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Induction by interleukin-1, tumor necrosis factor and lipopolysaccharides of histidine decarboxylase in the stomach and prolonged accumulation of gastric acid

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1 Injection of interleukin-1 (IL-1) into pylorus-ligated rats has been shown strongly to inhibit gastric secretion. However, in the present study, we found that an intraperitoneal injection of IL-1 into intact (non-pylorus-ligated) fasted mice rapidly (within 30 min) induced an accumulation of gastric acid ('early response'). When the dose of IL-1 was larger, the accumulation lasted for a longer period.

2 Injection of IL-1 also caused a later elevation of the activity of histidine decarboxylase (HDC), the histamine-forming enzyme, in the stomach ('later response').

3 Cimetidine, an antagonist of histamine H_2-receptors, suppressed the accumulation of gastric acid in both the early and later periods. An irreversible inhibitor of HDC, α-fluoromethylhistidine, partially inhibited the accumulation in the later period.

4 IL-1, when injected 1 h after feeding in mice fasted overnight, markedly retarded gastric emptying.

5 Tumour necrosis factor (TNF) and lipopolysaccharide (LPS) or endotoxin from *E. coli* both had IL-1-like effects on the stomach, and their effects are presumably mediated by IL-1.

6 These results support the idea that an inhibition of gastric emptying and an elevation of HDC activity in the stomach may explain the findings that a long-lasting accumulation of gastric acid is induced by IL-1 despite its potent inhibition of gastric acid secretion.

7 On the basis of these results, and in the light of the known actions of histamine, the possible roles of IL-1 in gastric inflammation and ulceration are discussed.

Keywords: Gastric acid; interleukin-1; histamine; histidine decarboxylase; lipopolysaccharide

Introduction

Gastric-acid secretion is known to be regulated by histamine, acetylcholine (*via* activation of the vagus nerve) and gastrin. Because the bouts of acid secretion induced by administration of acetylcholine, by stimulation of the vagus or by gastrin are all inhibited by antagonists of histamine H_2 receptors, histamine was long ago put forward as the final mediator in the pathway leading to gastric acid secretion (Code, 1965; Black *et al*., 1972).

We have reported elsewhere that low doses of lipopolysaccharides (LPS or endotoxin) and interleukin-1 (IL-1) enhance the activity of histidine decarboxylase (HDC), the enzyme which forms histamine, in tissues such as liver, lung, bone marrow and spleen (Endo, 1982, 1983a, 1989; Endo *et al*., 1986, 1992b). As there is a rapid increase in HDC mRNA after the injection of LPS, the enhancement of HDC activity seems likely to result from the induction of the HDC enzyme itself (Kikuchi *et al*., 1997). The histamine newly formed through the induction of HDC diffuses quite freely away from its site of formation without being stored (Schayer, 1966; Kahlson & Rosengren, 1968; Schayer, 1974; Beaven, 1978; Endo, 1982; Endo *et al*., 1992a). We suspected that IL-1 and LPS might induce HDC in the stomach, too, leading to stimulation of gastric acid secretion. In the present study, we have examined this hypothesis.

Pylorus-ligation is a widely used method in experiments on gastric-acid secretion. In the present study, in order to obtain information from animals that were in as near a natural state as possible, we used 'intact' mice without pyloric ligation. We measured the acid 'content' of the stomach (i.e. 'acid accumulation'). This measurement is a reflection of the relative rates at which acid is secreted into and lost from the stomach. Therefore, measurement of 'acid accumulation' in 'intact' mice will provide information that cannot be gained by measurement of acid secretion alone. Under these experimental conditions, we obtained data that suggested that IL-1, TNF and LPS induce an accumulation of gastric acid, and that the persistence of this accumulation may involve induction of HDC. Our findings suggest that the results previously obtained in anaesthetized, pylorus-ligated animals (Uehara *et al*., 1989; Wallace *et al*., 1991; Tache & Saperas, 1992), which showed that IL-1 inhibits the secretion of gastric acid, provide only a partial description of the effects of this agent on the stomach.

