

Effects of KW-5805, a New Antiulcer Agent, on Experimental Gastric and Duodenal Ulcers, Gastric Mucosal Lesions by Necrotizing Agents and Gastric Acid Secretion

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ABSTRACT—Effects of KW-5805, a new antiulcer agent, on various experimental ulcers, necrotizing agent-induced gastric lesions and gastric acid secretion in rats were compared with those of pirenzepine and cimetidine. KW-5805 showed antiulcer activities against experimental gastric and duodenal ulcers (ED_{50} = 1.2–10.0 mg/kg, p.o.). KW-5805 effectively inhibited gastric lesions induced by various necrotizing agents (ED_{50} = 4.5–39.8 mg/kg, p.o.). In addition, the cytoprotective effect of KW-5805 was not affected by indomethacin, but reserved by *N*-ethylmaleimide. These antiulcer and cytoprotective effects of KW-5805 were more potent than those of pirenzepine and cimetidine. In pylorus-ligated rats, intraduodenal KW-5805 administration at 30 mg/kg showed a weak antisecretory effect, which was 3–10 times less potent than those of pirenzepine and cimetidine. In rats with acute gastric fistula, intravenous injection of KW-5805 reduced methacholine-stimulated gastric acid secretion at doses of 10 and 30 mg/kg and inhibited tetragastrin-induced acid secretion at 30 mg/kg. These results indicate that KW-5805 has potent and broad antiulcer properties, which are probably exerted by its potent cytoprotective effect in addition to its antisecretory effect.

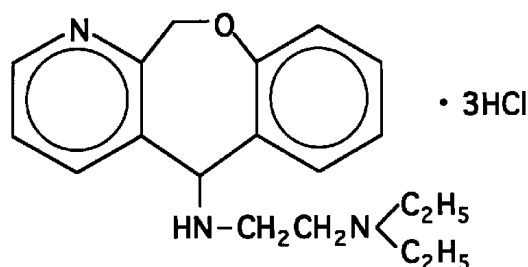
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It is generally accepted that peptic ulcers are caused by an imbalance of aggressive factors (acid and pepsin) and mucosal defensive factors (mucus, bicarbonate and blood flow) (1). Consequently, antiulcer therapy has been mainly directed toward the aggressive factors. Histamine (H_2)-receptor antagonists, anticholinergics, and antacids are known to lower acid secretion (2). Cimetidine, an H_2 -receptor antagonist, is widely used for the treatment of peptic ulcers. Some tricyclic compounds such as doxepine, an antidepressant, and pirenzepine, a selective muscarinic-receptor antagonist, exert antiulcerogenic effects mainly through antisecretory mechanisms (3–6).

On the other hand, Robert (7) first introduced the term “cytoprotection” to describe the ability of prostaglandins (PGs) to protect against the development of gastric lesions induced by necrotizing agents, and this phenomenon is independent of the inhibition of acid secretion. Since it was reported that endogenous PGs and nonprotein sulfhydryls (NP-SHs) were involved in cytoprotection (8, 9), many antiulcer compounds such as pirenzepine and the other antimuscarinic agents were

found to elicit inhibitory actions against gastric lesion models whose pathogenesises were unrelated to acid secretion (10–12).

5-[2-(Diethylamino)ethyl]amino-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine trihydrochloride (KW-5805) is a newly synthesized tricyclic compound (Fig. 1), which ex-



M.W. 420.81

Fig. 1. Chemical structure of KW-5805.

hibits low affinity to the muscarinic acetylcholine receptor as compared to pirenzepine and has antiulcer activity against experimental stress ulcer (13).

In the present study, we compared the antiulcer and cytoprotective properties of KW-5805 with those of pirenzepine and cimetidine. In addition, the cytoprotective effect of KW-5805 and its relationship to endogenous PGs and NP-SHs were studied. We also investigated the effect of KW-5805 on gastric acid secretion to clarify its mechanism of action.

MATERIALS AND METHODS

Animals

Male Donryu rats (Nihon Rat, Urawa) weighing 190–210 g were used. The animals were housed under controlled environmental conditions (room temperature 22–26°C and humidity 55–60%) and fed a standard diet (Funabashi Farmas, Funabashi).

