxylase activity by ulcerogenic drugs does not necessarily correlate with the ulcerogenic response. Moreover, histamine itself has both protective and injurious effects on the stomach. The protective effect of histamine suggests that the induction of histidine decarboxylase in the stomach is a fundamental event in a self-defence mechanism, as we proposed for histidine decarboxylase induction in other tissues in response to lipopolysaccharide, interleukin-1 or tumour necrosis factor (Endo et al., 1995). Thus, on the basis of our present knowledge, we cannot make the simple statement that an increase in histidine decarboxylase is good (or alternatively, bad) for the maintenance of gastric mucosal integrity; its effect may depend on the situation. However, we think it likely that despite the compensatory or protective effects of histamine, an abnormally elevated gastric histidine decarboxylase activity (or histamine production), which may be induced by combined ulcerogenic stimuli, may contribute to the initiation, development, exacerbation or recurrence of gastric lesions. In this context, the magnitude of the elevation in histidine decarboxylase activity, its duration, how frequently it occurs and whether it occurs at a time when the gastric mucosa is particularly vulnerable may all be important factors.

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