Duodenal Ulcers Induced by Diethyldithiocarbamate, a Superoxide Dismutase Inhibitor, in the Rat: Role of Antioxidative System in the Pathogenesis

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ABSTRACT—Pathogenesis of duodenal ulcers induced by diethyldithiocarbamate (DDC), a superoxide dismutase (SOD) inhibitor, was investigated in the rat. Repeated s.c. administration of DDC (750 mg/kg) every 12 hr induced duodenal ulcers in the fed rats, and the severity of the ulcers reached the maximum after three injections. DDC not only reduced basal acid output but also impaired duodenal alkaline secretion. These ulcers were significantly prevented by antioxidative agents such as SOD (50 000 units/kg, s.c.), allopurinol (50 mg/kg, s.c.) or glutathione (200 mg/kg, s.c.) as well as the antisecretory agent cimetidine (100 mg/kg, s.c.). The impaired HCO$_3$ response caused by DDC was partially but significantly reversed by either SOD (15 000 units/kg/hr, i.v.), allopurinol or glutathione; and SOD by itself significantly elevated the rate of basal alkaline secretion. 16,16-Dimethyl prostaglandin E$_2$ (10 μg/kg, s.c.) increased duodenal HCO$_3$ output in the presence of DDC and significantly prevented the development of duodenal ulcers in response to DDC. These results suggest that the mucosal antioxidative system including SOD may play a role in the regulatory process of alkaline secretion and contribute to the mucosal defensive ability in the duodenum. The insufficiency of this system may be involved in the pathogenesis of DDC-induced duodenal ulcers.

Diethyldithiocarbamate (DDC), a potent metal chelator, is known to induce damage in the gastrointestinal mucosa in rats (1, 2). Recently, we found that repeated administration of DDC to fed rats produced penetrating ulcers in the duodenum with a high incidence (3). Although inhibition of copper modulated cytosolic superoxide dismutase (SOD) is thought to be a significant factor in the pathogenesis of this toxicity, the precise mechanism remains unknown. Since the antioxidative system including SOD may play a role in maintaining the functional integrity of these organs, the pathogenesis of DDC-induced toxicity might involve the functional disorders related to the insufficiency of this system. We have previously shown that the impairment of alkaline secretion is commonly involved in the mechanism of experimental production of duodenal ulcers as induced by mepirizole, antiinflammatory drugs or digitoxin (4–7). Thus, it is of interest to study the relationship between the antioxidative system and duodenal alkaline secretion.

In the present study, we examined the effects of DDC and antioxidative drugs on duodenal alkaline secretion in the rat to investigate (a) the pathogenesis of DDC-induced duodenal ulcers and (b) the role of the antioxidative system in duodenal alkaline secretion.
MATERIALS AND METHODS

Male Sprague Dawley rats (Charles River, Shizuoka, Japan), weighing 250–280 g, were used. The animals were fed on chow and tap water during an experimental period of ulcer production, but in the secretory studies, they were deprived of food but allowed free access to tap water for 18 hr before the experiments. During fasting, the animals were kept in individual cages with raised mesh bottoms to prevent coprophagy. All studies were carried out using 5 to 10 rats per group.

Induction of duodenal ulcers

DDC, dissolved in 10% gelatin, was given s.c. to normally fed animals in a dose of 750 mg/kg every 12 hr for 2 days, and they were killed 12 hr after the final administration. This dose was selected based on the previous studies (1–3, 8) to inhibit SOD activity in the gastrointestinal mucosa by 60% and induce duodenal ulcers consistently when given once daily for 4 days. The animals were killed under deep ether anesthesia, and both the stomach and duodenum were removed, treated with 2% formalin to fix the tissues, and opened along the greater curvature and along the mesenteric attachment, respectively. The area of damage (mm²) observed in the corpus, antrum and the duodenum was measured separately under a dissecting microscope with a square grid (×10). The person measuring the lesions did not know the treatments given to the animals. The tissue samples were immersed in 10% formalin and processed for routine light microscopy for histological examination, sectioned at 5 μm, and stained with hematoxylin and eosin. Since the severity of ulcers in the duodenum reached the maximum with less mortality when DDC was given three times every 12 hr in a dose of 750 mg/kg, this dose regimen was used in the subsequent study. In some cases, we examined the effects of allopurinol (50 mg/kg), glutathione (200 mg/kg), SOD (50000 units/kg), cimetidine (100 mg/kg) and 16,16-dimethyl prostaglandin E₂ (dmPGE₂: 10 μg/kg) on the severity of the duodenal ulcers induced by DDC. The doses of these agents were selected to represent the inhibition of xanthine oxidase (9), radical scavenging activity (2, 10), inhibition of acid secretion (5) or stimulation of duodenal alkaline secretion (11); and they were given s.c. 10 min before each injection of DDC.

