Capsaicin-Sensitive Sensory Nerves in Recovery of Gastric Mucosal Integrity after Damage by Sodium Taurocholate in Rats

Koji Takeuchi, Tomohisa Ohuchi, Mitsuhiro Narita and Susumu Okabe

Department of Applied Pharmacology, Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

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ABSTRACT—We compared the recovery process of gastric mucosal integrity after damage by 20 mM sodium taurocholate (TC) in control, sensory deafferented and indomethacin-treated rats. Under anesthetized conditions, the stomach was mounted on a chamber and perfused with saline or 50 mM HCl. Application of TC (30 min) to the saline-perfused stomach produced a marked reduction in the potential difference (PD) (surface epithelial damage), followed by increases of gastric mucosal blood flow (GMBF) and luminal pH (alkalinization), but there was a rapid recovery of PD without development of gross lesions. Chemical ablation of capsaicin-sensitive sensory nerves had no influence on the PD reduction and luminal alkalinization, but significantly inhibited the rise in GMBF and the PD recovery. Indomethacin pretreatment (5 mg/kg, s.c.) significantly inhibited these changes seen after exposure to TC, except for PD reduction. In contrast, TC caused a sizable amount of H⁺ back-diffusion and a more pronounced and persistent rise in GMBF in the stomach perfused with 50 mM HCl, yet only minimal damage was observed in the control animals. Under these conditions, both sensory deafferentation and indomethacin inhibited such GMBF responses, leading to hemorrhagic damage without affecting the degree of H⁺ back-diffusion. These results suggest that capsaicin-sensitive sensory nerves contribute to the recovery of gastric mucosal integrity after damage, probably by maintaining GMBF responses associated with H⁺ back-diffusion and preventing the later extension to gross damage in the presence of acid.

Keywords: Capsaicin-sensitive sensory nerve, Taurocholate, Gastric injury, Recovery, Mucosal blood flow

Gastric epithelium is exposed to not only the noxious effect of endogenous substances but a variety of ingested substances as well. Each of them, either alone or in combination, may induce damage in the stomach (1–3). However, the gastric mucosa possesses the inherent capacity to reconstitute promptly after mild injury. There is some evidence to suggest that if the injury is restricted to the superficial epithelium and the basal lamina is preserved, the denuded surface is covered rapidly by migrating cells (restitution), restoring the mucosal integrity within hours (4, 5).

It has been recently shown that capsaicin-sensitive sensory neurons play an important role in the mucosal defensive mechanism of the stomach (6–8). Stimulation of these nerves causes a marked increase of gastric mucosal blood flow (GMBF), which is considered to be important for mucosal protection (8, 9). Holzer et al. (8) recently reported that these neurons are involved in the increase of GMBF caused by H⁺ back-diffusion following disruption of the gastric mucosal barrier. Since the process of restitution may be supported by the microclimate around the damage such as the mucus-bicarbonate barrier (4, 10) and GMBF (11), it is assumed that capsaicin-sensitive neurons may play some roles in the recovery from acute gastric mucosal injury.

In this study, we examined the effect of sensory deafferentation on the recovery of gastric mucosal integrity after damage by sodium taurocholate (TC) and investigated the role of GMBF in this phenomenon. The effect of indomethacin was also examined, since endogenous prostaglandins (PGs) are known to affect the process of restitution by increasing GMBF (10, 11).

MATERIALS AND METHODS

Animals

Male Sprague Dawley rats weighing 230–260 g (Charles River, Shizuoka) were used. The animals, which were kept in individual cages with raised mesh bottoms to prevent coprophagia, were deprived of food but allowed
free access to tap water for 18 hr before the experiments. All studies were performed with 6 rats per group.

Experimental protocol

The experiments were performed in control, chemically deafferented, and indomethacin-treated rats. In these groups of animals, the effects of mucosal application of TC on gastric potential difference (PD), luminal pH, GMBF, luminal acid loss (H⁺ back-diffusion) and morphological aspects of the gastric mucosa were examined under urethane anesthetized conditions. Chemical deafferentation was done by s.c. injection of capsaicin once daily for 3 consecutive days (20, 30, 50 mg/kg) 2 weeks before the experiments (12). Capsaicin injections were performed under ether anesthesia, and the rats were pretreated with terbutaline (0.1 mg/kg, i.m.) and aminophylline (10 mg/kg, i.m.) before capsaicin injection for counteracting the respiratory impairment associated with capsaicin injections. To check for the effectiveness of the treatment, a drop of 0.1 mg/ml solution of capsaicin was instilled into one eye of each rat, and the protective wiping movements were counted as previously reported (13). Indomethacin (5 mg/kg) was given s.c. 1 hr before treatment with TC. Control animals were also treated with terbutaline and aminophylline but received the vehicle instead of capsaicin.