Drugs

KW-5805 was synthesized in our laboratory. Other drugs and chemicals used were obtained from the following sources: pirenzepine dihydrochloride (Chemofin, Milano, Italy); cimetidine (Ricerchimica, Milano, Italy); aspirin, indomethacin and methacholine chloride (Sigma, St. Louis, MO, USA); mepirizole (Daiichi, Tokyo); sodium taurocholate (Difco Lab., Detroit, MI, USA); tetragastrin (Teikokuzoki, Tokyo); 1 N HCl and *N*-ethylmaleimide (Wako Pure Chem., Osaka); and ethanol (Kanto Chem., Tokyo).

KW-5805 and pirenzepine were dissolved in saline. Cimetidine was suspended in 0.3% carboxymethylcellulose sodium (CMC; Daiichi Pure Chem., Tokyo). These drugs were given orally in a volume of 0.5 ml/100 g body weight.

Experimental gastroduodenal ulcers

Water-immersion stress-induced gastric ulcer: Animals were deprived of food but allowed free access to water for 17 hr before the experiment. According to the method of Takagi and Okabe (14), each animal was placed in a restraint cage and then immersed in a water bath at 22–24°C. After 7 hr, the animals were sacrificed. The stomachs were removed and then cut along the greater curvature. Drugs were administered orally 10 min before the water-immersion. The length (mm) of each ulcer formed on the glandular stomach was measured under a magnifying glass (5×), and the sum of the lengths in each animal served as the measure of ulcer index.

Aspirin-induced gastric ulcer: Aspirin was suspended in 0.3% carboxymethylcellulose sodium (CMC) and administered orally at a dose of 200 mg/kg to 48-hr fasted

rats. The animals were sacrificed 20 hr after aspirin administration. Drugs were administered orally 30 min before aspirin treatment. The ulcer index was assessed as described above.

Indomethacin-induced gastric ulcer: Indomethacin (20 mg/kg) suspended in 0.3% CMC was administered to 48-hr fasted rats. The animals were sacrificed 20 hr after indomethacin administration. Drugs were administered orally 30 min before indomethacin treatment. The stomachs were excised and their ulcer index determined.

Mepirizole-induced duodenal ulcer: According to the previously reported method (15), the animals were fasted for 17 hr with access to water ad libitum. Mepirizole was suspended in 0.3% CMC and administered orally at a dose of 200 mg/kg. Drugs were given 30 min before mepirizole treatment. Twenty hours after mepirizole administration, the duodenum of each animal was excised. The area (mm²) of the ulcers were measured and summed. The total area per animal served as the measurement of ulcer index.

Experimental gastric lesions induced by necrotizing agents

Animals were fasted for 36 hr with access to drinking water ad libitum. The following necrotizing agents were administered orally in the volume of 1 ml: 99.5% ethanol, 0.6 N HCl, 0.5 N HCl + 50% ethanol (acidified ethanol), and 0.1 N sodium taurocholate + 0.2 N HCl, according to the method of Robert (7) and Konturek et al. (16). Drugs were given orally 30 min prior to the treatment of necrotizing agents. In addition, KW-5805 was injected subcutaneously 30 min before ethanol treatment. Thirty minutes after the administration of necrotizing agents, the animals were sacrificed. The stomach was removed and cut along the greater curvature. The length (mm) of each necrotic lesion was measured under a magnifying glass (5×), summed per stomach, and used as a lesion index. In acidified ethanol-induced gastric lesion-tests, indomethacin, a cyclooxygenase inhibitor (5 mg/kg), or *N*-ethylmaleimide, an SH blocker (5 mg/kg), was given subcutaneously 1 hr before KW-5805 treatment. KW-5805 was given orally 30 min before acidified ethanol administration.

Gastric secretion

Pylorus-ligated rats: Animals were fasted for 48 hr with access to water ad libitum. Drugs were given i.d. immediately after the pylorus ligation under ether anesthesia. Four hours after the pylorus ligation, the rats were sacrificed and the gastric contents were collected, its volume measured, centrifuged and subjected to analysis for titrable acidity against 0.05 N NaOH to pH 7.4 using a pH meter. The acid concentration was multiplied by the

volume to obtain the total acid output.

Rats with acute fistula: Animals were deprived of food but allowed free access to water for 24 hr. Each animal was then anesthetized with urethane (1 mg/kg, i.p.) and surgically prepared as described by Sasajima et al. (17). A small midline incision was made, and the stomach and duodenum were exposed. A dual polyethylene canula was inserted into the forestomach. Three milliliters of warm saline (37°C) was perfused into the gastric lumen, and the perfusate was collected at the end of 1 hr and titrated for acidity with 0.05 N NaOH. The following secretagogues were administered subcutaneously: methacholine at 1 mg/kg, histamine at 30 mg/kg and tetragastrin at 0.3 mg/kg. Drugs were injected intravenously 30 min before each secretagogue treatment.