Determination of gastric acid and duodenal alkaline secretion

Gastric acid and duodenal alkaline secretions were measured in fasted rats under unanesthetized conditions, according to the previously published method (5). Briefly, under ether anesthesia, the abdomen was incised and both the stomach and duodenum were exposed. An acute gastric fistula prepared by means of a polyethylene tube was implanted in the forestomach, and another polyethylene tube was inserted into the stomach through the pylorus from a small incision made in the duodenum. Both cannulas were withdrawn through the abdominal wall, and the stomach was perfused at the rate of 1 ml/min with saline that was gassed with 100% O₂, heated at 37°C and kept in a reservoir. Acid secretion was titrated at pH 7.4 using a pH-stat method (Hiranuma Comtite-7, Tokyo, Japan) and by adding 100 mM NaOH to the reservoir. On the other hand, duodenal alkaline secretion was measured in the proximal duodenal loop which was made between the pylorus and the area just above the outlet of the common bile duct (1.7 mm). In this case, gastric contents were continuously withdrawn through an acute fistula implanted in the forestomach to prevent distension caused by accumulation of gastric juice in the stomach. The duodenal loop was perfused with saline, similar to determination of acid secretion; and alkaline secretion was titrated at pH 7.4 using the pH-stat method and by adding 10 mM HCl to the reservoir. To stimulate alkaline secretion, the duodenal mucosa was acidified by perfusing the loop for 10 min with 10 mM HCl made isotonic with NaCl. DDC (750 mg/kg) was given s.c. as a single injection or repeatedly 3
times every 12 hr, and acid or alkaline secretion was measured for 4 hr thereafter. In some cases, the effects of SOD (15000 units/kg/hr, i.v.), allopurinol (50 mg/kg, s.c.), glutathione (200 mg/kg, s.c.) and dmPGE₂ (10 μg/kg, s.c.) on the duodenal alkaline secretion were examined in the animals treated with DDC (750 mg/kg) under basal and acid-stimulated conditions. On the other hand, the effects of these agents on gastric acid secretion were examined in pylorus-ligated rats. Briefly, under ether anesthesia, the abdomen was incised and the pylorus was ligated. Four hours later, the animals were killed under deep ether anesthesia, and the gastric contents were collected. After centrifugation for 15 min at 3000 r.p.m., each sample was measured for volume and titrated to pH 7.0 against 0.1 N NaOH using an automatic titrator (Radiometer, Copenhagen, Denmark). SOD (50000 units/kg), allopurinol (50 mg/kg), glutathione (200 mg/kg), dmPGE₂ (10 μg/kg) and cimetidine (100 mg/kg) were given s.c. immediately after pylorus ligation.

Preparation of drugs

Drugs used were diethyldithiocarbamate (Wako, Osaka, Japan), superoxide dismutase, glutathione, cimetidine (Sigma Chemicals, St. Louis, MO), allopurinol (Aldrich Chem Co., WI) and 16,16-dmPGE₂ (Funakoshi, Tokyo, Japan). DDC was dissolved in 10% gelatin (Wako). SOD was dissolved in saline, while both allopurinol and cimetidine were suspended in saline. DMPGE₂ was first dissolved in absolute ethanol and diluted with saline to the desired concentration. Each agent was prepared immediately before use and given s.c. in a volume of 0.5 ml per 100 g of body wt. or infused i.v. in a volume of 1.2 ml/hr.

