Stimulation of gastroduodenal HCO$_3^-$ secretion by lubiprostone mediated by different prostaglandin EP receptor subtypes

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Abstract. We examined the stimulatory effects of lubiprostone, a bicyclic fatty acid derived from prostaglandin E, and a chloride channel type-2 opener (ClC-2), on HCO$_3^-$ secretion in the rat stomach and duodenum, with a focus on the EP receptor subtypes involved in this action. Under urethane anesthesia, an ex-vivo chambered stomach or a duodenal loop was perfused with saline, and HCO$_3^-$ secretion was measured at pH 7.0 using a pH stat-method. Lubiprostone (0.1–30 µM) was perfused in the chamber or loop for 10 min. Indomethacin, ONO-8711 (an EP$_1$ antagonist), or AE5-599 (an EP$_4$ antagonist) was given s.c. 1 h before the lubiprostone treatment, while AE3-208 (an EP$_3$ antagonist) or CFTR$_{172}$ (a cystic fibrosis transmembrane conductance regulator (CFTR) inhibitor) was given i.p. 30 min before. Lubiprostone dose-dependently and significantly increased HCO$_3^-$ secretion in both the stomach (≥ 10 µM) and duodenum (≥ 1 µM). The stimulatory effect in the stomach was significantly abrogated by a pretreatment with the EP$_1$ antagonist, but not the EP$_3$/EP$_4$ antagonists or CFTR inhibitor, while that in the duodenum was significantly attenuated by the EP$_3$/EP$_4$ antagonists as well as the CFTR inhibitor. Indomethacin had no effect on the response of either tissue to lubiprostone. These results suggest that lubiprostone stimulated HCO$_3^-$ secretion in the stomach and duodenum in a manner that was mediated by different EP receptor subtypes; the former was mediated by EP$_1$ receptors, while the latter was mediated by both EP$_3$ and EP$_4$ receptors. CFTR/ClC-2 may be involved in the response observed in the duodenum, but not in the stomach.

Keywords: lubiprostone, HCO$_3^-$ secretion, prostaglandin EP receptor subtypes, stomach, duodenum, rat.

Introduction

Lubiprostone, a bicyclic fatty acid derived from prostaglandin (PG) E$_1$, has been used to treat chronic constipation and irritable bowel syndrome with constipation (Schey, Rao 2011). Its mechanism of action has been attributed to the stimulation of intestinal fluid secretion via the activation of ClC-2 chloride channels, which are located in the apical membranes of epithelial cells as a cystic fibrosis transmembrane regulator (CFTR) bypass channel in Cystic Fibrosis (Schwiebert et al. 1998; Cuppoletti et al. 2004). Previous studies demonstrated that lubiprostone activated PGE receptors (Bassil et al. 2008; Mizumori et al. 2009; Cuthbert 2011). These receptors have been pharmacologically subdivided into four subtypes, EP$_1$–EP$_4$ (Woodward et al. 2011). Among them, the EP$_4$ receptor appears to be the main target for lubiprostone. Cuthbert demonstrated that EP$_4$ receptors in sheep were the major target for lubiprostone to stimulate the secretion of anions in ovine airways (Cuthbert 2011). In addition, several studies showed that lubiprostone activated ClC-2/CFTR chloride channels via EP$_4$ receptors (Cuppoletti et al. 2004; Bassil et al. 2008; Bao et al. 2008). We previously reported that PGE$_4$ ameliorated indomethacin-induced small intestinal damage via the activation of EP$_4$ receptors (Kunikata et al. 2002; Hatazawa et al. 2006; Takeuchi 2014). In consistence with these findings, we recently...
confirmed that lubiprostone also prevented indomethacin-induced enteropathy via an EP$_4$ receptor-dependent mechanism (Hayashi et al. 2014).