Measurements of PD, pH and GMBF

Animals were anesthetized with urethane (1.25 g/kg) given i.p., and the trachea was cannulated to ensure a patent airway. Simultaneous measurement of GMBF, transmucosal PD and luminal pH was performed in the chambered stomach according to a previously published method (10, 14). Briefly, the abdomen was incised, the stomach was exposed, mounted on a chamber (exposed area: 3.1 cm²) and perfused at a flow rate of 0.7 ml/min with saline that was heated at 37°C and kept in a reservoir. An exiting tube was connected to a glass electrode of the flow type (Model 6901-25T; Horiba, Kyoto), by which the pH of the gastric perfusate was continuously measured. Transmucosal PD was determined by using two agar bridges, one positioned in the chamber and the other in the abdominal cavity. Changes in both pH and PD were simultaneously monitored on a two channel recorder (Unicorder U-228; Nippon Densi Kagaku, Kyoto). GMBF was measured by laser Doppler flowmetry (Model ALF-2100; Advance, Tokyo) and by placing the probe (1 mm in diameter) softly on the surface of the corpus mucosa using a balancer (9). At least 1 hr after all parameters had stabilized, the perfusion was discontinued; the luminal solution was removed, and then the mucosa was exposed for 30 min to 2 ml of 20 mM TC. After TC treatment, the mucosa was rinsed with saline, another 2 ml of saline was instilled and then the perfusion was resumed. Monitoring of the pH was interrupted for 30 min while the mucosa was exposed to TC, whereas the other parameters were continuously monitored during a 2-hr test period. In some experiments, the mucosa was perfused with 50 mM HCl made isotonic by NaCl in place of saline. In the same perfusion system, the effects of luminal application of capsaicin (0.3 mg/ml) on PD and pH responses induced by TC were also examined in normal rats. Capsaicin (2 ml) was applied into the chamber for 30 min immediately before exposure to TC. Ninety minutes after TC treatment, the mucosa was removed, examined for hemorrhagic damage under a dissecting microscope (×10) and then immersed into 10% formalin for histological observation; the tissue was processed for routine light microscopy, sectioned at 5 μm, and stained with hematoxylin and eosin.

Determination of acid back-diffusion

Acid back-diffusion was determined in the chambered stomach before, during and after exposure of the mucosa to 20 mM TC for 30 min in the animals given omeprazole (60 mg/kg, i.p.), where acid secretion is scanty. At the beginning of each experiment, the mucosa was rinsed several times with a solution of 50 mM HCl plus 100 mM NaCl. When the gastric exudate became clear, 2 ml of this acid solution was instilled into the chamber, and 15 min later, the content was recovered from the chamber. This procedure was repeated every 15 min, three times before and six times after exposure of the mucosa for 30 min to 20 mM TC. Control stomachs in normal rats were exposed to saline in place of TC. The collected samples were analyzed for volume and H⁺ concentration which was determined by automatic titration of the aliquot against 0.1 N NaOH to pH 7.0 (Autoburette, Model Comtite-7; Hiratunuma, Tokyo). The amount of H⁺ back-diffusion was calculated as the difference between the product of final volume and concentration and the product of the initial volume and concentration. Positive values indicate that the net flux was from the mucosa to the lumen, and the results were expressed as μEq/15 min.

Preparation of drugs

Drugs used were urethane (Tokyo Kasei, Tokyo), sodium taurocholate (Difco Laboratories, Detroit, MI, USA), capsaicin (Wako, Osaka), indomethacin (Sigma Chemicals, St. Louis, MO, USA), terbutaline (Bricanyl®; Fujisawa, Osaka), aminophylline (Neophylline®; Eisai, Tokyo) and omeprazole (Hessle, Mölndal, Sweden). Capsaicin was dissolved in Tween 80–ethanol solution (10% ethanol, 10% Tween 80, 80% saline) for s.c. injection and was suspended in 0.5% carboxymethylcellulose solution (CMC) for mucosal application. Indomethacin was
suspended in saline with a drop of Tween 80, while omeprazole was suspended in 0.5% CMC. Other agents were dissolved in saline. Each agent was prepared immediately before use and given in a volume of 0.5 ml/100 g of body wt. in the cases of s.c. and i.p. administration or in a volume of 0.1 ml/100 g of body wt. in the case of i.m. injection.