Statistics

Data are presented as the mean ± S.E. from 5 to 10 rats per group. Statistical analysis was performed using a two-tailed Dunnett's multiple comparison test (12), and values of

![Graph](image)

**Fig. 1.** Effect of repeated administration of diethyldithiocarbamate (DDC, 750 mg/kg) on the duodenal and gastric mucosa in fed rats. The animals were given DDC s.c. 1 to 4 times every 12 hr, and they were killed 12 hr after the final injection. Data are presented as the mean ± S.E. from 8 to 10 rats per group. Note that administration of DDC 3 times every 12 hr induced ulcers mainly in the duodenum with an incidence of 100% and mortality of less than 10%. ◯: corpus, ■: antrum, ▲: duodenum. □: mortality.
P < 0.05 were regarded as significant.

RESULTS

*Induction of duodenal ulcers induced by diethyldithiocarbamate*

Repeated administration of DDC (750 mg/kg, s.c.) every 12 hr produced ulcers in the duodenum of normally fed animals, depending upon the times of injection, and the severity of ulcers reached the maximum after 3 injections with an incidence of 100% and a mortality of less than 10% (Fig. 1). At this dose regimen, the ulcers were observed mainly in the duodenum with less damage in the stomach; the ulcer index in the duodenum was \(26.2 \pm 5.8 \, \text{mm}^2\) (Fig. 2A). Histological characteristics of the ulcers involved penetration to the muscularis mucosae and severe edema in the submucosa (Fig. 2B). In some cases, small but deep ulcers were also found in the antrum and/or the antr duodenal junction (Fig. 2, C and D). Although DDC induced more severe ulcers in the duodenum after four injections of 750 mg/kg each, this dose regimen resulted in a significant increase of mortality to 25% (2 of 8 rats). Based on these results, the subsequent studies were performed using repeated administration of DDC in a dose of 750 mg/kg, three times every 12 hr.

Fig. 2. Gross appearance of duodenal ulcers (A) and microscopical observation of duodenal ulcer (B) and antral ulcer (C and D) induced by repeated administration of diethyldithiocarbamate (DDC) in the rat. DDC was given s.c. in a dose of 750 mg/kg three times every 12 hr, and the animal was killed 12 hr after the final administration. MM indicates the muscularis mucosae.
Effects of diethyldithiocarbamate on gastric acid and duodenal alkaline secretion

Acid secretion: Control rats secreted acid at the rate of 30–40 μEq/10 min during a 5 hr test period. After a single administration of DDC (750 mg/kg, s.c.), acid secretion was markedly decreased to about 10 μEq/10 min and remained reduced for at least 4 hr (Fig. 3A). However, the third injection of DDC failed to produce a prompt inhibition against
acid secretory activity; acid output was gradually reduced from 2 hr after the administration and reached to the significantly lower values 3 hr later as compared to the controls.

Alkaline secretion: The proximal duodenum of control animals secreted alkali at the rate of 2–2.5 \( \mu \text{Eq/10 min} \) under unanesthetized conditions. DDC (750 mg/kg), given subcutaneously as a single injection, decreased the rate of alkaline secretion to about half of the control values, with a transient increase immediately after the injection (Fig. 3B). However, such decrease in the basal \( \text{HCO}_3^- \) secretion was not observed after the third injection of DDC; and in this case, the alkaline output rather showed a slight increase for the initial 1-hr period, similar to the case of acid secretion observed after the third injection of DDC. On the other hand, the duodenal mucosa responded to luminal acidification (10 mM HCl for 10 min) by a significant rise in \( \text{HCO}_3^- \) secretion from 1.6 ± 0.3 \( \mu \text{Eq/10 min} \) to 3.2 ± 0.3 \( \mu \text{Eq/10 min} \). A single or repeated administration of DDC significantly inhibited this increase of \( \text{HCO}_3^- \) output in response to mucosal acidification (Fig. 4). Although the degree of inhibition was more potent after the first injection than that of the third one, the values in \( \text{HCO}_3^- \) output in both cases remained significantly lower than those observed in control animals after exposure to acid.

