Cytoprotective Action of Mast Cell Stabilizers against Ethanol-Induced Gastric Lesions in Rats

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Accepted July 7, 1986

Abstract—We examined the effects of FPL-52694 and disodium cromoglycate (DSCG), mast cell stabilizers, on HCl-ethanol-induced gastric lesions in rats and investigated the factors involved in their protection. Oral (p.o.) administration of 1 ml of HCl-ethanol (60% in 150 mM HCl) induced linear hemorrhagic lesions in the gastric mucosa within 1 hr. FPL-52694 (1–30 mg/kg), given both p.o. and intraperitoneally (i.p.), prevented these lesions in a dose-related manner. DSCG (3–30 mg/kg) also dose-dependently reduced the formation of these lesions when this agent was given i.p. The protective effects of these drugs on HCl-ethanol-induced lesions were significantly attenuated by pretreatment with indomethacin (5 mg/kg, s.c.). Both gastric acid secretion and transmucosal potential difference were significantly reduced by topical application of FPL-52694 (>10 mg/kg), but were not affected by i.p. administration of FPL-52694 and DSCG. On the other hand, gastric motor activity measured as intraluminal pressure recordings was significantly inhibited for 2 hr by both FPL-52694 (p.o. and i.p.) and DSCG (i.p.), and these effects were also significantly antagonized with prior administration of indomethacin. A significant relationship was found between the effects of these two drugs on the lesion index and the motility index (r: 0.9214, P<0.01), but not other factors. These results suggest that mast cell stabilizers such as FPL-52694 and DSCG protect the gastric mucosa against HCl-ethanol through a systemic action, probably mediated with endogenous prostaglandins. Although the mechanism of cytoprotection remains unknown, this property may be related to their inhibitory effects on gastric motor activity.

Analogues of prostaglandins, at non-antisecretory doses, prevent gastric lesions induced by necrotizing agents such as absolute ethanol and concentrated acid or alkali, and this action is called "cytoprotection" (1). Although the pathogenesis of these lesions and the mechanisms of cytoprotection remain unknown, recent studies have shown that ethanol-induced gastric lesions were prevented in mast cell deficient mice (2) and by prior administration of compounds which inhibit histamine release from the mucosal store sites in rats (3–5). Disodium cromoglycate (DSCG) and FPL-52694 [5-(2-hydroxypropoxyl)-8-propyl-4-oxo-4H-benzopyran-2-carboxylic acid Na], mast cell stabilizers (6, 7), have antisecretory and antiulcer effects on stress-, aspirin- or compound 48/80-induced gastric lesions in rats (8–11). The latter agent is a derivative of DSCG, but is known to be well absorbed when taken orally (10). If these agents afford protection against ethanol-induced gastric lesions, then the cytoprotective action would at least partly account for their antiulcer effects observed in various lesion models.

In the present study, we therefore examined the effects of FPL-52694 and DSCG on HCl-ethanol-induced gastric lesions in rats, and investigated the influences of these drugs on various gastric functions to approach the possible mechanisms of their protection against these lesions.
Materials and Methods

Male Donryu rats (200–230 g), kept in individual cages with raised mesh bottoms, were deprived of food but allowed free access to tap water for 24 hr prior to the experiments. Each study was carried out using 3–10 rats per group.

Induction of gastric lesions by ethanol: Animals were given 1 ml of HCI-ethanol (60% ethanol in 150 mM HCl) orally by esophageal intubation, and they were killed 1 hr later (12). The stomachs were removed, inflated by injecting 12 ml of 2% formalin, immersed in 2% formalin for 10 min to fix both the inner and outer layers of gastric walls, and opened along the greater curvature. The length (mm) of each lesion induced by HCl-ethanol was measured under a dissecting microscope with square grid (×10), summed, and used as a lesion index. Either FPL-52694 (Fisons: 1–30 mg/kg) or DSCG (Fujisawa, Intal'R: 3–30 mg/kg), suspended in saline, was given either orally or intraperitoneally in a volume of 0.5 ml per 100 g of body weight 30 min before administration of HCl-ethanol. In some cases, indomethacin (Merck), suspended in saline with a trace of Tween 80 (Nakarai), was given subcutaneously in a dose of 5 mg/kg 1 hr before HCl-ethanol treatment. Control animals were given the vehicle alone. In the above studies, the person measuring the lesions did not know the treatment given to the animals.