Methods

Animals

Male BALB/c mice (6–7 weeks old) were obtained from a breeding colony maintained at our university. They were kept under a conditioned light (07.00 h to 19.00 h)/dark cycle and fed *ad libitum* until the morning of the experiment. All procedures conformed to the Guidelines for Care and Use of Laboratory Animals in Tohoku University.

Materials

The following recombinant cytokines were used: human IL-1α (Furutani *et al*., 1985), human TNFα (Yamada *et al*., 1985)

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and human IL-8 (Dainippon Pharmaceutical Co., Osaka, Japan), human IL-1β (Ohtsuka Pharmaceutical Co., Tokushima, Japan), human IL-2 and mouse interferon γ (IFNγ) (Shionogi Pharmaceutical Co., Osaka, Japan), mouse IL-12 (Genetics Institute, Cambridge, MA, U.S.A.), mouse granulocyte-macrophage colony-stimulating factor (GM-CSF)(Sumitomo Pharmaceutical Co., Osaka, Japan), human granulocyte colony-stimulating factor (G-CSF)(Chugai Pharmaceutical Co., Tokyo, Japan) and human macrophage colony-stimulating factor (M-CSF)(Morinaga Pharmaceutical Co., Tokyo, Japan). A lipopolysaccharide (LPS) of *Escherichia coli*: O55:B5, prepared by Boivin's method, was obtained from Difco Lab. (Detroit, MI, U.S.A.). DL-α-Monofluoromethylhistidine (FMH) was a gift from Dr Kollonitsch of Merck Sharp & Dohme Research Laboratories (Rahway, NJ, U.S.A.). Cimetidine was purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). These agents were each dissolved in sterile saline and injected intraperitoneally (i.p.) at 0.1 ml per 10 g body weight.

Measurement of gastric acid accumulation

On the morning (about 08:00 h) of the experiment, in order to ensure complete fasting, the mice were moved to a cage (5–6 mice/cage) with a suspended floor made of wire netting (7 mm mesh), some 2.5 cm above the real floor of the cage to prevent autocoprophagia and ingestion of bedding (wood shavings). Experiments were started at 12:00 h to 13:00 h. During the experiment the mice were also deprived of water. IL-1, TNF or LPS were injected into the mice between 12:00 h and 13:00 h. The mice were decapitated at the indicated times, and the stomachs removed carefully so as not to lose any gastric juice. After each stomach had been weighed, the gastric juice was collected in a test-tube by cutting the stomach open and washing it out with saline (3 ml). The mixture of gastric juice and saline was shaken on a Vortex-type mixer, and neutralized to pH 7 using 10 mM NaOH. The amount of gastric acid present, corresponding to the amount of NaOH required for the neutralization, was expressed in μeq HCl. After the gastric juice had been collected, the stomach was blotted on a filter paper, weighed, and stored at -80°C prior to the assay of HDC activity.

Measurement of gastric emptying

On the evening (about 17:00 h) before the day on which experiments on gastric emptying were to be performed, some mice were moved to a cage in which fresh wood shavings had been laid. They were deprived of food overnight and the next morning (10:00 h), a box containing food was put into the cage. One hour later, the mice were injected intraperitoneally with IL-1 or saline, moved to another cage with a suspended floor made of wire netting and deprived of food. The mice were decapitated at the indicated times and the stomach removed and weighed. The stomach contents were removed, and the stomach itself was blotted on a filter paper, weighed and stored at -80°C as described above. The weight of the gastric content was calculated as the difference between the weight of the stomach before and after the removal of its contents.

Assay of HDC activity

HDC activity in stomach and spleen was assayed by a previously described method (Endo, 1983b), but with a slight modification (Endo *et al*., 1992a). The spleen was removed from each animal at the same time as the stomach. HDC activity was expressed in terms of nmol of histamine formed over a 1 h period by the enzyme contained in 1 g of stomach tissue or spleen (nmol h^{-1} g^{-1}).