**Effects of various agents on duodenal ulcers and secretory responses induced by diethylthiocarbamate**

**Duodenal ulcers:** Repeated administration of DDC (750 mg/kg) subcutaneously, three times every 12 hr, caused one or two ulcers in the duodenum; the ulcer index was 25.8 ± 5.8 mm\(^2\). Pretreatment of animals with allopurinol (50 mg/kg \( \times \) 3, s.c.), glutathione (200 mg/kg, s.c.) and SOD (50000 units/kg \( \times \) 3, s.c.), given 10 min before each DDC injection, significantly decreased the severity of ulcers induced by DDC, the reduction being 74.9%, 46.5% and 52.2%, respectively (Table 1). Prior adminis-

![Fig. 4](image-url)  
*Fig. 4. Effects of a single (●) and repeated (■) s.c. administration of diethylthiocarbamate (DDC, 750 mg/kg) on alkaline secretory responses caused by acid in the duodenum. DDC was given s.c. once or three times every 12 hr, and the duodenal mucosa was exposed for 10 min to 10 mM HCl 1 hr after the last injection. Data are presented as the mean ± S.E. of values determined every 10 min from 6 rats per group. *Statistically significant difference from the controls (○) at P < 0.05.*
tration of dmPGE₂ (10 μg/kg × 3, s.c.) also significantly prevented the formation of duodenal ulcers in response to DDC; the lesion index was reduced to 3.3 ± 1.7 mm², the reduction being 87.2%. In addition, the development of duodenal ulcers induced by DDC was potently inhibited by cimetidine (100 mg/kg × 3, s.c.), the reduction in the ulcer index being 79.1%. The latter two agents significantly reduced the incidence as

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>No. of rats</th>
<th>Area of ulcers (mm²)</th>
<th>Inhibition (%)</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>10</td>
<td>25.8 ± 5.8</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>Allopurinol</td>
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<td>8</td>
<td>6.4 ± 2.1*</td>
<td>74.9</td>
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<tr>
<td>Glutathione</td>
<td>200</td>
<td>8</td>
<td>13.8 ± 2.1*</td>
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<td>100</td>
</tr>
<tr>
<td>SOD</td>
<td>50000 units/kg</td>
<td>6</td>
<td>12.1 ± 2.9*</td>
<td>52.2</td>
<td>100</td>
</tr>
<tr>
<td>dmPGE₂</td>
<td>0.01</td>
<td>7</td>
<td>3.3 ± 1.7*</td>
<td>87.1</td>
<td>42.9</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>100</td>
<td>7</td>
<td>5.4 ± 2.6*</td>
<td>79.1</td>
<td>57.1</td>
</tr>
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</table>

Values are presented as the mean ± S.E. from 6–10 rats per group. DDC was given s.c. repeatedly 3 times every 12 hr, and the animals were killed 12 hr after the final administration. Each drug was given s.c. three times, each 10 min before DDC treatment. *Statistically significant difference from the control at P < 0.05.

Fig. 5. Effects of allopurinol (▲, 50 mg/kg), glutathione (■, 200 mg/kg) and superoxide dismutase (SOD, ●, 15000 units/kg/hr) on duodenal alkaline secretion in rats treated with diethyldithiocarbamate (DDC, 750 mg/kg, s.c.). Allopurinol or glutathione was given s.c. 1 hr before administration of DDC, while SOD was infused i.v. during a test period starting 1 hr before DDC treatment. Data are presented as the mean ± S.E. of values determined every 10 min from 5–6 rats per group. *Statistically significant difference from the controls (○) at P < 0.05. The area shown by ■■■ indicates the levels of alkaline secretion observed in normal rats.

Table 1. Effects of various drugs on duodenal ulcers induced in rats by repeated administration of diethyldithiocarbamate
well as the severity of duodenal ulcers.