Statistics

Data are presented as the mean ± S.E. from 6–8 rats per group. Statistical analyses were performed with a two-tailed Dunnett's multiple comparison test (15) and values of P<0.05 were regarded to indicate a significant difference.

RESULTS

Gastric PD, pH and GMBF responses and mucosal injury induced by luminal application of taurocholate

Under chambered conditions, the stomachs of control rats generated a PD of −32~−38 mV (mucosa negative), secreted acid to keep the luminal pH of 3.5, and maintained relatively constant GMBF during a 2-hr test period. Exposure of the mucosa to 20 mM TC for 30 min caused a marked reduction of PD from −32.1±1.3 mV to −14.8±2.0 mV, but after the exposure, the reduced PD was normalized to basal values within 30 min with concomitant elevation of the luminal pH from 3.4±0.1 to the maximal values of 4.9±0.3 (Figs. 1 and 2). Sensory deafferentation did not influence the PD reduction in

Fig. 1. Representative recordings showing changes in PD, pH and GMBF responses in the stomach after exposure to TC (20 mM for 30 min) in the anesthetized rats. Figures show: A, control rat; B, sensory deafferented rat; C, indomethacin-treated rat. Note that the recovery of the PD after removal of TC was apparently delayed by chemical deafferentation or prior administration of indomethacin, while the increased pH response was inhibited only in the latter group.

Fig. 2. Effects of chemical deafferentation and indomethacin on the PD and pH responses of the stomach induced by TC (20 mM for 30 min) in the anesthetized rats. Indomethacin (5 mg/kg) was given subcutaneously 30 min before exposure to TC, while capsaicin pretreatment was done 2 weeks before the experiment. Data are presented as the means ± S.E. of values determined every 5 min from 6 rats (● normal, ■ capsaicin pretreatment, ▲ indomethacin). *Statistically significant difference from the normal group, at P<0.05.
response to TC, but significantly augmented the rise in pH and delayed the PD recovery after the exposure. In contrast, pretreatment with indomethacin (5 mg/kg) significantly attenuated both the increase of pH and the PD recovery seen after the mucosal exposure to TC, although PD reduction was similarly observed in response to TC. As evidenced in Fig. 3, the reduced PD in the normal rats was reverted completely within 40 min after removal of TC from the chamber, while this process of PD recovery was significantly inhibited not only by indomethacin but also by sensory deafferentation; the rate of PD recovery at 1-hr post exposure was 100.2±8.1%, 54.3±1.6% and 47.2±12.1% in the normal, indomethacin-treated and sensory deafferented groups, respectively.

Fig. 3. Effects of chemical deafferentation and indomethacin on the recovery of PD in the stomach after exposure to TC (20 mM for 30 min) in the anesthetized rats. Data are presented as % recovery of PD and represent the means ± S.E. of values determined every 5 min from 6 rats (○ normal, ■ capsaicin pretreatment, ▲ indomethacin). *Statistically significant difference from the normal group, at P<0.05.

On the other hand, GMBF was significantly elevated during exposure to TC, reaching the peak values of 80% increase, followed by a gradual return to the pre-exposure levels within 30 min (Figs. 1 and 4). The mucosal hyperemic response caused by TC was significantly inhibited by either ablation of sensory nerves or indomethacin pretreatment. Even in these two groups, GMBF showed a small rise (~20%) in response to TC, yet such changes were significantly less than those observed in the normal group. Application of capsaicin (0.3 mg/ml) by itself significantly increased GMBF but did not significantly affect both PD and pH responses caused by the subsequent exposure to TC; namely, the initial PD reduction followed by the gradual recovery with concomitant elevation in luminal pH (not shown).

Fig. 4. Effects of chemical deafferentation and indomethacin on GMBF responses induced by TC (20 mM for 30 min) in the anesthetized rats. Data are presented as % of the basal values and represent the means ± S.E. of values determined every 5 min from 6 rats (○ normal, ■ capsaicin pretreatment, ▲ indomethacin). Statistically significant difference at P<0.05: * from the basal values, # from the normal group.