Assay of IL-1β and TNFα in the serum

Blood was collected by decapitation, and the IL-1β and TNFα levels in the serum were determined using ELISA kits for mouse IL-1β and mouse TNFα (Endogen Inc., Cambridge, MA, U.S.A.).

Data analysis

Experimental values are given as mean $\pm$ standard deviation. The statistical significance of differences was analysed by Dunnett's multiple comparison test after ANOVA: P values less than 0.05 were considered to indicate significance.

Results

Time course of the accumulation of gastric acid and of the enhancement of HDC activity in the stomach induced by IL-1, TNF and LPS

Injection of IL-1α into mice at a dose of 20 μg kg^{-1} induced an accumulation of gastric acid (Figure 1). This effect began within 30 min of the injection of IL-1α, reached its peak at 0.5–1 h, and lasted for several hours. The injection of IL-1α also enhanced HDC activity in the stomach. However, the elevation of HDC began about 1.5 h after the effect on gastric acid, and HDC activity reached its peak about 3 h after the injection of IL-1α.

TNFα also induced an accumulation of gastric acid at a dose of 20 μg kg^{-1}. However, there were some differences between its effects and those of IL-1α: (i) there was no acid accumulation at 30 min after the injection of TNFα, (ii) the acid accumulation reached its peak at 1 h and was more

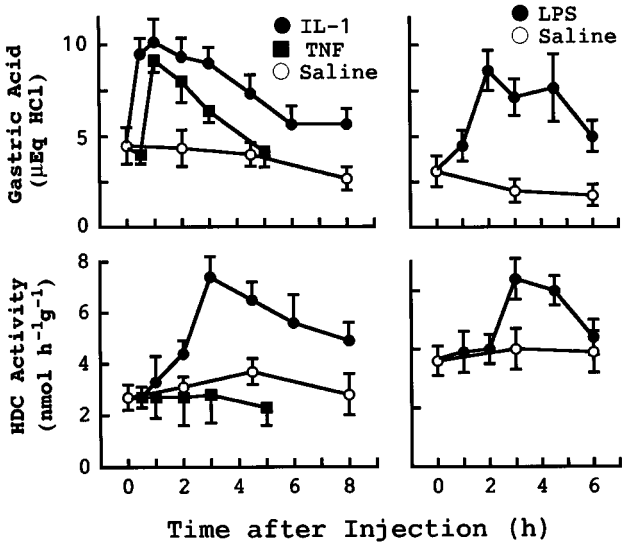

Figure 1 Gastric acid accumulation and elevation of HDC activity induced in the stomach of mice by IL-1, TNF and LPS. Gastric acid and HDC activity were each determined at the indicated times after intraperitoneal injection of IL-1α (20 μg kg^{-1}), TNF (20 μg kg^{-1}) or LPS (0.1 mg kg^{-1}). The dose of IL-1α used in this Figure represents a 'large' dose in the terms used in this study. Each value is the mean $\pm$ s.d. from five to 10 mice.

transient than that induced by IL-1α, and (iii) TNFα did not enhance HDC activity in the stomach at this dose. However, at a dose of 50 μg kg^{-1} or more, TNFα did elevate HDC activity in the stomach (data not shown).

LPS (100 μg kg^{-1}) also induced acid accumulation and an elevation of HDC activity. However, the peak values for acid accumulation and HDC activity occurred at 2 h and 3–4.5 h after the injection of LPS, respectively. Thus, the effect on acid accumulation (and possibly that on HDC activity) was delayed relative to that induced by IL-1α.

Dose-dependency of the effects on gastric-acid

We next examined the effects of various doses of IL-1α and TNFα on the accumulation of gastric acid, which was measured at 1 h after the injection of each stimulant (Figure 2-left panel). The minimum effective dose of IL-1α was 0.4 μg kg^{-1} (10 ng per mouse) or less. The effective dose of TNFα was in excess of 2 μg kg^{-1}. IL-1α and TNFα did not enhance gastric HDC activity during this early period (data not shown).

