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The effect of prostaglandins on gastric parietal and non-parietal secretion in the anaesthetized rat

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The effects of prostaglandin E_2 (PGE_2), 16,16-dimethyl prostaglandin E_2 ($dmPGE_2$) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) on gastric secretion have been examined in the anaesthetized rat. The prostaglandins stimulated the secretion of a non-parietal juice which was rich in Na^+ and Cl^- with smaller amounts of K^+ and HCO_3^-. Doses of the prostaglandins that stimulated gastric non-parietal secretion also inhibited histamine stimulated gastric acid secretion, and thus the same rank order of potency was obtained for the prostaglandins on the two secretory mechanisms, viz. $dmPGE_2 > PGE_2 > PGF_{2\alpha}$. During the secretion of endogenous gastric acid the secretagogue effect of the prostaglandins on non-parietal secretion was diminished, and this effect appeared to be due to the presence of intraluminal acid since it was mimicked by application of exogenous HCl to the gastric mucosal surface. Thus, the present results show that prostaglandins affect both the parietal and non-parietal secretions in the rat stomach and that these mechanisms show some interdependence.

It is well documented that prostaglandins of the E series stimulate gastric non-parietal secretion both in-vivo and in-vitro (reviewed by Flemstrom & Garner 1982), and since this secretion is alkaline it has been proposed that gastric bicarbonate output is an important aspect of the gastric protective mechanism against intraluminal acid (Allen & Garner 1980; Flemstrom & Garner 1982). Indeed, this hypothesis has been strengthened by the observation that, in both amphibian isolated gastric mucosa (Heylings et al 1984) and the canine Heidenhain pouch (Garner & Hurst 1981), bathing the luminal surface with acid stimulates bicarbonate output. In the present work the nature of this inter-relationship between gastric parietal (acid) and gastric non-parietal secretion was examined in the anaesthetized rat following intragastric administration of E and F prostaglandins. Some of the results are at variance with those previously reported in the literature (see above), and question some aspects of the present view of the control of gastric non-parietal secretion; the data are presented herein.

In addition, although it has previously been reported that E prostaglandins stimulate gastric non-parietal secretion in the rat (Bolton et al 1978; Tao & Wilson 1984) and that this secretion contains bicarbonate (Van Kolfschoten et al 1983; Whittle et al 1984), a more detailed description of the composition of the secretion has not been made; this is provided in the present study.

METHODS

Surgical procedure

Female Wistar rats, 100–120 g, were fasted for 48 h before use, but allowed free access to a salt/sugar solution (0·9% NaCl, 8% sucrose w/v). The rats were injected with indomethacin, 14 μmol kg^{-1} s.c., to inhibit endogenous prostaglandin formation and then anaesthetized with pentobarbitone, 50 mg kg^{-1} i.p. A jugular vein was cannulated and atropine, 3 μmol kg^{-1} i.v., injected to inhibit basal gastric acid secretion. The abdomen was opened by midline incision and the pylorus and oesophagus were ligated close to the stomach. An incision was made in the rumen of the stomach and the gastric lumen rinsed thoroughly with 300 mM mannitol solution. A small polythene fistula was then inserted and tied into the ruminal incision and the abdomen closed so that the distal end of the gastric fistula was exteriorized. At this stage a maintenance infusion of pentobarbitone, 100 μg kg^{-1} min^{-1} i.v., was commenced.

Stimulation of secretion

Following a 10 min stabilization period, gastric non-parietal secretion was stimulated by intragastric administration of a prostanoid via the gastric fistula; the dose volume was 0·25 mL/100 g b.w. and the control vehicle was 275 mM mannitol/25 mM theophylline. Preliminary experiments showed that addition of theophylline to the instillate did not change the level of basal or prostaglandin-stimulated

secretion, but in the presence of 25 mM theophylline the prostanoids stimulated more consistent secretory responses; 275 mM mannitol was added to provide an isotonic solution. In experiments on the effects of intraluminal acid, the solution instilled via the gastric fistula was 175 mM mannitol/50 mM HCl/25 mM theophylline. Where appropriate, gastric acid secretion was stimulated by infusion of histamine, 100 μg kg^{-1} min^{-1} i.v. In all experiments, gastric secretion was collected over 1 h after which the stomach was removed without damaging the oesophageal and pyloric ligatures. The intragastric contents were then expressed into a suitable container via the gastric fistula and the volume measured.

Expression of results

Secretory volumes were calculated as the volume of juice collected from the stomach above the volume of intragastric vehicle injected at the beginning of the 1 h secretory period.

Results are expressed as mean ± s.e. mean. Statistical comparisons were made using Student's *t*-test for unpaired data; a P value of less than 0·05 was considered to be significant.