The secretion of HCO$_3^-$ from surface epithelial cells is one of the main processes involved in mucosal defense and plays an important role in protecting the gastroduodenal mucosa against acid (Flemström, Garner 1982; Flemström, Turnberg 1984; Takeuchi et al. 1986). The physiological regulation of HCO$_3^-$ secretion involves several factors such as PGs, nitric oxide, and neuronal factors (Flemström, Garner 1982; Heylings et al. 1984; Takeuchi et al. 1991; Hogan et al. 1993; Sugamoto et al. 2001; Takeuchi et al. 1997). Mizumori et al. (2009) reported that lubiprostone stimulated CFTR-dependent duodenal HCO$_3^-$ secretion in rats, and this action was mediated by the activation of EP$_4$ receptors. PGE$_4$ has been shown to stimulate HCO$_3^-$ secretion in the stomach and duodenum in a manner that is mediated by different EP receptors; EP$_2$ receptors in the stomach and EP$_2$/EP$_4$ receptors in the duodenum (Takeuchi et al. 1997; Takeuchi et al. 1999; Aoi et al. 2004; Aihara et al. 2007).

However, it currently remains unknown whether lubiprostone stimulates HCO$_3^-$ secretion in the stomach similar to PGE$_2$, and which EP receptors are responsible for its effects in the stomach.

In the present study, we examined the stimulatory effects of lubiprostone on HCO$_3^-$ secretion in the rat stomach and duodenum, with a focus on the EP receptor subtypes involved in these effects. Since lubiprostone is a CIC-2 chloride channel opener (Schwiebert et al. 1998; Cuppoletti et al. 2004), we also determined the contribution of CIC-2/CFTR channels to its HCO$_3^-$ stimulatory effects in these tissues.

**Materials and methods**

**1. Animals**

Male Sprague-Dawley rats (200–260 g; Nippon Charles River, Shizuoka, Japan) were acclimated to standard laboratory conditions (12:12 h light-dark cycle, temperature of 22 ± 1°C). Animals were kept in individual cages with raised mesh bottoms and deprived of food, but allowed free access to tap water for 18 h before the experiments. Experiments were carried out using four to six rats per group under urethane anesthesia (1.25 g/kg, i.p.). Body temperature was monitored intermittently using a rectal thermometer (Natsume, Tokyo, Japan) and maintained at ~35 °C by placing the animals on a heat pad and exposing them to an external heat lamp (40 W) (Takeuchi et al. 1986; Takeuchi et al. 1997). All experimental procedures described were approved by the Experimental Animal Research Committee of Kyoto Pharmaceutical University.

**2. Determination of HCO$_3^-$ secretion**

The secretion of HCO$_3^-$ was measured in a chambered stomach or duodenal loop as described previously (Takeuchi et al. 1997; Takeuchi et al. 1990). The abdomen was incised, and the stomach was exposed and mounted on a chamber (exposed area: 3.1 cm$^2$), while a duodenal loop (17 mm) was made between the pyloric ring and area just above the outlet of the common bile duct to exclude the influences of bile and pancreatic juice (fig. 1).

![Fig. 1. Schematic illustration of the perfusion system and order of connection of the loop to determine HCO$_3^-$ secretion in the whole stomach (A) or proximal duodenum (B) of an anesthetized rat. The tissue was continuously perfused at a rate of 0.2 ml/min with saline, which was gassed with 100% O$_2$, heated at 37°C, and kept in a reservoir. HCO$_3^-$ secretion was measured at pH 7.0 using a pH-stat method](image)