Statistical analysis

Data were presented as the mean \pm S.E. The 50% effective dose (ED₅₀) values of test drugs for experimental gastroduodenal ulcers and gastric lesions induced by various necrotizing agents were calculated according to Filler's theorem. Statistical analysis was performed by Student's *t*-test or Aspin-Welch test. A difference with a *P* value < 0.05 was considered significant.

RESULTS

Experimental gastroduodenal ulcers

Oral administration of KW-5805 dose-dependently inhibited the development of gastric ulcers induced by stress, aspirin and indomethacin. KW-5805 was also effective for preventing duodenal ulcers produced by mepirizole. The ED₅₀ values of KW-5805 for each ulcer model ranged from 1.2 to 10 mg/kg (Table 1). Pirenzepine and cimetidine also dose-dependently prevented the ulcers, but both drugs showed a weak antiulcer activity against indomethacin-induced gastric ulcer. The ED₅₀ values are listed in Table 1. Antiulcer effects of KW-5805 were 3–10 times more potent than those of pirenzepine and cimetidine.

Cytoprotection studies

KW-5805 protected gastric mucosa against all the necrotizing agents used (99.5% ethanol, 0.6 N HCl and 0.2 N HCl + 0.1 N sodium taurocholate). The oral ED₅₀ values ranged from 4.5 to 39.8 mg/kg (Table 2). Oral pirenzepine (30 mg/kg) failed to protect the gastric mucosa against acidified taurocholate. Cimetidine did not show any effect on gastric lesions induced by 0.6 N HCl even at a dose of 300 mg/kg (p.o.) (Table 2).

Table 1. Antiulcer effects of KW-5805, pirenzepine and cimetidine on stress-, aspirin- and indomethacin-induced gastric ulcers and mepirizole-induced duodenal ulcer in rats

| Compounds | ED ₅₀ (mg/kg, p.o.) (95% C.L.) | | | |
|-------------|---|----------------|-------------------|------------------|
| | Stress | Aspirin | Indomethacin | Mepirizole |
| KW-5805 | 3.5 (2.2–5.0) | 1.2 (0.4–2.2) | 10.0 (7.5–13.5) | 6.8 (5.3–8.7) |
| Pirenzepine | 10.4 (8.8–12.4) | 3 (2.5–3.5) | 89.9 (73.4–117.5) | 4.0 (3.4–4.7) |
| Cimetidine | 28.7 (21.8–37.4) | 7.0 (3.3–10.7) | 100< | 39.5 (35.5–44.2) |

Data were obtained for each of the compound in 9–35 animals per dose, using 3–4 doses. ED₅₀ (95% confidence limits) was calculated by Filler's theorem.

Table 2. Cytoprotective effects of KW-5805, pirenzepine and cimetidine in rats

| Compounds | ED ₅₀ (mg/kg, p.o.) (95% C.L.) | | |
|-------------|---|------------------|------------------|
| | 99.5% Ethanol | 0.6 N HCl | HCl + TAC |
| KW-5805 | 4.5 (2.8–6.3) | 39.8 (30.4–54.8) | 11.8 (9.7–14.6) |
| Pirenzepine | 19.0 (13.6–24.6) | 26.7 (16.7–41.7) | 30< |
| Cimetidine | 193.1 (162.7–236.2) | 300< | 13.1 (10.3–17.3) |

Each drug was orally given p.o. 30 min before the necrotizing agent treatment. Data were obtained for each of the compounds in 9–16 animals per dose, using 3–4 doses. ED₅₀ (95% confidence limits) was calculated by Filler's theorem. HCl + TAC, 0.2 N HCl + 0.1 N sodium taurocholate.

