Stimulation by Capsaicin of Gastric Alkaline Secretion in Anesthetized Rats

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Received December 20, 1991 Accepted February 18, 1992

ABSTRACT—Effects of mucosal application of capsaicin on alkaline secretion were examined in the stomachs of anesthetized rats and compared with those in the duodenum. The stomach (acid secretion was inhibited by omeprazole given i.p.) or the duodenum was perfused with saline (pH 4.5); both the pH of the perfusate and transmucosal potential difference (PD) were continuously monitored; and the HCO_3^- output was determined by the pH change. Under these conditions, the mucosal application of capsaicin (0.3–6 mg/ml for 30 min) caused significantly increased pH and HCO_3^- output in a concentration-related manner in both tissues, while PD increased in the duodenum and decreased in the stomach. The HCO_3^- stimulatory action of capsaicin was markedly attenuated by sensory deafferentation, significantly mitigated by prior administration of indomethacin, and exhibited a marked tachyphylaxis after the repeated exposure at a high concentration (6 mg/ml). None of these treatments had any effect on the pH, PD and HCO_3^- responses induced by prostaglandin E_2 (300 $\mu\text{g}/\text{kg}$, i.v.) in these tissues. These results indicate that mucosal application of capsaicin increased the gastroduodenal HCO_3^- output by stimulation of capsaicin-sensitive sensory neurons. This action may be in part mediated by endogenous prostaglandins.

Keywords: Capsaicin, HCO_3^- secretion, Stomach, Duodenum, Capsaicin-sensitive afferents

Capsaicin-sensitive sensory neurons have been shown to participate in various aspects of the pathophysiology of the gastrointestinal tract such as changes in acid secretion, blood flow regulation or the maintenance of the mucosal integrity against chemical hazards (1–3). We recently reported that these sensory neurons are involved in the regulatory mechanism of acid-induced HCO_3^- secretion in the duodenum (4). However, the role of these nerves in gastric HCO_3^- secretion is yet unexamined. Since HCO_3^- secretion plays an important role in the mucosal defensive ability of the gastric mucosa in collaboration with mucus (5–7), it is worthwhile to investigate the relation of these neurons to HCO_3^- secretion in the stomach.

In the present study, we examined the effects of capsaicin applied topically to the mucosa on HCO_3^- secretion in the rat stomach, in comparison with those in the duodenum. In addition, since endogenous prostaglandins (PGs) play an important role in the regulatory mechanism of HCO_3^- secretion (5, 8) and since some of the capsaicin effects are considered to be mediated by PGs (9–11), the effect of indomethacin on the

HCO_3^- secretory response to capsaicin was also investigated.

MATERIALS AND METHODS

Male Sprague Dawley rats (250–300 g; Charles River, Japan), kept in individual cages with raised mesh bottoms, were deprived of food but allowed free access to tap water for 18 hr before the experiments.

General procedures

Animals were anesthetized with urethane (1.25 g/kg) given intraperitoneally. Simultaneous measurements of luminal pH and transmucosal potential difference (PD) were performed according to the previously published method (12, 13). Briefly, the abdomen was incised, and both the stomach and duodenum were exposed. The stomach was mounted on a lucite chamber, superfused at a flow rate of 0.7 ml/min with saline that was adjusted to pH 4.5 and kept in a reservoir. An exiting tube was connected to a glass electrode of the flow type (Horiba Model 6901-25T, Kyoto, Japan), by which the

pH of the gastric perfusate was continuously monitored. Gastric PD was measured 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 Co., Kyoto, Japan). To unmask HCO_3^- secretion, acid secretion was inhibited by intraperitoneal administration of omeprazole (60 mg/kg). For the duodenal preparation, a duodenal loop was made between the pyloric ring and the area just proximal to the outlet of the common bile duct (1.7 cm), excluding the influences of bile and pancreatic juice. This loop was perfused with acidified saline similar to the case of gastric preparation. In both cases, HCO_3^- output was determined by back-titration of the perfusate to pH 4.5 using a pH stat method (Hiranuma Comtite-7, Tokyo, Japan) and/or pH change (13) and expressed as μmol .