Determination of acid secretion: The effects of FPL-52694 and DSCG on gastric acid secretion were investigated in pylorus-ligated rats. Under ether anesthesia, the abdomen was opened and the pylorus was ligated. Four hr later, the animals were killed, and the gastric contents were collected and centrifuged at 3000 r.p.m. for 15 min. Each sample was measured for volume and titrated to pH 7.4 with 0.1 N NaOH for titratable acidity using an automatic burette (Radiometer, Copenhagen). Acid output was calculated and expressed as μEq/hr. FPL-52694 (3–30 mg/kg) or DSCG (30 mg/kg) was given either orally or intraperitoneally immediately after pylorus ligation. Control animals were given the vehicle alone.

The effects of FPL-52694 and DSCG on gastric motor activity were examined whether FPL-52694 and DSCG induced mucosal protection by mild irritation to the gastric mucosa, gastric transmucosal potential difference (PD) and HCO₃⁻ output were measured following administration of these two drugs. Measurements of gastric PD and HCO₃⁻ output were performed in rats anesthetized with urethane (Nakarai, 1.25 g/kg), intraperitoneally, according to previous papers (13, 14). Briefly, the abdomen was opened, and the stomach and duodenum were exposed. An acute gastric fistula with a three way tap was provided in the forestomach. Another polyethylene tube was inserted into the stomach through a slit in the duodenum, and this was held in place by a ligature around the pylorus. Then, the stomach was perfused at a flow rate of 1 ml/min with saline (154 mM NaCl). The PD was measured using two agar bridges, one positioned in the glandular part of the stomach and the other positioned in the abdominal cavity. After basal PD had been stabilized, either FPL-52694 (3–30 mg/kg) or DSCG (30 mg/kg) was applied topically to the stomach for 30 min through the tap or by intraperitoneal administration. The PD was monitored on a Hitachi recorder (Model 056) for a total period of 2 hr. Gastric HCO₃⁻ output was measured using a pH-stat method by introduction of an automatic titrator (Hiranuma Comtite-7) in the above perfusion system. To unmask HCO₃⁻ in the lumen, acid secretion was completely inhibited by intraduodenal administration of omeprazole (Hassle, 30 mg/kg) (13). After basal HCO₃⁻ secretion had been stabilized, either FPL-52694 (3–30 mg/kg) or DSCG (30 mg/kg) was applied topically to the stomach for 30 min or by intraperitoneal administration. HCO₃⁻ output was measured for 1 hr each before and after the administration of the above agents, and the results were expressed as μEq/hr.

Determination of gastric motor activity: Since gastric lesions induced by necrotizing agents such as HCl-ethanol are largely confined to the crest of the rugae in the gastric mucosa (15), alterations in gastric motor activity (muscle action) may affect the development of these lesions (16).
fore, the effects of FPL-52694 and DSCG on gastric motor activity were examined in conscious rats using a balloon positioned in the glandular part of the stomach, according to a previous paper (16). Briefly, under ether anesthesia, a balloon (containing about 1 ml of water), the support catheter and another catheter for intragastric administration of drugs were placed in the glandular stomach through an incision of the forestomach. The animals were then placed in Bollman cages, and the support catheter was connected to a pressure transducer and polygraph device (Nihon Kohden). Gastric motor activity was continuously monitored on a Hitachi recorder (Model 056) as intraluminal pressure recordings. Quantitative analysis of gastric motor activity was performed by measuring the amplitude of contractions and by counting the number of contractions with the amplitude of 15 cm H$_2$O or greater. Either FPL-52694 (10 mg/kg) or DSCG (30 mg/kg) was given intragastrically through the cannule or intraperitoneally after basal motor activity had been well stabilized. In some cases, indomethacin was given subcutaneously in a dose of 5 mg/kg 30 min before the administration of the above agents. Control animals were given the vehicle alone. Gastric motor activity was measured for a total period of 3 hr.

Statistics: Data are presented as means± S.E. from 3 to 10 rats per group. Statistical analysis was performed using Dunnett's multiple comparison test (17) for unpaired variates, and values of P<0.05 were regarded as significant. A regression analysis was used to determine a correlation coefficient between two different variates.