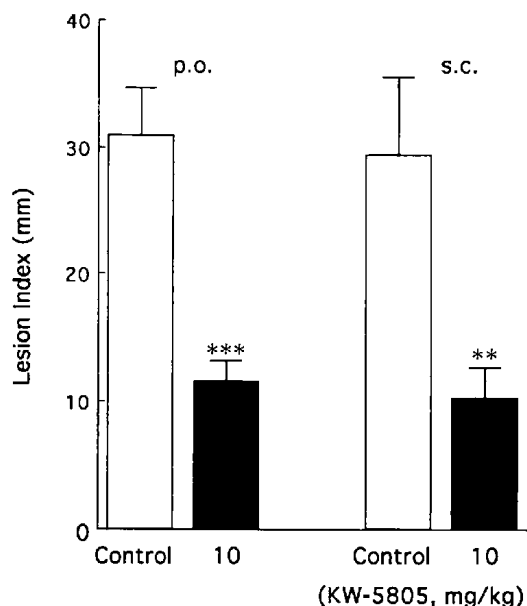


Fig. 2. Effect of KW-5805 on 99.5% ethanol-induced gastric lesions in rats. KW-5805 (10 mg/kg) was given either orally (p.o.) or subcutaneously (s.c.) 30 min before ethanol administration. Data represent the mean \pm S.E. from 14–34 rats per group. ** $P < 0.01$, *** $P < 0.001$, significantly different from the respective control.

KW-5805, given orally or subcutaneously at 10 mg/kg, significantly prevented the formation of gastric mucosal

lesions induced by ethanol; the lesion indices were 12 ± 2 and 10 ± 2 , respectively (Fig. 2).

Subcutaneous treatment with indomethacin (5 mg/kg) or *N*-ethylmaleimide (5 mg/kg) did not affect acidified ethanol-induced gastric lesions. Pretreatment with indomethacin also did not influence the cytoprotective effect of KW-5805 against acidified ethanol-induced gastric mucosal lesions; the lesion index (% of control) was 42 ± 4 without and 40 ± 5 with indomethacin. *N*-Ethylmaleimide, given subcutaneously at a dose of 5 mg/kg, significantly reduced the protective effect of KW-5805 against the lesions; the lesion index (% of control) was 31 ± 4 without and 56 ± 7 with *N*-ethylmaleimide (Fig. 3).

Gastric secretion

KW-5805, only at dose of 30 mg/kg, significantly decreased the volume and acid output in the pylorus-ligated (4 hr) rats. Pirenzepine and cimetidine significantly reduced gastric acid secretion dose-dependently. The anti-secretory effect of KW-5805 was about 3–10 times less potent than those of pirenzepine and cimetidine (Table 3).

In rats with acute gastric fistula, KW-5805, administered intravenously at 10 and 30 mg/kg, showed a significant inhibition of methacholine-stimulated gastric acid secretion (Fig. 4). Pirenzepine (1 and 3 mg/kg, i.p.) also inhibited methacholine-stimulated gastric acid secretion.