Experimental protocols

The experiments were done in normal and sensory deafferented rats. Chemical deafferentation was performed by systemic capsaicin injections (20, 30, 50, mg/kg, s.c.) once daily for 3 days 2 weeks before the experiments (9). All capsaicin injections were performed under ether anesthesia; and to counteract the respiratory impairment associated with capsaicin injection, the rats were pretreated with terbutaline (0.1 mg/kg, i.m.) and aminophylline (10 mg/kg, i.m.) before capsaicin injection. To check for the effectiveness of the treatment, a drop of a 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 (9). Animals treated with capsaicin that showed any wiping movements were excluded from the study. At least 1 hr after both pH and PD had stabilized, the following treatments on pH, PD and HCO_3^- output were examined: capsaicin (0.3–6 mg/ml) was topically applied to the mucosa for 30 min, while prostaglandin E_2 (PGE_2 ; 300 $\mu\text{g/kg}$) was given i.v. as a single bolus injection. In the former, the perfusion was interrupted while the mucosa was exposed to capsaicin. After the exposure, the mucosa was rinsed with saline (pH 4.5) and the perfusion resumed. In some cases, the effects of indomethacin on pH and HCO_3^- responses induced by capsaicin and PGE_2 were examined. Indomethacin (5 mg/kg) was given s.c. 30 min before treatment with these agents. In another experiment, the effects of repeated application of capsaicin on pH and HCO_3^- responses were examined in both the stomach and duodenum. In each test, capsaicin (6 mg/ml) was applied to the mucosa for 30 min repeatedly every 90 min, and PGE_2 (300 $\mu\text{g/kg}$) was given i.v. at the end of

the experiment.

Preparation of drugs

Drugs used were urethane (Tokyo Kasei, Tokyo, Japan), PGE_2 (Funakoshi, Tokyo, Japan), capsaicin (Wako, Osaka, Japan), terbutaline (Bricanyl®: Fujisawa, Osaka, Japan), aminophylline (Neophyllin®: Eisai, Tokyo, Japan) and indomethacin (Sigma Chemicals, St. Louis, MO). PGE_2 was first dissolved in absolute ethanol and diluted with saline to the desired concentration. Capsaicin was dissolved in the solution consisting of 10% ethanol, 10% Tween 80 (Wako) and 80% saline for s.c. injection (chemical deafferentation) and was suspended in 0.5% carboxymethylcellulose solution (CMC) for mucosal application. Both indomethacin and omeprazole were suspended in 0.5% CMC, and other agents were dissolved in saline. Each agent was prepared immediately before use and given i.v. or i.m. in a volume of 0.1 ml/100 g of body wt. or s.c. in a volume of 0.5 ml/100 g body wt. Capsaicin was applied to the mucosa in a volume of 2 ml/rat in the stomach and in a volume of 0.5 ml/rat in the duodenum.

Statistics

Data are presented as the mean $\pm$ S.E. from 5 to 7 rats per group. Statistical analyses were performed using a two-tailed Dunnett's multiple comparison test (14), and values of $P < 0.05$ were regarded to indicate significant differences.

RESULTS

Effects of capsaicin on pH, PD and HCO_3^- responses

When the stomach mounted on a chamber (under acid inhibition caused by omeprazole) or the proximal duodenal loop was perfused at a flow rate of 0.7 ml/min with saline (pH 4.5), the pH in fluid emerging from the chamber or the loop was around 5.0–5.3 and remained in this range during a test period. Intravenous administration of PGE_2 (300 $\mu\text{g/kg}$) produced a marked elevation of pH for 40 min in both preparations, but the PD responded to this agent by a decrease in the stomach and an increase in the duodenum. When the gastric mucosa was exposed to capsaicin for 30 min, the pH was increased in a concentration-dependent manner (0.3–6 mg/ml) (Fig. 1A). Capsaicin at 6 mg/ml increased the pH from 4.9 ± 0.2 to 5.6 ± 0.2 with a slight decrease in PD; the HCO_3^- output was $5.2 \pm 0.7 \mu\text{mol}$ which is about 60.4% of that induced by PGE_2 (300 $\mu\text{g/kg}$) (Fig. 2A). In contrast, the duodenum responded to i.v.-injection of PGE_2 (300 $\mu\text{g/kg}$) by a significant increase of pH and HCO_3^- out-

Fig. 1. Representative recordings showing the effects of capsaicin (0.6–6 mg/ml) on the pH and PD in the stomach [A] and duodenum [B] of anesthetized rats. Capsaicin was applied to the mucosa for 30 min. Note that capsaicin application increased the pH in a concentration-related manner in these tissues.