**Alkaline secretion:** As shown earlier, a single injection of DDC (750 mg/kg, s.c.) not only reduced basal HCO₃⁻ output but attenuated the increased HCO₃⁻ responses caused by mucosal acidification as well. The reduction in basal HCO₃⁻ secretion caused by DDC was significantly reverted by either allopurinol (50 mg/kg, s.c.), glutathione (200 mg/kg, s.c.) or SOD (15000 units/kg/hr, i.v.); and in the animals treated with SOD, the HCO₃⁻ output was significantly increased over the values found in the control group (Fig. 5). Although the acid-induced HCO₃⁻ output was partially but significantly restored by SOD in the presence of DDC, these responses remained inhibited by DDC in the animals treated with allopurinol and glutathione (Fig. 6). Especially, the rate of HCO₃⁻ secretion was elevated gradually after the onset of SOD infusion and reached to statistically significant levels 45 min later. On the other hand, dmPGE₂ (10 μg/kg, s.c.) increased the rate of alkaline secretion even in the presence of DDC; the degree of stimulation was equivalent to that observed in normal rats. In these animals, the HCO₃⁻ output elevated from 2.4 ± 0.3 μEq/10 min to 3.5 ± 0.5 μEq/10 min, and the values were significantly higher when compared to the animals treated with DDC alone (Fig. 7). Although cimetidine did not significantly affect both basal and acid-stimulated alkaline secretion, acid secretion was markedly inhibited by this agent in the presence of DDC (not shown).

**Acid secretion:** Subcutaneous administration of cimetidine (100 mg/kg) significantly inhibited gastric acid secretion in pylorus-ligated rats, the inhibition of the acid output being 83.6%. DMPGE₂ (10 μg/kg) tended to inhibit

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Fig. 6. Effects of allopurinol (▲, 50 mg/kg), glutathione (■, 200 mg/kg) and superoxide dismutase (SOD, ●, 15000 units/kg/hr) on alkaline secretory responses caused by mucosal acidification (10 mM HCl for 10 min) in the rats treated with diethyldithiocarbamate (DDC, 750 mg/kg, s.c.). Allopurinol or glutathione was given s.c. 2 hr before exposure of the mucosa to acid, while SOD was infused i.v. during a test period. DDC was given subcutaneously 1 hr before the exposure to acid. Data are presented as the mean ± S.E. of values determined every 10 min from 5–6 rats per group. *Statistically significant difference from the control (○) at P < 0.05. The area shown by ■■■■ indicates the levels of alkaline response caused by acid in the normal rats without DDC treatment.
the acid output (25.6%), but this effect was not statistically significant. Neither SOD (50000 units/kg), allopurinol (50 mg/kg) nor glutathione (200 mg/kg) significantly affected the acid output in the pylorus-ligated animals (not shown).

DISCUSSION

The present study confirmed our previous finding (3) that the repeated administration of DDC to normally fed animals consistently produced duodenal ulcers with less lesions in the stomach. Since DDC inhibits SOD activity in the gastrointestinal mucosa (1, 2, 8), it is supposed that the pathogenesis of these ulcers may be attributable to accumulation of superoxide radicals induced by low SOD activity.

The ulcerogenic action of DDC in the rat stomach was first introduced by Ogino et al. (1, 2, 13) who showed that DDC given subcutaneously at 1.5 g/kg to fasted rats induced damage in the antrum within 7 hr. Takamasu et al. (8) later found that the same dose of DDC aggravated cysteamine-induced duodenal ulcers in rats and produced damage in the duodenum in the presence of acid hypersecretion caused by histamine. We reported that DDC by itself caused duodenal ulcers after repeated administration to fed rats at much lower dose (750 mg/kg) (3). As evidenced in the present study, this dose schedule was ulcerogenic in the duodenum but not in the stomach, suggesting an involvement of factors specific to duodenal ulcer in the pathogenesis.