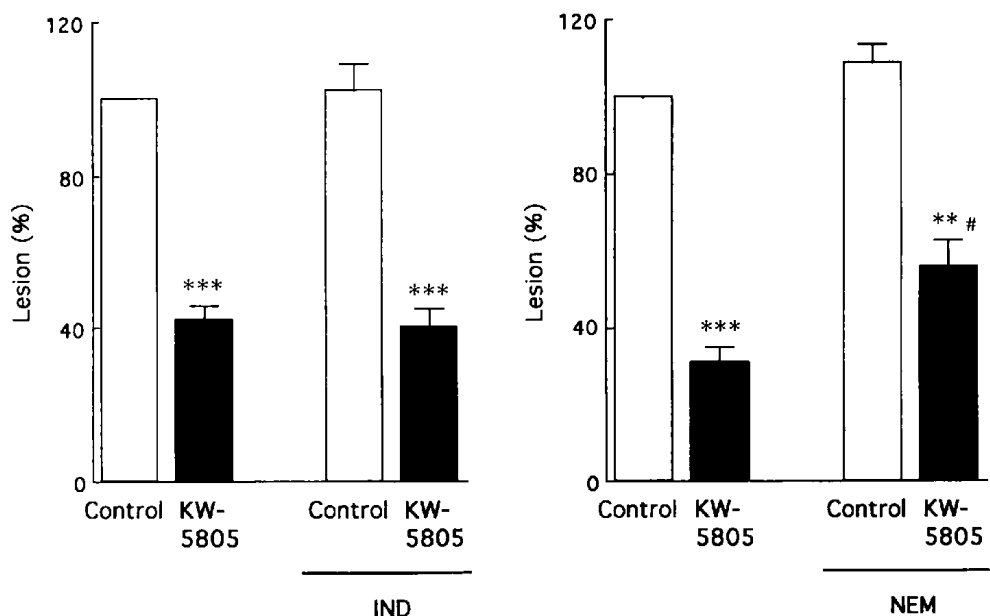


Fig. 3. Effect of pretreatment with indomethacin (IND) and *N*-ethylmaleimide (NEM) on KW-5805 cytoprotection. Subcutaneous IND (5 mg/kg) or NEM (5 mg/kg) was given 60 min before KW-5805 administration. KW-5805 was given orally 30 min before acidified ethanol administration. Lesions were expressed as a percentage of the control values of the lesion index without IND or NEM. Data represent the mean \pm S.E. from 8–10 rats per group. ** $P < 0.01$, *** $P < 0.001$, significantly different from the respective control. # $P < 0.05$, significantly different from the KW-5805-treated group without NEM.

Table 3. Effects of KW-5805, pirenzepine and cimetidine on gastric secretion in pylorus-ligated rats

| Compound | Dose (mg/kg) | N | Volume (ml) | Inhibition (%) | Total acid output (μ Eq/hr) | Inhibition (%) |
|-------------|--------------|----|------------------|----------------|----------------------------------|----------------|
| Control | | 10 | 4.0 \pm 0.3 | | 116.6 \pm 9.0 | |
| KW-5805 | 3 | 9 | 4.0 \pm 0.3 | 0 | 115.5 \pm 9.4 | 1 |
| | 10 | 10 | 4.1 \pm 0.4 | -3 | 120.9 \pm 13.7 | -4 |
| | 30 | 9 | 2.8 \pm 0.3* | 30 | 82.0 \pm 10.7* | 30 |
| Control | | 9 | 4.6 \pm 0.6 | | 128.5 \pm 18.1 | |
| Pirenzepine | 3 | 10 | 3.4 \pm 0.5 | 26 | 91.4 \pm 17.5 | 29 |
| | 10 | 10 | 3.0 \pm 0.3* | 35 | 83.7 \pm 11.5* | 35 |
| | 30 | 10 | 1.1 \pm 0.3*** | 76 | 26.2 \pm 7.3*** | 80 |
| Control | | 10 | 5.1 \pm 0.5 | | 155.3 \pm 17.3 | |
| Cimetidine | 3 | 10 | 3.6 \pm 0.3* | 29 | 100.8 \pm 9.9* | 35 |
| | 10 | 9 | 3.1 \pm 0.4** | 29 | 84.1 \pm 12.5** | 46 |
| | 10 | 9 | 3.1 \pm 6.9** | 39 | 77.6 \pm 6.9*** | 50 |

Each compound was administered intraduodenally immediately after the pylorus ligation. Four hours later, the gastric juice was collected. Data represent the mean \pm S.E. *P<0.05, **P<0.01, ***P<0.001, significantly different from the respective control.

The antisecretory effect of KW-5805 at dose of 30 mg/kg was similar to that of pirenzepine at 1 mg/kg (Fig. 4). KW-5805 at 30 mg/kg also reduced tetragastrin-stimulated acid secretion, but did not affect histamine-induced secretion. The inhibitory effect of KW-5805 was weak as compared to that against methacholine-stimulated acid secretion (Fig. 5).

DISCUSSION

The present studies demonstrated that KW-5805 had marked antiulcer effects against various kinds of experimental ulcers in rats. Its antiulcer activity was 3–10 times more potent than those of pirenzepine and cimetidine.