Fig. 2. Effects of capsaicin (0.3–6 mg/ml) and PGE_2 (300 $\mu\text{g/kg}$) on HCO_3^- output in the stomach [A] and duodenum [B] of anesthetized rats. Capsaicin was applied to the mucosa for 30 min, while PGE_2 was given i.v. as a single bolus injection. Data are presented as the mean $\pm$ S.E. from 6–8 rats.

put for about 40 min with a concomitant rise in PD (Fig. 1B). Intraduodenal application of capsaicin for 30 min also produced an increase of duodenal pH with a small rise in PD, in a concentration-dependent manner (0.3–6 mg/ml). At 6 mg/ml of capsaicin, the pH was increased from 5.2 ± 0.2 to the maximal values of 6.5 ± 0.2 and the HCO_3^- output was $7.8 \pm 0.6 \mu\text{mol}$, which is about 78.6% of that induced by PGE_2 (Fig. 2B). In some cases, we prepared tissue samples after exposure of the gastric mucosa for 30 min to capsaicin at 6 mg/ml and examined microscopically whether capsaicin produced damage in the epithelial cells. However, neither of these tissues showed histological damage in the mucosa and the surface epithelial cells were kept intact even after exposure to capsaicin for 30 min (not shown).

Characteristics of HCO_3^- responses induced by capsaicin

Effect of sensory deafferentation: Since capsaicin is a selective probe for sensory neuronal mechanisms (15), we further examined whether the HCO_3^- stimulatory effect of capsaicin is mediated by capsaicin-sensitive sensory neurons. For this purpose, these afferent neurons were functionally ablated by capsaicin pretreatment 2 weeks before the experiments. As shown in Fig. 3, the increase pH responses induced by capsaicin (6 mg/ml for 30 min) in the stomach were significantly reduced in the sensory deafferented animals. After exposure of the mucosa to capsaicin, the pH was increased from 5.0 ± 0.2 to the maximal values of 5.3 ± 0.2 ; the HCO_3^- output was $0.8 \pm 0.3 \mu\text{mol}$, which is only

Fig. 3. Representative recordings showing the effects of sensory deafferentation and indomethacin on the increased pH responses induced by mucosal application of capsaicin (6 mg/ml) and i.v.-injection of PGE₂ (300 µg/kg) in the stomachs of anesthetized rats. Deafferentation was performed by capsaicin pretreatment 2 weeks before the experiment. Indomethacin (5 mg/kg) was given s.c. 30 min before mucosal application of capsaicin.

15.4% of that obtained in the normal rats (5.2 ± 0.7 µmol) (Fig. 4). Similarly, the increased pH and HCO₃⁻ responses caused by capsaicin in the duodenum were also significantly attenuated by sensory deafferentation; the pH was increased from 5.3 ± 0.2 to 5.8 ± 0.3 at the maximum, and the HCO₃⁻ output was only 2.5 ± 0.4 µmol (not shown). However, chemical deafferentation did not significantly alter the pH and HCO₃⁻ responses induced by i.v.-injection of PGE₂ (300 µg/kg); the HCO₃⁻ output was 7.8 ± 1.2 µmol in the stomach and 9.6 ± 0.8 µmol in the duodenum.