The ex-vivo chambered stomach or duodenal loop was perfused at a rate of 0.2 ml/min with saline, which was gassed with 100% O$_2$ and kept in a reservoir. The secretion of HCO$_3^-$ was measured at pH 7.0 using a pH-stat method (Hiranuma Comtite-8, Mito, Japan) and by the addition of 2 mM HCl to the reservoir. To unmask HCO$_3^-$ in the stomach, the secretion of acid was completely inhibited by omeprazole, which was administered i.p. at a dose of 60 mg/kg. Omeprazole at this dose has been shown to have no influence on gastric HCO$_3^-$ secretion in rats (Flemström, Mattsson 1986). After the basal secretion of HCO$_3^-$ had been stabilized, the chamber or loop was perfused at a rate of 0.2 ml/min for 10 min with lubiprostone (0.1–30 μM) made isotonic with NaCl. In some cases, HCO$_3^-$ secretion was stimulated in both the stomach and duodenum by PGE$_2$ (1 mg/kg) given intravenously (i.v.). Indomethacin (a cyclooxygenase inhibitor:
5 mg/kg), ONO-8711 (an EP₁ antagonist: 10 mg/kg), or AE5-599 (an EP₁ antagonist: 10 mg/kg) was given subcutaneously (s.c.) 1 h before the application of lubiprostone or administration of PGE₂, while AE3-208 (an EP₃ antagonist: 10 mg/kg) or CFTR inh-172 (an inhibitor of CFTR: 1 mg/kg) was given intraperitoneally (i.p.) 30 min before. The doses of these EP and CFTR antagonists were selected in order to induce the respective pharmacological actions according to the findings of previous studies (Hayashi et al. 2014; Takeuchi et al. 2011; Takeuchi et al. 2002; Norimatsu et al. 2012).

3. Determination of gene expression of the ClC-2 chloride channel and EP₁-EP₄ receptors

The gene expression of the ClC-2 chloride channel and EP₁-EP₄ receptors was measured in the gastric and duodenal mucosa by a reverse transcriptional polymerase chain reaction (RT-PCR). The stomach or duodenum was removed under deep ether anesthesia, and stored at -80 ºC prior to use. Total RNA was extracted from tissue samples using Sepasol RNA I (Nacalai Tesque, Kyoto, Japan). Total RNA was reverse-transcribed with a first strand cDNA synthesis kit (ReverTra Ace alpha, TOYOBO, Osaka, Japan). The sequences of the sense and antisense primers for the rat ClC-2 chloride channel and EP₁-EP₄ receptors, and each product size, are shown in Table 1. An aliquot of the RT reaction product served as a template in 35 cycles of PCR with 0.5 min of denaturation at 95 ºC and 1 min of extension at 68 ºC using the Advantage 2 polymerase mixture (CLONTECH, Mountain View, CA) in a thermal cycler (PC-806, ASTEC, Fukuoka, Japan). A portion of the RT reaction mixture was electrophoresed in 1.5 % agarose gel in Tris-acetic acid-EDTA buffer (40 mM Tris, 20 mM acetic acid, and 2 mM EDTA; pH 8.1), and the gel was stained with ethidium bromide and photographed (Bio Doc-It Imaging System; UVP, Upland, CA, USA). Images were analyzed with Image J (version 1.39).

4. Preparation of drugs

The drugs used were prostaglandin E₂, indomethacin (Sigma Chemicals, St. Louis, MO), lubiprostone (Abbott Japan Co., Ltd. Tokyo, Japan), ONO-8711 (an EP₁ antagonist), AE5-599 (an EP₁ antagonist), AE3-208 (an EP₃ antagonist) (Ono Pharmaceutical Co., Ltd., Osaka, Japan), CFTR inh-172 (a CFTR inhibitor; Wako Pure Chemicals, Osaka, Japan), and urethane (Tokyo Kasei, Tokyo, Japan). Prostanoids, including lubiprostone, were dissolved in absolute ethanol and diluted with saline to the desired concentrations. Indomethacin was suspended in a 0.5 % hydroxypropylcellulose solution (Wako Pure Chemicals). Other drugs were dissolved in saline. All drugs were prepared immediately before use, perfused intraluminally at a rate of 0.2 ml/min, and administered subcutaneously (s.c.) or intraperitoneally (i.p.) in a volume of 0.5 ml/100 g body weight or intravenously (i.v.) in a volume of 0.1 ml/100 g body weight. Control animals received the vehicle alone.

5. Statistical analyses

Data are presented as means ± SE for four to eight rats per group. Statistical analyses were performed using a two-tailed unpaired t-test and Dunnett’s multiple comparison test, and values of P < 0.05 were considered significant.