Production of gastric ulcers by stress and non-steroidal

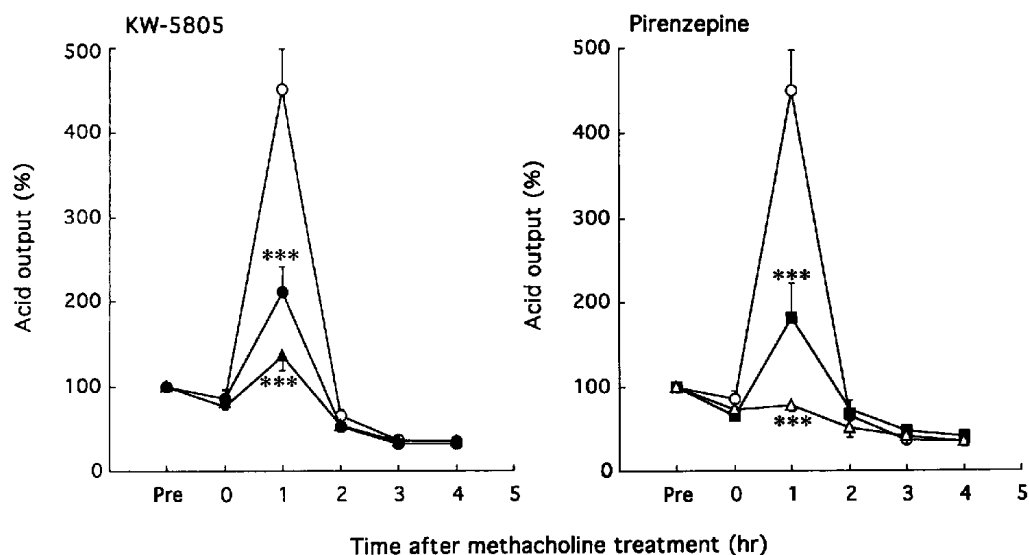


Fig. 4. Effects of KW-5805 and pirenzepine on methacholine-stimulated acid secretion in rats with acute gastric fistula. Drugs were injected intravenously 30 min before subcutaneous methacholine (1 mg/kg) administration. Data were expressed as a percentage of the value of acid secretion 1 hr prior to methacholine treatment. Each point represents the mean \pm S.E. of 5–10 animals. ***P<0.001, significantly different from the respective control. ○: control; ●: KW-5805, 10 mg/kg; ▲: KW-5805, 30 mg/kg; ■: pirenzepine, 1 mg/kg; △: pirenzepine, 3 mg/kg.

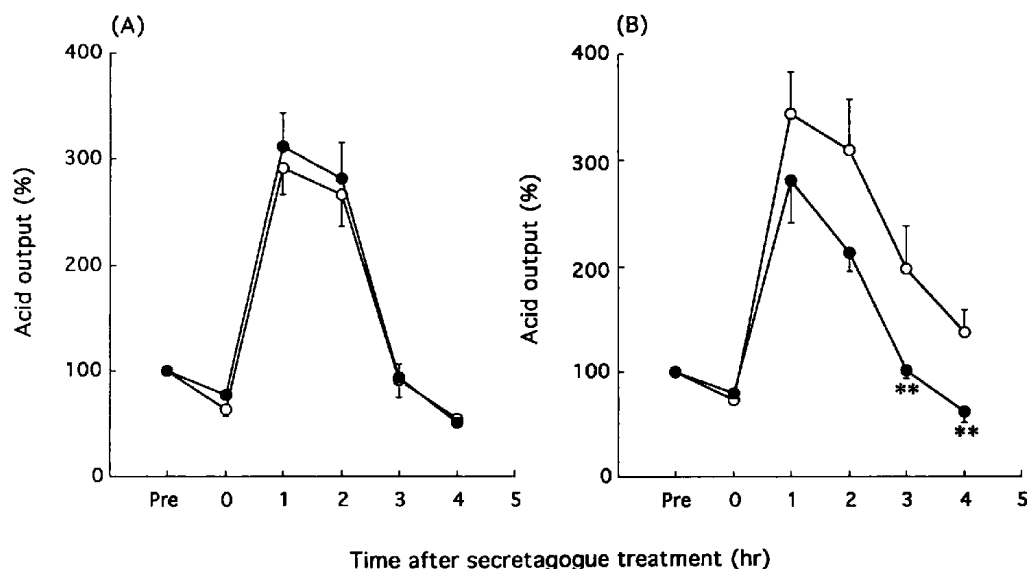


Fig. 5. Effect of KW-5805 on histamine (A)- and tetragastrin (B)-stimulated acid secretion in rats with acute gastric fistula. KW-5805 (30 mg/kg) was injected intravenously 30 min before subcutaneous histamine (30 mg/kg) or tetragastrin (0.3 mg/kg) administration. Data were expressed as a percentage of the value of acid secretion 1 hr prior each secretagogue treatment. Each point represents the mean \pm S.E. of 9–10 animals. ** $P < 0.01$, significantly different from the control. ○: control, ●: KW-5805.