Results

Effects of FPL-52694 and DSCG on HCl-ethanol-induced gastric lesions

Oral administration of HCl-ethanol (60% in 150 mM HCl) induced streak necrotic lesions in the gastric mucosa 1 hr later, mostly confined to the crest of the rugae in the corpus region. Pretreatment with FPL-52694, given both orally and intraperitoneally, prevented the development of gastric lesions induced by HCl-ethanol in a dose-related manner (Fig. 1A and 1B). The effect of orally administered FPL-52694 was significant at the dose of 3 mg/kg or greater, while a significant effect was achieved at over 10 mg/kg when this agent was given intraperitoneally. The inhibition at 3, 10 and 30 mg/kg of oral FPL-52694 was 62.7%, 92.4% and 99.8%, respectively, and that of intraperitoneal administration was 46.5%, 82.5% and 95.7%, respectively. On the other hand, DSCG also dose-dependently reduced the formation of HCl-ethanol-induced gastric lesions, only when this agent was given intraperitoneally, and a significant effect was observed at 30 mg/kg. The inhibition of DSCG was 21.7%, 50.2% and 78.8% at the doses of 3, 10 and 30 mg/kg, respectively.

Indomethacin treatment: Pretreatment with subcutaneously administered indomethacin (5 mg/kg) did not significantly affect the development of gastric lesions in response to 60% ethanol in 150 mM HCl. However, the
inhibitory effects of intraperitoneally administered FPL-52694 (10 mg/kg) and DSCG (30 mg/kg) almost totally disappeared in the presence of indomethacin (Fig. 2). The protective effect of orally administered FPL-52694 on HCl-ethanol-induced gastric lesions was also partially attenuated by this agent. The degree of inhibition (56.4%) induced by oral administration of FPL-52694 (10 mg/kg) in the presence of indomethacin was significantly lower than that (92.4%) obtained in the absence of this agent.

Effects of FPL-52694 and DSCG on gastric functions

Acid secretion: Oral administration of FPL-52694 dose-dependently decreased gastric acid output in pylorus-ligated rats (4 hr), and the effect was significant at a dose of 30 mg/kg (Fig. 3). The volume of gastric juice was not significantly affected by orally administered FPL-52694 at any of the doses used. Intraperitoneal administration of FPL-52694 and DSCG, however, had no effect on acid secretion even at the dose of 30 mg/kg. In a previous study (18), we have shown that the inhibitory effect of intragastric administration of FPL-52694 on acid secretion was partially antagonized by indomethacin at a dose of 5 mg/kg.

Gastric PD and HCO$_3^-$ output: The normal stomach generated PD of -35 to -40 mV (mucosa negative) and secreted HCO$_3^-$ in an amount of 1.5–2 μEq/hr under acid inhibition with omeprazole (30 mg/kg). Intraperitoneal administration of FPL-52694 (30 mg/kg) and DSCG (30 mg/kg) had no effect on both PD and HCO$_3^-$ output (Fig. 4A and 4B). However, when the stomach was exposed for 30 min to FPL-52694 (3–30 mg/kg), the PD was reduced in a dose-related manner, the maximal PD reduction being 12.3±2.1 mV at the dose of 30 mg/kg. In association with PD reduction, gastric HCO$_3^-$ output was increased in a dose-related manner, and it reached the levels of 4.1±0.4 μEq/hr after exposure to 30 mg/kg of FPL-52694. Both the PD reduction and increased HCO$_3^-$ output caused by topical application of FPL-52694 were not sig-

![Fig. 2. Effects of FPL-52694 and DSCG on HCl-ethanol-induced gastric lesions in rats pretreated with indomethacin. Each drug was given either orally or intraperitoneally 30 min before HCl-ethanol treatment. Indomethacin was given subcutaneously in a dose of 5 mg/kg 1 hr before administration of HCl-ethanol. Data are presented as means±one S.E. from 10 rats. *Statistically significant difference from the controls, at P<0.05.](image)

![Fig. 3. Effects of FPL-52694 and DSCG on gastric acid secretion in pylorus-ligated rats (4 hr). Each drug was given either orally or intraperitoneally immediately after pylorus ligation. Data are presented as means±one S.E. from 8 rats. *Statistically significant difference from the controls, at P<0.05.](image)
Fig. 4. Effects of FPL-52694 and DSCG on gastric transmucosal potential difference (PD) (A) and HC03 (B) in anesthetized rats. Each drug was given either by topical application to the stomach for 30 min or by intraperitoneal administration. Data are presented as means±one S.E. from 3 to 6 rats.

*Statistically significant difference from the controls, at P<0.05.

significantly affected by prior administration of indomethacin (5 mg/kg) (not shown). Topical application of DSCG (30 mg/kg) into the stomach had no effect on PD and HC03 output.