As already mentioned (Figure 1), peak HDC activity was observed 3 h after the injection of IL-1α. For this reason, the effects were compared of various doses of IL-1α on both gastric acid and HDC activity during this later phase (Figure 2-right panel). IL-1α increased gastric HDC activity at this later time in a dose-dependent manner, and this relationship roughly paralleled the dose-response curve for the accumulation of gastric acid. However, a statistically significant increase in gastric acid was not observed until the dose of IL-1α used was 20 μg kg^{-1}, indicating that to increase the acid accumulation in the later period requires a larger dose than in the early phase (1 h after injection, Figure 2-left panel).

Effect of drugs on the early acid accumulation induced by IL-1 and TNF

Figure 3 shows the effects of atropine (an antagonist of muscarinic acetylcholine receptors), cimetidine (an antagonist of histamine-H_2 receptors) and FMH (an irreversible inhibitor of HDC; Kollonitsch *et al*., 1978), on the early accumulation of gastric acid (i.e. at 1 h after the injection of IL-1α or TNFα). The early accumulation induced by either IL-1α or TNFα was significantly reduced by both atropine and cimetidine, but not by FMH.

Effect of drugs on the later acid accumulation and HDC activity in the stomach induced by IL-1

Figure 4 shows the effects of these same drugs on the levels of gastric acid and HDC activity measured at 3 h after the injection of IL-1α. Cimetidine reduced the effect of IL-1α in this later period, too. However, the effect of atropine did not reach significance. Unlike the early acid accumulation, the later accumulation was significantly reduced by FMH, although the inhibition was partial. However, this agent completely inhibited the HDC activity in the stomach.

Effect of various cytokines on gastric acid and on HDC activity

IL-1β (20 μg kg^{-1}, i.p.), like IL-1α, caused an accumulation of gastric acid that exhibited both early and later phases

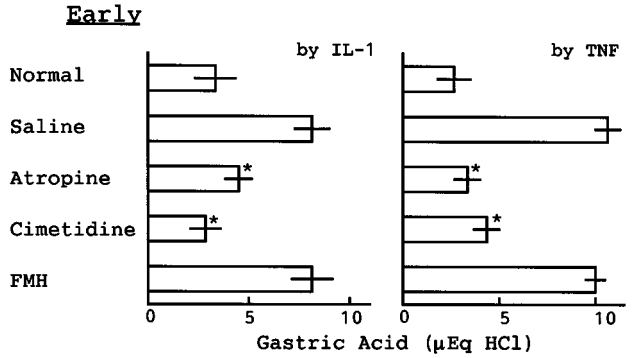

Figure 3 Effect of drugs on the early accumulation of gastric acid induced by IL-1 (left panel) or TNF (right panel). Drugs were injected 10 min after an intraperitoneal injection of IL-1 or TNF (20 μg kg^{-1} each), and gastric juice was collected 1 h after the injection of IL-1 or TNF. Saline (0.25 ml), atropine (10 mg kg^{-1}), cimetidine (100 mg kg^{-1}) and FMH (50 mg kg^{-1}) were each injected intraperitoneally. 'Normal' values indicate the levels without injection of IL-1 or TNF. *$P<0.01$ *vs* saline-injected mice. Each value is the mean±s.d. from five to 10 mice.

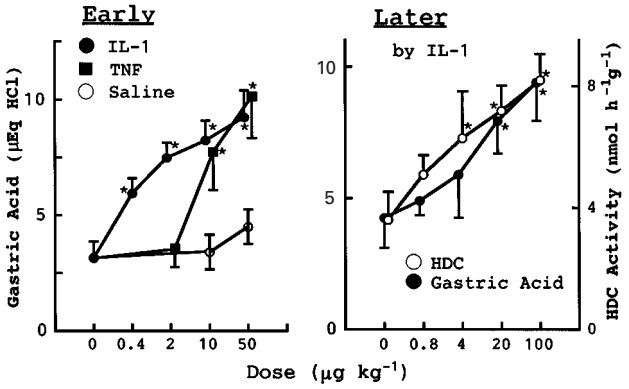

Figure 2 Dose-dependency of (i) the early gastric acid accumulation induced by the injection of various doses of IL-1 or TNF (left panel) and (ii) of the later gastric acid accumulation and HDC activity induced by IL-1 (right panel). Values for early and later acid accumulation were obtained 1 h and 3 h after the injection, respectively. *$P<0.05$ *vs* saline-injected mice. Each value is the mean±s.d. from five to 10 mice.