inflammatory drugs (NSAIDs) are thought to result from reinforcement of aggressive factors such as gastric acid and pepsin or lowering of mucosal defensive factors such as gastric mucus and microcirculation (18–25). Mepirizole-induced duodenal ulcers in rats are markedly inhibited by antacids and antisecretory agents (26). It is supposed that gastric acid is a very important factor in the pathogenesis of gastric and duodenal ulcers. We, therefore, investigated the effect of KW-5805 on gastric secretion. In pylorus-ligated rats, intraduodenal administration of KW-5805 at doses of 3 and 10 mg/kg did not affect gastric acid secretion, but showed a weak inhibitory effect at 30 mg/kg. It was disclosed that the inhibitory doses of KW-5805 against experimental gastroduodenal ulcers were lower than the dose at which it suppressed the gastric secretion in pylorus-ligated rats. It is most likely that the antiulcer effect of KW-5805 is exerted not only by inhibition of gastric acid secretion but also by activation of gastric mucosal defensive factors. In fact, KW-5805 showed an increase of gastric mucus secretion and improved mucosal microcirculation (27).

Moreover, we revealed the mechanisms of the inhibitory action of KW-5805 on gastric acid secretion by using rats with acute gastric fistula. KW-5805 inhibited methacholine-stimulated gastric secretion, but the inhibition was 30-fold weaker than that by pirenzepine. KW-5805 also inhibited tetragastrin-stimulated acid secretion. KW-5805 has a tricyclic chemical structure like many antidepressants. Several tricyclic antidepressants were

reported to be effective in the treatment of gastroduodenal ulcers by their antisecretory action mediated through blockade of muscarinic receptors or histamine H_2 -receptors and uptake inhibition of noradrenaline or serotonin (3, 4, 28, 29). KW-5805, however, has a very weak muscarinic receptor binding (1/30 of pirenzepine) (13) and no effect on H_2 -receptors and noradrenaline uptake (A. Ishii et al., unpublished data). The mode of the antisecretory action of KW-5805 is thus apparently different from those of cimetidine and tricyclic antidepressants and may be mediated at least partly through its weak antimuscarinic action as compared to pirenzepine. Furthermore, it is likely that the inhibitory effect of KW-5805 on gastric acid secretion is mediated by its effect on parietal cells or enterochromaffin-like (ECL) cells in the stomach, since gastrin stimulates acid secretion directly mediated by the gastrin receptors on parietal cells (30) or indirectly mediated by the stimulation of endogenous histamine release from ECL cells (31). It has also been reported that KW-5805 inhibits gastric acid secretion stimulated by 2-deoxy-D-glucose, mainly via centrally mediated mechanisms (32), and would be beneficial for the prevention of stress-induced gastric ulceration, which is closely associated with an increase in acid secretion (19). The antisecretory activity of KW-5805 is suggested to be partly involved in its antiulcer effects.

KW-5805 exerted inhibitory effects on various gastric mucosal lesions caused by necrotizing agents, and an especially marked effect was observed in ethanol-induced le-

sions. This effective dose of KW-5805 was lower than that for its antisecretory effect in pylorus-ligated rats. These findings indicate that KW-5805, like prostaglandins, has a "cytoprotective" effect according to the definition of Robert (7). It seems likely that KW-5805 shows such a cytoprotective effect mainly through a systemic action because both oral and subcutaneous administration of KW-5805 were effective. The cytoprotection of KW-5805 was not induced through the mechanism of a mild irritant. Oral administration of pirenzepine also inhibited the ethanol-induced lesions, although these effective doses were higher than that of KW-5805. The protective doses of pirenzepine were similar to its antisecretory doses. Cimetidine at the antisecretory dose inhibited the gastric lesions induced by acidified taurocholate; and at the non-antisecretory dose, it did not inhibit ethanol- and HCl-induced gastric lesions. These results suggest that there is a possibility that the inhibition of necrotizing agents-induced gastric lesions by pirenzepine and cimetidine may be related to their antisecretory effects.

The inhibition of PGs synthesis by pretreatment with indomethacin did not antagonize the protective effect of KW-5805 against acidified ethanol-induced lesions. This result suggests that the effect of KW-5805 is not mediated by synthesis of cytoprotective PGs. In addition to PGs, NP-SHs are also involved in cytoprotection (9). Pretreatment with *N*-ethylmaleimide, resulting from decreased levels of endogenous SHs, significantly suppressed the inhibitory effect of KW-5805 against acidified ethanol-induced gastric lesion. This result suggests that endogenous SHs may be partly involved in the mechanism of gastric cytoprotection afforded by KW-5805.

In conclusion, these results indicate that KW-5805 has potent and broad antiulcer properties, which depend not only on its anisecretory effect but also on its enhancement of gastric mucosal defensive factors.

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