Measurement of ions

The gastric samples were centrifuged and the supernatant fluid used for the assays. Sodium and potassium outputs were measured by flame photometry. Chloride output was measured by coulometric titration. The outputs of acid or bicarbonate were measured by back-titration as follows. To 0·1 mL of gastric aspirate were added 0·1 mL of 50 mM H_2SO_4 and 1 mL of distilled water, and the samples heated at 100 °C for 15 min to expel residual CO_2. The total acid in these samples was then determined by automatic titration to pH 7 using 0·1 M NaOH, from which the output of acid or bicarbonate was calculated.

Materials

Histamine acid phosphate (BDH) was dissolved in isotonic saline for intravenous infusion; the dose is expressed as weight of the base. Indomethacin (Sigma) was dissolved at 10 mg mL^{-1} in 10% w/v $NaHCO_3$ solution, further dilutions were then made with isotonic saline. Mannitol (Sigma) and theophylline (BDH) were dissolved in distilled water to give an isotonic solution for intragastric instillation. Solutions of prostaglandin E_2 (Prostin E, Upjohn), prostaglandin $F_{2\alpha}$ (Lutalyse, Upjohn) and 16,16-dimethyl prostaglandin E_2 (Cayman Chemical and Glaxo) were diluted appropriately with the mannitol/theophylline solution for intragastric instillation.

RESULTS

In the present experiments the rats were pretreated with atropine (3 μmol kg^{-1} = 1 mg kg^{-1} i.v.) to inhibit basal gastric acid secretion; this dose has been shown to inhibit completely such secretion in the rat (Hedges & Parsons 1977). In addition, available evidence indicates that atropine does not affect non-parietal secretion under basal conditions (Flemstrom & Garner 1980; Hirst et al 1980). Indeed, atropine was a particularly convenient choice as inhibitor of basal acid secretion in the present work since it allowed stimulation of acid secretion by histamine in subsequent experiments. In addition, indomethacin was used to inhibit endogenous prostanoid formation; previous experiments have shown that indomethacin reduces basal levels of gastric non-parietal secretion in the rat (Bunce & Clayton 1987), and such treatment allows a clearer demonstration of the effect of exogenous prostaglandins in gastrointestinal epithelia (Flemstrom et al 1982).

Stimulation of gastric non-parietal secretion by prostaglandins

Details of the composition of basal non-parietal secretion and the effect of PGE_2 on this secretion are shown in Fig. 1. Under control conditions the secretory rate was 0·22 ± 0·06 mL h^{-1} and PGE_2 stimulated a dose-related increase in secretion to a rate of 1·08 ± 0·12 mL h^{-1} at a dose of 0·3 μmol kg^{-1} intragastrically. This secretion consisted principally of Na^+ and Cl^- ions with smaller amounts of K^+. Since H^+ and HCO_3^- were measured by titration, comment cannot be made on the absolute outputs of these ions but rather on the acidity or alkalinity of the gastric juice; under control conditions the gastric juice was slightly acidic and PGE_2 stimulated the secretion of an alkaline juice. In Table 1 a comparison is made of the composition of the gastric juice stimulated by each of the prostanoids studied; the response to the largest dose of each compound is recorded. These results show that, like PGE_2, $dmPGE_2$ and $PGF_{2\alpha}$ also stimulated the secretion of a juice rich in Na^+ and Cl^- with lesser amounts of K^+ and HCO_3^-. The data in Table 1 also reveal that under control conditions and with each prostanoid there was no significant difference between the outputs of total cations and total anions, and this result indicates that no major ionic component of the gastric juice was omitted from analysis.

Na^+ is a major component of non-parietal juice both under basal conditions (several reports cited by Makhlouf 1981) and also during stimulation of non-parietal secretion by prostaglandins in the dog