Results

1. Effects of lubiprostone on gastric HCO₃⁻ secretion

Under urethane anesthesia, the rat chambered stomach spontaneously secreted HCO₃⁻ at a steady rate of 0.1~0.2 µEq/10 min, and secretion remained unaltered after the perfusion of saline for 10 min at a rate of 0.2 ml/min. The perfusion of the chambered stomach with lubiprostone (1~30 µM) for 10 min increased the secretion of HCO₃⁻ in a concentration-dependent manner. The rate of HCO₃⁻ secretion was significantly increased by lubiprostone perfusion at 30 µM compared to saline (fig. 2A), while the net HCO₃⁻ output was significantly greater at 10 µM and 30 µM than that in the saline-perfused stomach; ΔHCO₃⁻ outputs at 1, 10, and 30 µM were 1.11 ± 0.42, 2.15 ± 0.36, and 3.53 ± 0.37 µEq/h, respectively (fig. 2B). The HCO₃⁻ response to lubiprostone in the stomach persisted for ap
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proximately 2 h. Based on these results, lubiprostone was perfused in the chambered stomach at 30 µM in subsequent experiments.

2. Effects of lubiprostone on duodenal HCO\(_3\)\(^-\) secretion

The rat duodenum spontaneously secreted HCO\(_3\)\(^-\) at a steady rate of 0.3~0.5 µEq/10 min under urethane anesthesia, and its secretion remained unaltered after the perfusion of saline for 10 min at a rate of 0.2 ml/min. However, lubiprostone (0.1~10 µM) perfused luminally in the duodenal loop for 10 min increased the secretion of HCO\(_3\)\(^-\) in a concentration-dependent manner, and its secretion was significantly greater at concentrations of 1 µM and 10 µM than that in the saline-perfused duodenum; ∆HCO\(_3\)\(^-\) outputs at 0.1, 1, and 10 µM were 1.62 ± 0.42, 5.35 ± 0.31, and 4.78 ± 0.32 µEq/h, respectively (figs. 3A and 3B). Based on these results, lubiprostone was perfused in the duodenal loop at 1 µM in subsequent experiments.

3. Effects of EP\(_1\), EP\(_3\), and EP\(_4\) antagonists on lubiprostone-stimulated gastric HCO\(_3\)\(^-\) secretion

The luminal perfusion of lubiprostone (30 µM) in the chambered stomach for 10 min potently increased HCO\(_3\)\(^-\) secretion, with ∆HCO\(_3\)\(^-\) output at 3.73 ± 0.41 µEq/h, which was significantly higher than that (0.96 ± 0.08 µEq/h) in the control. The stimulatory effects of lubiprostone were significantly attenuated by the pretreatment of animals with ONO-8711 (10 mg/kg, s.c.), the EP\(_1\) antagonist, but not by either AE5-599 (10 mg/kg), the EP\(_3\) antagonist, or AE3-208 (3 mg/kg), the EP\(_4\) antagonist, with the degrees of inhibition being 70.3 %, 16.2 %, and -16.1 %, respectively (fig. 4).

4. Effects of EP\(_1\), EP\(_3\), and EP\(_4\) antagonists on lubiprostone-stimulated duodenal HCO\(_3\)\(^-\) secretion

The luminal perfusion of lubiprostone (1 µM) in the duodenal loop for 10 min significantly elevated HCO\(_3\)\(^-\) secretion over that in the control group treated with saline; ∆HCO\(_3\)\(^-\) output was 5.38 ± 0.41 µEq/h. The HCO\(_3\)\(^-\) stimulatory effect of lubiprostone was significantly attenuated by the pretreatment of animals with AE5-599 (10 mg/kg, s.c.) and AE3-208 (3 mg/kg, i.p.), but not with ONO-8711 (10 mg/kg, s.c.), and the degrees of inhibition were 48.2 %, 75.9 % and 5.5 %, respectively (fig. 5).