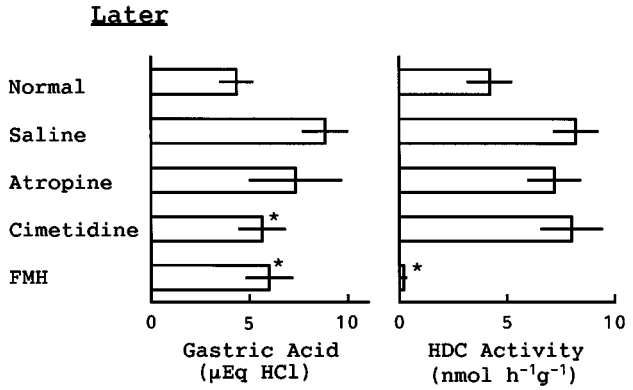

Figure 4 Effect of drugs on the later gastric acid accumulation and HDC activity induced by IL-1. Drugs were injected 1 h after an intraperitoneal injection of IL-1 (20 μg kg^{-1}), and gastric juice was collected 3 h after the injection of IL-1. Saline (0.25 ml), atropine (10 mg kg^{-1}), cimetidine (100 mg kg^{-1}) and FMH (50 mg kg^{-1}) were each injected intraperitoneally. 'Normal' values indicate the levels without injection of IL-1. *$P<0.05$ *vs* saline-injected mice. Each value is the mean±s.d. from five to 10 mice.

(data not shown). However, none of the other cytokines tested (IL-2 and IL-8 (40 μg kg^{-1}); IL-12, G-CSF and IFNγ (50 μg kg^{-}); M-CSF and GM-CSF (20 μg kg^{-1})) showed such activity (data not shown). Among these cytokines, only IL-1α and IL-1β enhanced HDC activity in the stomach at 3 h. As reported previously (Endo *et al*., 1992a), GM-CSF and G-CSF both enhanced HDC activity in the spleen at 3 h. However, these agents were ineffective in inducing HDC in the stomach (data not shown).

Increase in IL-1 and TNF in the serum after injection of LPS

In order to examine whether IL-1 and/or TNF could be involved in the accumulation of gastric acid and elevation of HDC activity induced by LPS, the serum levels of these cytokines were determined following the injection of LPS. As shown in Figure 5, at the times at which there was an LPS-induced accumulation of gastric acid (at about 2 h) or an elevation of HDC activity (at 3–5 h) (see Figure 1-right panels), there were peaks in the serum levels of TNFα and IL-1β, respectively.

Effect of IL-1 on gastric acid in rats

As described in the Introduction, IL-1 and LPS have been shown to inhibit gastric acid secretion soon after their injection into pylorus-ligated rats. However, as shown in Table 1, when IL-1α was injected into intact (non-pylorus-ligated) rats, it induced a clear accumulation of gastric acid and gastric juice at 1 h following its injection. These experiments were conducted under essentially the same conditions as those on mice.

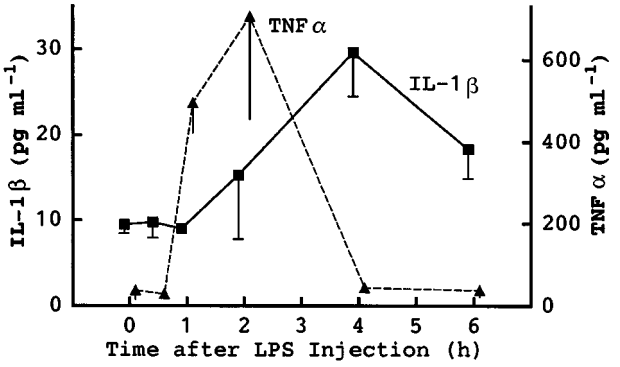

Figure 5 IL-1β and TNFα levels in the serum following intraperitoneal injection of LPS (0.1 mg kg^{-1}). Each value is the mean$\pm$s.d. from 4 mice.