In any of the groups, TC treatment by itself did not cause macroscopically visible damage in the gastric mucosa but found to produce complete sloughing of the surface epithelial cells when examined histologically. However, the damage in the surface epithelial cells induced by TC was healed within 90 min in parallel with PD recovery in the normal group, while the histological restitution was apparently prevented in the other two groups (not shown).

Effect of acid perfusion on GMBF response, acid back-diffusion and mucosal damage induced by taurocholate

Perfusion of the mucosa with acid (50 mM HCl at 0.7 ml/min) kept luminal pH at around 1.3 during the test period, but did not significantly affect both generation of PD (~38.5±4.3 mV, N=18) and basal values of GMBF. Under these conditions, the gastric mucosa responded to TC by a more pronounced rise in GMBF when compared to the mucosa perfused with saline. As shown in Fig. 5, GMBF was increased in response to TC, reached peak values (242.0±26.3% of basal values) during the exposure and remained elevated (50–60% increase) even after removal of TC from the chamber. Sensory deafferentation following capsaicin pretreatment almost completely blocked the increase of GMBF caused by TC, and the values remained unchanged before, during, and after exposure to TC. Such GMBF responses induced by TC also subsided in the indomethacin-treated group, and the values of GMBF during and after exposure to TC were sig-
significantly lower than those in the control rats. In these rats, GMBF showed a small increase (43.2 ±7.8Wo) during the exposure, yet it reverted to the basal levels immediately after removal of TC.

When the mucosa was exposed to 50 mM HCl, small but significant loss of luminal H⁺ was consistently observed under normal conditions; ΔH⁺ was less than 10 μEq/15 min. After TC application, the loss of H⁺ was significantly increased and reached the maximal values (ΔH⁺: 32.1±2.6 μEq/15 min) immediately after the exposure, followed by a gradual decrease to the pre-exposure levels 90 min later (Fig. 6). Similar increases in the mucosal permeability to H⁺ were observed after exposure to TC in both sensory deafferented and indomethacin-treated rats; the magnitude of H⁺ loss observed immediately after TC treatment was 30.0± 3.1 μEq/15 min and 28.4±2.3 μEq/15 min, respectively, and was not significantly different from that in the control rats.

Mucosal application of TC or acid perfusion by itself did not induce gross damage in the gastric mucosa, but these treatments given together produced hemorrhagic damages in the gastric mucosa of the control rats; the lesion score was 5.6±2.9 mm² (Fig. 7). These lesions were significantly aggravated by either indomethacin or ablation of sensory neurons, the lesion score being 35.8±5.8 mm² and 22.8±2.5 mm², respectively.

Fig. 5. Effects of chemical deafferentation and indomethacin on GMBF responses induced by TC (20 mM for 30 min) in the rat stomach perfused with acid under anesthetized conditions. The stomach was perfused with 50 mM HCl before and after exposure to TC. Data are presented as a % of the basal values and represent the means ±S.E. of values determined every 5 min from 6 rats (normal, capsaicin pretreatment, indomethacin). Statistically significant difference at P<0.05: * from the basal values, * from the normal group.

Fig. 6. Effects of chemical deafferentation and indomethacin on the degree of H⁺ back-diffusion induced by TC (20 mM for 30 min) in the stomach of anesthetized rats. The stomach was perfused with 50 mM HCl before and after exposure to TC. Data are presented as the means±S.E. of values determined every 15 min from 6 rats. *Statistically significant difference from the basal values obtained before TC treatment in the corresponding groups, at P<0.05.

Fig. 7. Effects of chemical deafferentation and indomethacin on the development of hemorrhagic lesions induced by TC (20 mM for 30 min) in the stomach perfused with 50 mM HCl in the anesthetized rats. The animals were killed 90 min after exposure of the stomach to TC. Data are presented as the means±S.E. from 6 rats. *Statistically significant difference from the normal group, at P<0.05. CP: Capsaicin pretreatment, IM: Indomethacin.
DISCUSSION

The balance between gastric mucosal injury and repair is a dynamic process involving multiple mechanisms and maintains the mucosal integrity despite exposure to a variety of damaging substances. These mechanisms involve the mucosal restitution which occurs by migration of still viable cells from areas adjacent to the injured surface cells before appearance of an extensive inflammatory response or cell proliferation and is associated with the electrophysiological changes of the tissue (4, 5). The present study showed that functional ablation of capsaicin-sensitive sensory neurons impaired the rapid recovery of the mucosal integrity and led to extension of the surface injury to hemorrhagic damage. These neurons may contribute to the repair of acute gastric mucosal injury, probably by maintaining the GMBF response to injury.