Gastric motor activity: Normal stomachs showed contractions at a frequency of 1-2/min when measured as intraluminal pressure recordings. Intragastric application of FPL-52694 (10 mg/kg) showed a marked inhibition of gastric motor activity, and the effect lasted for over a 2 hr experimental period (Fig. 5). Potent inhibition of gastric motor activity was also seen after intraperitoneal administration of both FPL-52694 (10 mg/kg) and DSCG (30 mg/kg) (Fig. 6). As evidenced in Fig. 7, these drugs significantly inhibited both the amplitude and the frequency of contractions for around 2 hr. Administration of saline, either intragastrically or intraperitoneally, had no effect on gastric contractions. On the other hand, subcutaneously administered indomethacin (5 mg/kg) by itself increased slightly, though not significantly, the amplitude of contractions, but did significantly antagonize the inhibitory effects of FPL-52694 and DSCG on gastric motor activity (Fig. 8). Although the inhibition of gastric motor activity caused by intraperitoneally administered FPL-52694 (10 mg/kg) and DSCG (30 mg/kg) was still observed in the presence of indomethacin, the duration of their action was much shortened, and the significant inhibition was observed for only 10-20 min after administration. On the other hand, the duration of significant inhibition caused by intragastrically administered FPL-52694 and DSCG was plotted against % inhibition of HCl-ethanol-induced gastric lesions caused by these drugs, there was a highly significant relationship between these two factors, the correlation coefficient (r) being 0.9214 (P<0.01) (Fig. 9).

Discussion

The present results clearly showed that both FPL-52694 and DSCG protected the gastric mucosa from the insult of HCl-ethanol in rats. Such protection is demonstrated in rats after administration of prostaglandins, and it is considered to be independent of their antisecretory effects (1). It seems likely that the protective effects of these mast cell stabilizers also are not associated with the antisecretory or acid neutralizing action for the following reasons: (a) ethanol was given into the stomach together with sufficient amount of exogenous acid (150 mM HCl), (b) intraperitoneally administered FPL-52694 and DSCG significantly prevented HCl-ethanol-induced gastric lesions, but had no antisecretory effect. Although orally administered FPL-52694 (30 mg/kg) affected acid secretion significantly, the potency of antilesion activity (99.4%) was much greater as compared to that of antisecretory activity (43.9%). Therefore, the mucosal protection induced by these agents appears to be quite
similar to prostaglandin cytoprotection.

The drugs which affect ethanol-induced gastric lesions would be classified roughly into two types. Prostaglandins are the first type of drugs which effectively act on the stomach by either route of administration such as orally or parenterally (1). The other type of drugs are represented by omeprazole and many other compounds which inhibit these lesions only when they are given orally (19). Mild irritants are included in the latter group, but these protective effects are mediated by endogenous prostaglandins, inasmuch as their effects disappear in the presence of indomethacin (20, 21). Thus, FPL-52694 would be classified into the first group, while DSCG may be categorized into a new type of drug, since the effect was observed only by parenteral administration (intraperitoneally). These findings suggest that both FPL-52694 and DSCG exert such protection mainly through a systemic action rather than a local effect on the gastric mucosa.

Since the protective effects of intraperitoneally administered FPL-52694 and DSCG totally disappeared in the presence of indomethacin, their action may be mediated with endogenous prostaglandins. On the other hand, the protection induced by orally administered FPL-52694 was only partially antagonized by pretreatment with indomethacin. As mentioned above, ethanol-induced gastric lesions are significantly prevented by oral administration of mild irritants such as low concentrations of ethanol or bile salts (20-22). These substances by themselves produce mild injury in the gastric mucosa and thereby result in PD reduction and luminal alkalinization (13, 22, 23). Since topical application of FPL-52694 induced PD reduction and increase of HCO₃⁻ output (diffusion), a part of the protective effect of oral FPL-52694 may be due to mild irritation to the gastric mucosa. Since mild injury itself is known to increase fluid output from the damaged portion (24), in addition to enhancement of prostaglandin formation (21), the observed protection in the presence of indomethacin may be ascribed to the dilution effect caused by an increased fluid output.

Although the phenomenon of pro-

Fig. 5. Representative figures showing the effect of intragastrically administered FPL-52694 (10 mg/kg) on gastric motor activity in a rat measured as intraluminal pressure recordings.
Staglandin cytoprotection has been well documented, the mechanisms involved remain unknown. An increase of mucus, HCO$_3^-$ secretion, or mucosal blood flow has been proposed as the possible explanation (25–27), but these factors, either alone or in combination, cannot account for the occurrence of lesions in a specific shape and site: the “band-like” lesions confined to the crest of the rugae in the stomach.