Table 1 Effect of IL-1 on gastric acid and juice in rats

	Gastric juice (mg)	*Gastric acid* (*μEq HCl*)
Saline	213$\pm$69	7.0$\pm$1.4
IL-1	516$\pm$96*	10.4$\pm$0.7*

Wistar rats starved overnight were intraperitoneally injected with 2 μg (about 13 μg kg^{-1}) of IL-1α. The stomach was removed 1 h later, and its gastric juice collected and neutralized with 10 mM NaOH (as in the mice experiments). The values are mean$\pm$s.d. from four rats. *$P<0.05$ *vs* saline-injected control.

Effect of IL-1α on gastric emptying

In mice not injected with IL-1, the weight of the gastric contents decreased rapidly after a 1 h bout of feeding and returned to the level seen before feeding within 2–3 h of the cessation of feeding (Figure 6: left panel). The feeding also increased HDC activity in the stomach. The HDC activity peaked at about 3 h after the start of feeding and returned to normal within 6 h (Figure 6: right panel). IL-1 injection into mice after a 1 h bout of feeding markedly retarded gastric emptying. Surprisingly, the stomach contents in the mice injected with IL-1 were still mostly in a solid state even 5 h after the end of feeding. In the mice injected with IL-1, the elevation of HDC activity lasted longer than that in mice not given IL-1. In another experiment using the same basic protocol (see Figure 4), we examined the effect on gastric emptying of FMH (50 mg kg^{-1}) given 1 h after the IL-1 injection. However, FMH had no significant effect on the inhibition of gastric emptying induced by IL-1: indeed, there was, if anything, a tendency for there to be an increase in the weight of the gastric contents measured 3 h after the injection of FMH (data not shown).

Discussion

An injection of IL-1 or TNF induced an accumulation of gastric acid in 'intact' mice. The IL-1-induced accumulation was detectable 30 min after its injection, and as little as 0.4 μg kg^{-1} of IL-1α was sufficient to induce this rapid effect. This rapid action of IL-1 or TNF was inhibited by atropine and cimetidine. During this initial accumulation of gastric acid, there was no elevation of HDC activity. These results might seem to indicate that IL-1α stimulates the secretion of gastric acid through the release of histamine, although HDC activity is not involved in this rapid response. However, our data do not reflect secretion alone, because the amount of gastric juice or acid present in the stomach is determined by the relative rates of secretion into, and loss from the stomach.

It is well established that IL-1 strongly inhibits gastric secretion. On the other hand, IL-1 and TNF have also been shown to inhibit gastric emptying (Robert *et al*., 1991) and fundus motility (Montuschi *et al*., 1994). Therefore, even if IL-1 inhibited, say, 90% of basal acid secretion, a complete inhibition of gastric emptying would result in an accumulation

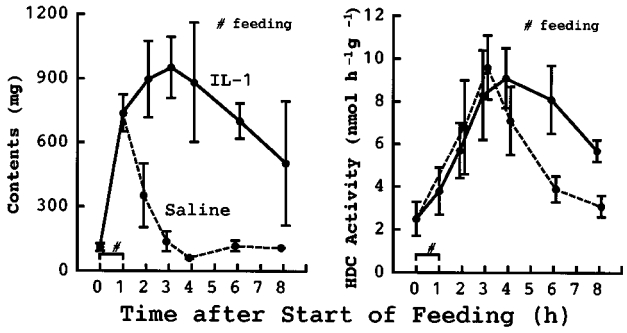

Figure 6 Effect of IL-1 on gastric emptying and gastric HDC activity. After mice had been starved overnight, they were given access to feed for 1 h. Immediately after the cessation of feeding, IL-1 (20 μg kg^{-1}) or saline was injected intraperitoneally. The stomach was removed at the indicated time after the start of feeding, the contents weighed and HDC activity assayed. Each value is the mean$\pm$s.d. from four mice.