Effect of indomethacin: Since some of the capsaicin actions were reportedly mitigated by PG deficiency (9–11), we examined the effect of indomethacin on the pH and HCO₃⁻ responses induced by capsaicin. Pretreatment of the animals with indomethacin (5 mg/kg) significantly attenuated the pH and HCO₃⁻ responses to capsaicin (6 mg/ml) in the stomach (Figs. 3 and 4) as well as in the duodenum (not shown). The inhibition by indomethacin was 60.3% in the stomach and 57.3% in the duodenum. Indomethacin, however, did not affect the increase of pH and HCO₃⁻ output in response to

Fig. 4. Effects of sensory deafferentation and indomethacin on HCO₃⁻ output induced by capsaicin and PGE₂ in the stomach of anesthetized rats. Capsaicin (6 mg/ml) was applied to the mucosa for 30 min, while PGE₂ (300 µg/kg) was given i.v. as a bolus injection. Data are presented as the mean $\pm$ S.E. from 6–8 rats. *Statistically significant difference from the corresponding control, at $P < 0.05$.

PGE₂ in either of these tissues. The HCO₃⁻ output induced by PGE₂ (300 µg/kg, i.v.) was 8.6 ± 0.7 µmol in the stomach and 10.2 ± 1.1 µmol in the duodenum in the presence of indomethacin, and these values were significantly different from those obtained by PGE₂ under normal conditions (8.6 ± 0.7 µmol in the stomach and 9.9 ± 0.8 µmol in the duodenum).

Effect of repeated application: The stimulatory action of capsaicin on HCO₃⁻ secretion exhibited a marked tachyphylaxis in these tissues. As demonstrated in Fig. 5, when the mucosa was repeatedly exposed for 30 min to the same concentration of capsaicin (6 mg/ml) every 1.5 hr later, both pH and HCO₃⁻ responses became diminished depending upon the times of application. The third application of capsaicin caused only a minimal increase of pH in the stomach as well as in the duodenum; the HCO₃⁻ output was 0.7 ± 0.1 µmol in the stomach and 1.7 ± 0.1 µmol in the duodenum, which is only 14% and 25% of the normal responses in these tissues, respectively (Fig. 6).

Fig. 5. Representative recordings showing the pH and PD responses in the stomach and duodenum after repeated application of capsaicin. The mucosa was exposed for 30 min to capsaicin (6 mg/ml) repeatedly at 1.5-hr intervals; and at the end of experiment, PGE₂ (300 µg/kg) was given i.v. as a single bolus injection. Note that the magnitude of the pH response to capsaicin was markedly reduced after the 2nd application of capsaicin.

DISCUSSION

The present study demonstrated that intraluminal application of capsaicin increased HCO_3^- secretion in the stomach as observed in the duodenum (4) and suggested the involvement of capsaicin-sensitive sensory neurons in the regulation of HCO_3^- secretion in the gastroduodenal mucosa.

We have previously shown that the pH method for HCO_3^- determination is accurate and well-responds to a variety of agents including PGs and cholinergic agents (13, 16). Using this system, we recently found that mucosal application of capsaicin increased HCO_3^- output in the duodenum (4). As expected, capsaicin applied to the stomach also produced an increase of HCO_3^- output in a concentration-related manner, although the magnitude of HCO_3^- response was different in these two tissues. The mucosal area used for HCO_3^- determination in this study was 3.1 cm² in the stomach and 1.7 cm² in the duodenum. However, the net HCO_3^- output induced by PGE₂ or capsaicin was greater in the duodenum than that in the stomach, sug-

Fig. 6. Effects of repeated application of capsaicin HCO_3^- responses in the stomach and duodenum of anesthetized rats. The mucosa was exposed for 30 min to capsaicin (6 mg/ml) three times in the same animals, and each treatment was performed at a 90-min interval. Data are presented as the mean $\pm$ S.E. from 6–8 rats. *Statistically significant difference from the corresponding control, at $P < 0.05$.