5. Effects of indomethacin and CFTR(inh)-172 on HCO\(_3\)\(^-\) responses induced by lubiprostone in the stomach and duodenum

Since the HCO\(_3\)\(^-\) response to lubiprostone was significantly attenuated by EP antagonists, this effect may be mediated by endogenous PGs. Lubiprostone has also been shown to activate ClC-2 chloride channels (De Lisle et al. 2010; Schiffhauer...
et al. 2013). In order to investigate the possible involvement of endogenous PGs and ClC-2 chloride channels in the HCO₃⁻ stimulatory action of lubiprostone, we examined the effects of indomethacin and CFTR(inh)-172 on HCO₃⁻ responses to lubiprostone in the stomach and duodenum.

When lubiprostone was perfused for 10 min into the chambered stomach or duodenal loop at 30 µM or 1 µM, respectively, the secretion of HCO₃⁻ was significantly increased; ∆HCO₃⁻ output was 3.68 ± 0.46 µEq/h in the stomach or 5.50 ± 0.32 µEq/h in the duodenum, respectively. As shown in Fig. 6A, HCO₃⁻ responses in the stomach and duodenum were not significantly affected by the pretreatment of animals with indomethacin (5 mg/kg, s.c.); the responses observed were similar to those in control tissues. On the other hand, CFT(inh)-172 (1 mg/kg, i.p.), the inhibitor of CFTR, significantly attenuated the HCO₃⁻ response to lubiprostone (1 µM) in the duodenum, but not in the stomach, with inhibition at 41.6% in the former and 23.6% in the latter (fig. 6B).


To confirm the involvement of specific EP receptor subtypes in the HCO₃⁻ response to PGE₂ in the stomach and duodenum, we examined the effects of various EP antagonists on PGE₂-induced HCO₃⁻ secretion in these tissues. The intravenous administration of PGE₂ (1 mg/kg) significantly increased the secretion of HCO₃⁻ in the stomach and duodenum; ∆HCO₃⁻ output was at 3.48 ± 0.96 µEq/h
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Fig. 7. Effects of various subtype-selective EP antagonists on PGE₂-stimulated HCO₃⁻ secretion in the stomach (A) and duodenum (B) of anesthetized rats. PGE₂ was administered i.v. at 1 mg/kg. ONO-8711 (an EP₁ antagonist: 10 mg/kg) or AE5-599 (an EP₃ antagonist: 10 mg/kg) was given s.c. 1 h before the administration of PGE₂. AE3-208 (an EP₄ antagonist: 3 mg/kg) was given i.p. 30 min before. Data are presented as the mean ± SE for 4–7 rats. Significant difference at P < 0.05; * from the control; # from the vehicle.

Fig. 8. Gene expression of EP receptor subtypes (EP₁-EP₄) (A) and CIC-2 (B) in the rat stomach and duodenum.

and 5.43 ± 0.62 µEq/h, respectively (fig. 7). The response in the stomach was significantly inhibited by ONO-8711 (10 mg/kg, s.c.), but not by AE5-599 (10 mg/kg, s.c.) or AE3-208 (5 mg/kg, i.p.), while the response in the duodenum was significantly attenuated by both AE5-599 and AE3-208, but not by ONO-8711.


Since EP₁ and EP₃/EP₄ receptors were found to be involved in the HCO₃⁻ stimulatory action of lubiprostone in the stomach and duodenum, respectively, we examined the gene expression of various EP receptor subtypes (EP₁-EP₄) in addition to the CIC-2 chloride channel. As shown in fig. 8A, EP₁ and EP₃ receptors were expressed in both the gastric and duodenal mucosa, although differences were observed in the intensity of their expression. The gene expression of the CIC-2 chloride channel was also clearly detected in both tissues (fig. 8B).