of gastric acid. As shown in Figure 6, gastric emptying was strongly, perhaps completely, inhibited soon after and for some hours after injection of IL-1 (since the weight of the gastric contents increased rather than decreased for 2 h or so after an injection of IL-1). If IL-1 or TNF were completely to inhibit acid secretion, there could be no accumulation of gastric acid in the stomach. Therefore, a possible explanation to explain the results that atropine and cimetidine inhibited the accumulation of gastric acid is that IL-1 or TNF might have almost completely inhibited gastric emptying but partially inhibited basal gastric secretion, and that it was the residual basal secretion that was inhibited by atropine and cimetidine.

When the dose of IL-1 was 20 μg kg^{-1} or more, the accumulation of gastric acid persisted for several hours (Figure 1). Cimetidine reduced the later acid accumulation, too (i.e. at 3 h after the injection of IL-1α). At this later time, there was an elevation of gastric HDC activity. FMH, an irreversible inhibitor of HDC, inhibited partially, but significantly, the acid accumulation seen at this time (i.e. after 3 h). Although IL-1 can inhibit both the basal and gastrin-induced secretion of gastric acid, it has been shown to have no effect on the acid secretion induced by an injection of histamine (Wallace *et al*., 1991). Taken together, these results suggest that the histamine produced through the late elevation of HDC activity may, at least in part, in fasted mice, contribute to a prolongation of this accumulation, possibly by stimulating the secretion of gastric acid. As mentioned above, TNF also induced an accumulation of gastric acid, but at larger doses than the required dose of IL-1. At 20 μg kg^{-1}, TNF produced a transient acid accumulation but, at this dose, it did not elevate gastric HDC activity. However, larger doses of TNF, 50 μg kg^{-1} or more, induced both a long-lasting acid accumulation and an enhancement of HDC activity in the stomach. These results also support the idea that an enhancement of HDC activity underlies the prolonged phase of the accumulation of gastric acid.

The inhibitory effect of IL-1 on gastric acid secretion has mostly been demonstrated in rats, and it seemed conceivable that the rapid accumulation of gastric acid seen in mice might not occur in rats. However, IL-1 caused an early accumulation of gastric acid and juice in 'intact' rats, too (Table 1), suggesting that there is no essential difference between the effects of IL-1 in these two species, at least in their 'normal or intact' state.

On the basis of the arguments presented above, our observations can be explained as follows. In intact animals, lower doses of IL-1 may inhibit both acid secretion and emptying in the stomach, resulting in an accumulation of gastric acid. In addition to these effects, higher doses of IL-1 elevate gastric HDC activity and produce histamine, leading to a prolonged accumulation of gastric acid.

The acid accumulation induced by LPS occurred later than that induced by IL-1 and TNF and that induced by TNF was later than that induced by IL-1. Moreover: (i) LPS is a potent stimulator of the production of these cytokines from macrophages or endothelial cells (Dinarello, 1991); (ii) among the various cytokines tested here, only IL-1 and TNF were active in inducing an acid accumulation and (iii) TNF stimulates the production of IL-1 (Dinarello, 1991). All this suggests that the acid accumulation induced by the injection of LPS or TNF may be mediated by IL-1. Indeed, we confirmed that TNF and IL-1 were elevated in the serum after LPS injection (Figure 5).

It was notable that the stomach contents in mice injected with IL-1 were still mostly in a solid state even 5 h after the end of feeding. Although FMH reduced the accumulation of gastric acid seen at the later time (Figure 4), this agent was not effective in reducing the weight of gastric contents after a 1 h bout of feeding. This could be explained by supposing that the decrease in gastric acid induced by FMH caused a slowing of digestion and a delay in the movement of gastric contents from stomach to intestine.