The ability of DDC to impair the activity of one of the components of the antioxidant machinery, copper-modulated cytosolic SOD, is thought to be a significant factor in DDC-induced cellular toxicity (14). The reactivity of DDC with sulfhydryl groups may also impair the antioxidative activity of glutathione (15, 16). Oka et al. (13) reported that gastric ulcers induced by DDC were significantly prevented by SOD and catalase, suggesting a pathogenic role of superoxide radical and hy-
drogen peroxide in this ulcer model. The recent study by Salim (17) implicated these oxygen-derived free radicals in the etiological mechanism of duodenal ulcers. They observed that duodenal ulcers induced by pentagastrin plus carbachol were prevented by allopurinol, dimethyl sulfoxide or L-cysteine and suggested that mucosal irritation by acid activates xanthine oxidase, the enzyme which converts hypoxanthine to xanthine in the presence of oxygen, resulting in formation of superoxide anion. Inhibition by DDC of SOD activity may lead to accumulation of these radicals and enhances their toxic action. We also observed that DDC-induced duodenal ulcers were significantly inhibited by allopurinol, an inhibitor of xanthine oxidase (9), as well as SOD and glutathione. Since oxyradicals promote lipid peroxidation and membrane damage by cross-linking proteins, lipids, and nucleic acids (8, 18), the increased radical formation caused by DDC may be detrimental to the integrity of duodenal tissues and may be responsible for their injury. However, inhibition by DDC of SOD activity occurred only at high concentrations, more than 15-fold higher than that required to demonstrate cellular toxicity (16). This may call into question the significance of alterations in SOD activity as a mechanism of DDC toxicity. Yet, since duodenal ulcers were induced only by high doses of DDC (> 750 mg/kg) (3), it seems likely that the deleterious effect of DDC in the present study is related to inhibition of SOD activity. Certainly, the possibility cannot be totally excluded that DDC is a toxin for the duodenal mucosa and that the efficacy of SOD and glutathione on DDC-induced duodenal ulcers relates to their ability to bind DDC in the serum, preventing it from interacting with the duodenal mucosa, as it is known that DDC binds to these agents in vitro (16).

The relation of SOD inhibition to acid and alkaline secretion seems complex; DDC reduced not only alkaline secretion in the duodenum but gastric acid secretion as well, though the effects became less marked after the repeated administration. The acid secretion changes by DDC may be explained by the observation of Dickinson et al. (19) who showed that the repeated injection of DDC (400 mg/kg × 3) rather increased both basal and gastrin-stimulated acid output, probably causing up-regulation of gastrin receptors. On the other hand, the diminished effect of DDC on alkaline secretion may be attributable to an increased diffusion of HCO₃⁻ due to the mucosal damage. Because macroscopic lesions were observed already in the duodenum after the second injection of DCC. Yet, the acid-induced HCO₃⁻ secretion was significantly inhibited even by the third injection of DDC, suggesting that HCO₃⁻ secretory disorders may be more important in the pathogenesis of DDC-induced duodenal ulcers. This is consistent with the previous observation showing that the impairment of acid-induced HCO₃⁻ secretion is more closely associated with the pathogenesis of duodenal ulcers as induced by cysteamine, mepirizole, or indomethacin plus histamine (4–7, 20). Certainly, acid is essential to the development of duodenal ulcers induced by DDC, since they were significantly prevented by cimetidine which inhibits acid secretion without any effect on HCO₃⁻ secretion (5).

As expected, SOD infusion (i.v.) significantly reversed the impaired alkaline secretion in the presence of DDC. Both allopurinol and glutathione also significantly antagonized the inhibitory effect of DDC on basal HCO₃⁻ secretion, though they did not ameliorate the impaired HCO₃⁻ response to acid. These results may suggest that the DCC effect on alkaline secretion results, at least in part, from the insufficiency of the antioxidative system in the mucosa. Inhibition by DDC of SOD leads to accumulation of free radicals, probably deriving from both the hypoxanthine-xanthine oxidase system and a neutrophil-dependent process (1, 12). SOD scavenges superoxide anion generated in both pathways, while allopurinol inhibits radical formation in the former pathway and glutathione contributes to reducing the reactive oxygen-mediated cytotoxicity (21, 22). This may explain why SOD is the most
effective in counteracting the deleterious action of DDC on alkaline secretion. On the other hand, since alkaline secretion depends on active, energy-requiring process (23), it might be possible that the observed effect of DDC on HCO₃⁻ secretion is due to more general cellular toxicity caused by this agent (22, 24). Yet, since the duodenal mucosa responded to dmPGE₂ in the presence of DDC by a similar magnitude of increase in HCO₃⁻ output as that induced by this agent in normal rats, the general toxicity of DDC cannot totally explain the secretory disorder observed in the present study.

The present study indicates that DDC, an inhibitor of SOD, induced duodenal ulcers when given repeatedly to fed rats, probably due to the HCO₃⁻ secretory disorders caused by the impairment of the antioxidant system. Since DDC did not increase but rather decreased acid secretion, the integrity of the duodenal mucosa including the alkaline secretory ability is more crucial than the state of acid secretion in the mechanism of duodenal ulceration.

REFERENCES

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