Intraperitoneally administered FPL-52694 and DSCG had no effect on acid secretion, PD and HCO$_3^-$ output, but potently inhibited gastric motor activity. The contribution of gastric motility to the development of gastric lesions has been shown in rats after stress or administration of non-steroidal anti-inflammatory drugs (28–31). The lesions induced by the above treatments show a marked localization on the crest of the rugae in the gastric mucosa (15), just like as those induced by HCl-ethanol. Mersereau and Hinchey (15, 32) reported the importance of mucosal folds in the pathogenesis of such lesions. In fact, these lesions are prevented by drugs which inhibit gastric motor activity (16, 28–30). We previously reported that 16,16-dimethyl prostaglandin E$_2$ and a mild irritant (1 M NaCl) potently inhibited gastric motor activity in rats, and the latter effect was partly antagonized by indomethacin (16). Similarly, the inhibitory effects of FPL-52694 and DSCG on gastric motor activity were significantly mitigated by prior administration of indomethacin as well as their protective effects against HCl-ethanol-induced gastric lesions. Furthermore, a significant correlation ($r: 0.9214$, $P<0.01$) was
Fig. 7. Effects of FPL-52694 and DSCG on the amplitude and frequency of gastric contractions in rats measured as intraluminal pressure recordings. FPL-52694 was given either intragastrically or intraperitoneally in a dose of 10 mg/kg, while DSCG was given intraperitoneally in a dose of 30 mg/kg. Data are expressed as % of the corresponding control values and are presented as means±one S.E. from 5 rats. *Statistically significant difference from the control groups, at P<0.05.

found between their effects on gastric lesions and motor activity. These results suggest that a motility factor may be involved in the formation and prevention of HCl-ethanol-induced gastric lesions in rats. Since inhibition of gastric motor activity may lead to dissolution of mucosal folds, it may be assumed that the mucosal surface area exposed to HCl-ethanol would be significantly increased when compared with the small area (rugal crest) formerly exposed to the high volume and concentration of HCl-ethanol in the lumen (33). Further study to investigate an association between the formation of these lesions and stomach folds must be warranted. Although the mechanism by which FPL-52694 and DSCG affect gastric motor activity remains unknown, endogenous prostaglandins may be involved in this phenomenon, inasmuch as these effects were also antagonized by indo- methacin.

There has been evidence showing that a significant amount of histamine is released in the gastric mucosa after damage with ethanol (5). Aures et al. (34), however, reported that ethanol-induced gastric lesions in rats were not significantly affected by further access of exogenous histamine, and that 16,16-dimethyl prostaglandin E2 inhibited these lesions without any influence on histamine release in the mucosa. In con-
Fig. 8. Effects of FPL-52694 and DSCG on the amplitude of gastric contractions measured as intraluminal pressure recordings in rats pretreated with indomethacin (IND). FPL-52694 was given either intragastrically or intraperitoneally in a dose of 10 mg/kg, while DSCG was given intraperitoneally in a dose of 30 mg/kg. Indomethacin was given subcutaneously in a dose of 5 mg/kg 30 min before administration of the above agents. Data are expressed as % of the corresponding control values, and they are presented as means±one S.E. from 5 rats. *Statistically significant difference from the control groups, at P<0.05.

Fig. 9. A correlation between the degrees of inhibition of gastric lesions and gastric motor activity (amplitude) induced by FPL-52694 and DSCG, in the absence or presence of indomethacin (IND) (5 mg/kg). Data are taken from Figs. 1, 2, 7 and 8. The values for gastric motor activity (amplitude) were obtained at 30 min after administration of FPL-52694 (10 mg/kg) and DSCG (30 mg/kg).

The present results taken all together suggest that mast cell stabilizers such as FPL-52694 and DSCG have mucosal protective activity similar to prostaglandins, and this may in part account for their antulcer effects observed in various gastric lesion models (8, 10, 11). Although the detailed mechanism by which these agents exert such protection remains unknown, this property may be ascribed, at least partly, to their inhibitory effects on gastric motor activity, and both may be mediated by endogenous prostaglandins. Conclusive proof for the above possibility requires the determination of prostaglandins, ideally, as prostaglandin synthesis by the gastric mucosa, following...
administration of these mast cell stabilizers.

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