Discussion

Lubiprostone has been used to treat chronic constipation (Schey, Rao 2011), and its mechanism of action has been attributed to the stimulation of intestinal fluid secretion via the activation of CIC-2 chloride channels (Schwiebert et al. 1998; Cuppoletti et al. 2004). This drug is a bicyclic fatty acid derived from PGE₁ and has been shown to activate PGE receptors (Bassil et al. 2008; Mizumori et al. 2009; Cuthbert 2011). We recently reported that lubiprostone prevented indomethacin-induced small intestinal damage via the activation of EP₂ receptors, similar to PGE₂ (Hayashi et al. 2014; Flemström, Garner 1982), suggesting the prophylactic use of this drug against NSAID-induced enteropathy. In the present study, we demonstrated for the first time that lubiprostone stimulated HCO₃⁻ secretion in both the stomach and duodenum via different EP receptor subtypes; its effect in the stomach was mediated by EP₁ receptors, while that in the duodenum was mediated by both EP₃ and EP₄ receptors.

The secretion of HCO₃⁻ from the surface epithelium is one of the mucosal defensive mechanisms and plays an important role in protecting the gastroduodenal mucosa. Various analogues of PGs or agents that enhance the biosynthesis of endogenous PGs stimulate HCO₃⁻ secretion, while nonsteroidal anti-inflammatory agents decrease the secretion of HCO₃⁻ by inhibiting PG generation (Flemström, Garner 1982; Flemström, Turnberg 1984; Takeuchi 1986; Takeuchi et al. 2011). We previously reported that PGE₂ affected HCO₃⁻ secretion via distinctive mechanisms in the stomach and duodenum concerning the EP receptor subtypes involved in this process; its effect in the stomach was mediated by EP₁ receptors coupled with elevations in intracellular Ca²⁺, while that in the duodenum was associated with the intracellular accumulation of both Ca²⁺ and 3'5'-cyclic adenosine monophosphate (cAMP) caused by the activation of EP₂/EP₄ receptors (Takeuchi et al. 1997; Takeuchi et al. 1999; Aoi et al. 2004; Alhara et al. 2007; Takeuchi et al. 2011).

Since lubiprostone is derived from PGE₂ and induces its pharmacological effects through EP receptors (Schwiebert et al. 1998; Cuppoletti et al. 2004),
this drug may increase the secretion of HCO$_3^-$ in the stomach and duodenum via EP receptors. Mizumori et al. (2009) was the first to report that lubiprostone stimulated duodenal HCO$_3^-$ secretion via the activation of EP$_4$ receptors in rats, and suggested the possibility of its protection of the duodenum from acid-induced injury. We confirmed the HCO$_3^-$ stimulatory effect of lubiprostone in the duodenum via EP$_4$ receptors and further showed that this effect was mediated by the activation of not only EP$_4$ receptors, but also EP$_3$ receptors. As expected, we also found that this drug increased the secretion of HCO$_3^-$ in the stomach, and this effect was significantly attenuated by the pretreatment with ONO-8711, the EP$_1$ antagonist, but not by the EP$_3$ or EP$_4$ antagonist, suggesting that its action in the stomach was mediated by the activation of EP$_3$ receptors. Lubiprostone is unlikely to have stimulated HCO$_3^-$ secretion by increasing endogenous PG levels, because this effect was observed even under PG-deficient conditions caused by indomethacin. This was also supported by previous findings in which lubiprostone prevented the intestinal ulcerogenic response caused by indomethacin via EP$_3$ receptors (Takeuchi 2014; Hayashi et al. 2014). In a preliminary study, we also observed the effects of lubiprostone in an isolated mouse stomach in vitro, which suggested its direct action on epithelial cells without involving intrinsic and extrinsic nerves (Takeuchi 2014).