Mucosal application of TC caused PD reduction followed by an increase of luminal pH and GMBF, but did not induce any gross lesions in the mucosa even in the presence of acid. Many investigators found that luminal alkalinization occurred in the stomach exposed to mucosal damaging agents, resulting from both diffusion of HCO$_3^-$ and inhibition of acid secretion (16, 17). In agreement with our previous findings (10, 16, 17), indomethacin significantly blocked both the pH and GMBF responses caused by TC and delayed PD recovery, resulting in the development of gross lesions in the presence of acid. Since it has been shown that such pH and GMBF responses in the stomach after damage are mediated by endogenous PGs (3), the present results with indomethacin may be associated with PG deficiency caused by cyclooxygenase inhibition by this agent (17). Morris and Wallace (18) showed that if H$^+$ remains in the lumen after injury, the basal lamina is destroyed, and thus the substratum necessary for restoration of epithelial continuity is removed. Svanes et al. (19) reported that this process of mucosal repair is inhibited by low luminal pH and promoted by high nutrient HCO$_3^-$. Luminal alkalinization may provide the beneficial microclimate for the process of mucosal repair and for prevention of further extension to hemorrhagic damage.

The most important finding in the present study is that chemical ablation of capsaicin-sensitive sensory neurons significantly delayed the process of PD recovery and morphologic restitution in the stomach exposed to TC. These deleterious effects can not be accounted for by the impairment of luminal alkalinization, because such treatments did not mitigate the increased pH responses caused by TC. Certainly, injury to the mucosa by TC was accompanied by a large amount of H$^+$ back-diffusion, but this process was not significantly altered by either ablation of sensory nerves or indomethacin. Yet, sensory deafferentation as well as indomethacin significantly attenuated the increase of GMBF induced by TC and H$^+$ back-diffusion, resulting in extension to hemorrhagic lesions. Recently, Holzer et al. (8) showed that sensory neurons monitor H$^+$ back-diffusion in superficial mucosa and signal for a protective increase in GMBF. The present results confirmed their finding and further suggested the importance of these neurons in the adaptive GMBF response to damage as induced by TC and suggest that the reduced GMBF may be more closely associated with delay in the mucosal repair and extension to hemorrhagic damage following chemical deafferentation. Stimulation by capsaicin of the sensory neurons did increase GMBF but affected neither the reduction nor the recovery of PD in the stomach after exposure to TC. It may be assumed that intragastric capsaicin is not capable of causing further stimulation of these sensory nerves, because the sensory neurons within the stomach can be stimulated sufficiently by the mucosal irritation by TC alone.

How GMBF contributes to the recovery of gastric mucosal injury remains speculative for now. Injury to the gastric mucosa is associated with an increase in GMBF (20). Whittle (21) reported that application of acidified TC to the stomach induced a hyperemic response, and this GMBF response was inhibited by concurrent administration of indomethacin, in agreement with the present findings. Ablation of capsaicin-sensitive sensory neurons also inhibited the hyperemic response induced by TC. Ritchie's study in dogs indicate that acid, bile salts and ischemia were necessary to induce gastric mucosal lesions (22). His studies led to the following hypothesis for the role of GMBF in the genesis of gastric lesions. Under normal conditions, the gastric mucosa is effectively impermeable to luminal H$^+$. Once the barrier has been broken by bile salts, the rate at which leaked H$^+$ can be eliminated via GMBF becomes important in the development of hemorrhagic lesions. However, the present study showed that GMBF may also be important in maintaining the process of restitution of which the rate would be critical in the ultimate generation of gastric damage. Sensory deafferentation delayed the recovery of PD as well as epithelial damage after exposure to TC, irrespective of whether the stomach was perfused with saline or acid, but hemorrhagic lesions ensued only in the presence of acid. These results suggest that the inhibitory effect of sensory deafferentation on the tissue recovery may be in part due to insufficiency of such GMBF responses after damage. GMBF contributes to maintenance of cellular activity by supplying oxygen and nutrients and by removing toxic substances, in addition to buffering H$^+$.

In conclusion, the present study suggests that capsaicin-sensitive sensory neurons may contribute to the recovery of the gastric mucosal integrity by maintaining
GMBF responses to injury itself and H\(^+\) in the damaged mucosa. These sensory nerves may be important in providing a beneficial microclimate for the damaged mucosa to repair quickly without developing to gross lesions.

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