gesting that HCO_3^- secretion was more efficient in the duodenum. On the other hand, PD responded to capsaicin or PGE₂ by a decrease in the stomach and an elevation in the duodenum, yet HCO_3^- output was increased in both tissues. The PD response to capsaicin in the stomach disagreed with our previous observation that intragastric capsaicin did not cause any decrease in the PD of the stomach (9). The reason for this discrepancy remains unexplained, but may be due to the different experimental conditions; the previous study was performed in the stomach with normal acid secretion, while in the present study, acid secretion was completely inhibited by omeprazole and the stomach showed much higher PD values (~ -50 mV) than those (~ -35 mV) observed in the absence of omeprazole. Such different PD responses were observed with PGE₂ in the stomach depending on the acid secretory conditions (13, 17). Anyway, the generation of PD across the mucosa is complex, involving changes in electrogenic ion transport as well as in passive ion permeability. It is, however, unlikely that such PD and HCO_3^- responses caused by capsaicin are attributable to changes in

mucosal permeability, inasmuch as the mucosa was kept intact histologically after exposure to this agent, indicating no disintegration of the mucosal barrier. At present, the reason why the PD of the stomachs responded to these agents differently from that of the duodenum remains unknown.

Mucosal application of capsaicin induced various changes in the gastric function by stimulating the sensory nerves within the mucosa (1–4, 9–11). As observed in the duodenum (4), the HCO_3^- stimulatory effect of capsaicin in the stomach was almost completely attenuated by sensory deafferentation. These results suggest that capsaicin also increased HCO_3^- secretion by stimulating capsaicin-sensitive sensory nerves. This contention may be supported by the following finding that the capsaicin action to stimulate HCO_3^- output showed a tachyphylaxis at a high concentration (6 mg/ml); the HCO_3^- response induced by the 2nd or 3rd application of capsaicin was significantly reduced as compared to those observed after the first application. Such phenomena were not observed when the mucosa was repeatedly exposed to capsaicin at a low concentration (0.6 mg/ml) (not shown). Similar findings were reported by Maggi et al. (18) in capsaicin-induced contraction of the isolated guinea pig bladder or inhibition of twitches of the isolated rat vas deferens. Thus, it would be reasonable that a potent stimulation of these neurons depletes the transmitter substances in the nerve endings, resulting in subsidence of sensory-mediated biological actions. Chemical deafferentation seems to be specific to the capsaicin action, because this treatment did not affect the HCO_3^- secretory response to PGE_2 . On the other hand, we previously reported that capsaicin-induced duodenal HCO_3^- output was effectively suppressed by hexamethonium and atropine, suggesting an interaction with cholinergic neurons (4). However, it remains unknown whether the effect of capsaicin on HCO_3^- secretion is mediated by local myenteric reflexes arising from antidromic stimulation of sensory fibers or involves higher centers of neural integration. In addition, no information has been available on the neurotransmitter that may be responsible for the HCO_3^- response induced by stimulation of these sensory neurons.

The HCO_3^- secretion induced by capsaicin was significantly reduced by indomethacin pretreatment in addition to sensory deafferentation. This finding may suggest that endogenous PGs may be involved somewhere in the stimulatory process of HCO_3^- secretion by capsaicin. Other studies also showed involvement of PGs in the cytoprotective action of capsaicin against ethanol (9, 10) or in the capsaicin-induced gastric hyperemic response (11). However, the relation of capsaicin to PG

generation is not without controversy; capsaicin may enhance the formation of PGs in vascular tissues of rabbits (19), while no effect on PG generation is observed in the rat gastric mucosa and other tissues (2, 20). Indomethacin has several other effects that are unrelated to PGs (21, 22), and these actions might be associated with suppression of the HCO_3^- response to capsaicin. Yet, we have observed that indomethacin did not significantly affect the HCO_3^- responses to other agents such as PGE_2 and carbachol (4, 16, 17).

In conclusion, the present study clearly showed that stimulation of capsaicin-sensitive sensory neurons increased HCO_3^- secretion in the stomach, similar to the duodenum. Since HCO_3^- secretion is considered to play an important role in the mucosal defensive ability in the upper gastrointestinal tract (5–7), this effect may be one of the mechanisms by which stimulation of these neurons protects the gastroduodenal mucosa against acid. The present results also suggested the interaction of capsaicin-sensitive sensory neurons with endogenous PGs, but this point must be further investigated for a better understanding of how these neurons and PGs interact and what is the site of this interaction.

Acknowledgments

This work was supported in part by grants from the Ministry of Education, Science and Culture of Japan.

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