At present, it is not clear in what cells HDC activity may be enhanced in the stomach in response to IL-1, TNF or LPS. It is thought that HDC is induced in the histamine-storage cells, enterochromaffin-like (ECL) cells (Nissinenn *et al*., 1992), and that it then replenishes the histamine stores. HDC activity in the stomach is decreased by starvation, but increased by refeeding and by injection of gastrin (Kahlson *et al*., 1964; Rosengren & Sevensson, 1969; Hakanson *et al*., 1974). Moreover, gastrin stimulates the formation of HDC-mRNA (Dimaline *et al*., 1993). On this basis, it might be thought that the IL-1-induced elevation of HDC activity is mediated by gastrin: in other words, IL-1 might stimulate the release of gastrin and thus induce HDC in ECL cells. However, Kondo *et al*. (1994) have shown that IL-1 actually inhibits the gastrin-induced elevation of HDC activity. There are several factors which may account for this apparent discrepancy. In their experiments, IL-1 itself did not elevate gastric HDC activity. With respect to this potential discrepancy, we think as follows. In addition to the fact that rats in their experiments are not in an intact state (treated with various surgical procedures and an antibiotic), their dose of IL-1β (5 μg kg^{-1}, i.v.) seems to be not sufficient to induce a detectable elevation of HDC activity. Now, LPS can induce HDC in various tissues in mast-cell-deficient mice (Endo & Nakamura, 1993), and we have presented elsewhere a line of evidence suggesting that HDC can be induced by IL-1 or TNF in vascular endothelial cells in non-haematopoietic organs, such as liver and lung (Endo *et al*., 1995), and possibly in skeletal muscle, too (Endo *et al*., 1998). Therefore, it seems more likely that HDC is also induced in vascular endothelial cells in the gastric microcirculation in response to IL-1, TNF or LPS, although a proper examination of this idea will require further experiments.

Finally, the following paragraphs set out in brief some of our ideas about the possible roles of IL-1 and HDC in the stomach.

(1) The IL-1-induced accumulation of gastric acid and inhibition of gastric emptying (leading to the trapping of bacteria) may act as a form of self-defence mechanism, because gastric acid could well be important as a means of inactivating or degrading bacteria ingested with food.
(2) IL-1 has been shown to reduce experimental gastric injuries by effects mediated either by prostaglandins (PG)(Tache & Saperas, 1992) or by nitric oxide (NO)(Esplugues *et al*., 1993). PGI_2 and PGEs help to maintain the integrity of the gastric mucosa (Campbell, 1990; Garrison, 1990). Histamine induces dilatation of fine blood vessels and increases capillary permeability. PGI2 and NO are involved in the vasodilatation induced by histamine (Garrison, 1990). Thus, the IL-1-induced production of histamine may in this way contribute to an increase in blood flow and to the protection of the gastric mucosa. Indeed, administration of small doses of histamine has been shown to protect against gastric damage (Takeuchi *et al*., 1988).
(3) Histamine has deleterious effects, too, as shown by the fact that H_2-receptor blockers are of great value in reducing gastric ulcers. Moreover, FMH reduces gastrin-induced acid secretion in rats and decreases the incidence of stress-induced gastric lesions (Bouclier *et al*., 1983a; b; c).

(4) LPS or endotoxin is a component of the cell walls of gram-negative bacteria that is released during the cell division of such bacteria. Recent studies have shown that infection in the stomach with the gram-negative bacterium, *Helicobacter pylori*, is an important cause of both chronic inflammation and ulcers of the gastric mucosa (Graham & Klein, 1987; Engstrand *et al*., 1991). In addition, TNF has been shown to be present in the gastric mucosa in patients with *H. pylori*-associated gastritis (Crabtree *et al*., 1991). Therefore, it would be of interest to know whether *H. pylori*-LPS leads to an elevation of HDC activity in the stomach.

In conclusion, although this idea is highly speculative, we think that the inhibition of gastric emptying and the elevation of HDC activity by IL-1 may represent the onset of a defence mechanism. Moderate production of histamine (in magnitude and/or duration) may be beneficial in terms of its protective effect on the gastric mucosa. However, its prolonged and/or excessive production locally in the stomach may contribute to the initiation, development or exacerbation of gastric inflammation or ulcer.

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