Several studies demonstrated that lubiprostone activated CIC-2/CFTR chloride channels via EP$_4$ receptors (Bassil et al. 2008; Mizumori et al. 2009; Cuthbert 2011). Lubiprostone has been shown to stimulate CFTR-dependent duodenal HCO$_3^-$ secretion without changing net Cl$^-$ secretion, which suggested that lubiprostone acts as a dual activator of CFTR-independent Cl$^-$ secretion and as a PG receptor agonist (Mizumori et al. 2009). In the present study, we confirmed the gene expression of CIC-2 chloride channels as well as EP$_3$-EP$_4$ receptors in both rat stomach and duodenum, with some differences in the intensity of their expression. Although the cell types that express each EP receptor subtype and CIC-2 chloride channels have not yet been identified, we assumed that CIC-2/CFTR channels are expressed in epithelial cells, even in the stomach. However, we noted that the prior administration of CFTR(inh)-172, an inhibitor of CFTR, significantly attenuated the HCO$_3^-$ stimulatory effect of lubiprostone in the duodenum, but not in the stomach. Since the activation of EP$_4$ receptors increases intracellular cAMP (Regan 2003), and elevations in cAMP, in turn, activate CFTR (Li, Naren 2005), CFTR-dependent HCO$_3^-$ secretion by lubiprostone appeared to be consistent with the activation of EP$_4$ receptors by lubiprostone. Norimatsu et al. (2012) also confirmed that CFTR was activated by lubiprostone via the EP$_1$ receptor in oocytes, even though the drug had no direct effect on either CIC-2 or CFTR channels expressed in oocytes. It has not yet been determined why the effect of lubiprostone in the stomach was unaffected by the CFTR inhibitor; however, these results suggest that the direct activation of CFTR/CIC-2 chloride channels does not contribute to the HCO$_3^-$ stimulatory action of lubiprostone in the stomach.

Another interesting finding was that the effective dose of lubiprostone markedly differed between the stomach and duodenum; the stimulation of HCO$_3^-$ secretion was observed at ≥ 10 µM in the stomach and at ≥ 1 µM in the duodenum. Consistent with our previous findings (Takeuchi et al. 1997; Takeuchi et al. 1999; Aoi et al. 2004; Aihara et al. 2007; Takeuchi et al. 2011), PGE$_2$, stimulated HCO$_3^-$ secretion in both the stomach and duodenum at the same dose level (1 mg/kg, i.v.); however, these effects were mediated via different EP receptors in these tissues, similar to those of lubiprostone. Although this difference remains unexplained, it may have been due to different affinities to the EP receptor subtypes and/or CIC-2/CFTR-dependency; higher affinity to both EP$_3$/EP$_4$ receptors than EP$_1$ receptors and CIC-2/CFTR-dependency in the duodenum, but not in the stomach.

The present results suggest that lubiprostone, a bicyclic fatty acid derived from PGE$_2$, stimulated HCO$_3^-$ secretion in the stomach and duodenum, similar to PGE$_2$, and these effects were mediated by different EP receptor subtypes in these tissues; the effect observed in the stomach was mediated by EP$_3$ receptors, while that in the duodenum was mediated by both EP$_3$ and EP$_4$ receptors. In addition, CFTR was involved in modulating HCO$_3^-$ secretion in the duodenum, but not in the stomach. Considering the findings in the present study, it is assumed that beyond treatment of constipation, irritable bowel syndrome and enteropathy, lubiprostone may have potential to be used more for protection against gastritis and peptic ulcer diseases, since it does stimulate the secretion of HCO$_3^-$ in both the stomach and duodenum. Furthermore, because duodenal HCO$_3^-$ secretion was shown to be impaired in patients with Helicobacter pylori (Tuo et al. 2004; Tuo et al. 2009), it is also possible that lubiprostone may be useful for treatment of Helicobacter pylori-related diseases.
Lubiprostone stimulated gastroduodenal \( \text{HCO}_3^\text{-} \) secretion, and these stimulatory effects differed in the two tissues examined; the effect observed in the stomach was mediated by \( \text{EP}_3 \) receptors and independent of CFTR channels, while that in the duodenum was mediated by both \( \text{EP}_3 \) and \( \text{EP}_4 \) receptors and dependent on CFTR channels. Lubiprostone appeared to protect the stomach and duodenum against acid injury by stimulating the secretion of \( \text{HCO}_3^\text{-} \).

References


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