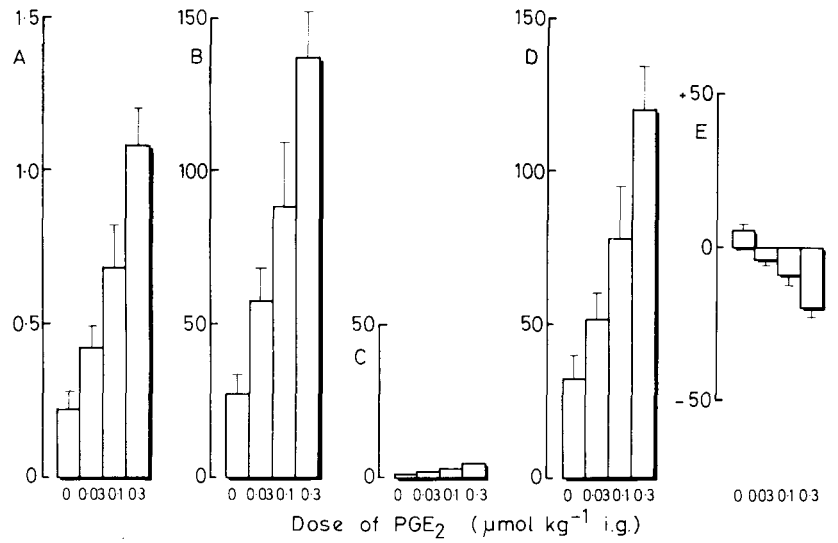

FIG. 1. The effect of intragastric prostaglandin E_2 on secretory volume and net ion outputs in the stomach of the anaesthetized rat. Vertical lines show s.e. mean. Each point is the mean of 5–6 experiments. Key: A, volume (mL h^{-1}); B, Na^+; C, K^+; D, Cl^-; E, H^+/HCO_3^- (μequiv h^{-1}). For H^+/HCO_3^- output: + = H^+ output, − = HCO_3^- output.

Table 1. The effect of prostanoids on ion fluxes in rat gastric mucosa.

Treatment	n	[a]Volume	[b]Na^+	[b]K^+	[b]Cl^-	[b,c]H^+/HCO_3^-	[b,d]Total cations	[b,d]Total anions
Control	6	0·22 ± 0·06	27·4 ± 6·1	1·1 ± 0·3	32·3 ± 7·5	+5·8 ± 1·8	34·3 ± 7·7	32·3 ± 7·5
PGE_2, 0·3 μmol kg^{-1} topically	5	1·08 ± 0·12	136·9 ± 15·3	4·7 ± 0·9	119·6 ± 14·4	−19·8 ± 3·1	141·5 ± 15·9	139·4 ± 17·5
$dmPGE_2$, 0·1 μmol kg^{-1} topically	5	0·95 ± 0·08	130·0 ± 10·1	3·7 ± 0·2	107·7 ± 7·4	−17·2 ± 2·1	133·7 ± 10·3	124·8 ± 8·9
$PGF_{2\alpha}$, 3 μmol kg^{-1} topically	4	0·95 ± 0·19	125·3 ± 24·8	4·0 ± 1·1	108·9 ± 18·9	−15·3 ± 4·4	129·3 ± 25·8	124·2 ± 23·3

[a] Values show net secretion of fluid in mL h^{-1}.
[b] Values show net secretion of ions in μequiv h^{-1}.
[c] For H^+/HCO_3^-; + indicates net H^+ secretion, and − indicates net HCO_3^- secretion.
[d] In each test there was no significant difference ($P > 0·05$) between the total outputs of cations and anions.
Results are expressed as mean ± s.e. mean. All prostanoids stimulated a significant increase ($P < 0·05$) in each parameter compared with the corresponding control.

(Bolton & Cohen 1978), cat (Smeaton & Hirst 1984) and rat (Main & Melarange 1980; present study). Since Na^+ is only a minor component of parietal juice (Makhlouf 1981), this ion was used as the index of non-parietal secretion in subsequent investigations. Thus, by measuring the increase in Na^+ output above the corresponding mean basal level, a comparison of the effect of the prostaglandins on non-parietal secretion is shown in Fig. 2. Like PGE_2, $dmPGE_2$ and $PGF_{2\alpha}$ stimulated a dose-related increase in Na^+ output and, taken at a ΔNa^+ output of 70 μequiv h^{-1}, $dmPGE_2$ was 2·3 times more potent than PGE_2 and 22·2 times more potent than $PGF_{2\alpha}$.

Effects of prostaglandins on ion outputs during stimulation of gastric acid secretion

The ion outputs during stimulation of gastric acid secretion by histamine and the effect of PGE_2 is shown in Fig. 3. Under control conditions histamine stimulated a net acid output of 61·8 ± 5·4 μequiv h^{-1}; the rats also secreted non-parietal juice and the Na^+ output (38·9 ± 2·1 μequiv h^{-1}) was not significantly different from the control value observed in the absence of histamine stimulation shown in Fig. 1 and Table 1 (27·4 ± 6·1 μequiv h^{-1}, $P = 0·13$). A dose of PGE_2 of 0·3 μmol kg^{-1} intragastrically stimulated a significant increase in the output of Na^+ and doses of 0·1 and 0·3 μmol kg^{-1} intragas-

trically significantly inhibited H^+ output. There was no significant change in Cl^- output and this was probably because while the secretion of parietal Cl^- was inhibited by PGE_2 the secretion of non-parietal Cl^- was stimulated. $PGF_{2\alpha}$ and $dmPGE_2$ produced qualitatively similar effects on ion outputs during histamine infusion, and a comparison of the activities of the prostaglandins as inhibitors of acid secretion is shown in Fig. 4. All three compounds produced a dose-related inhibition of acid secretion; taken at a 50% inhibitory level, $dmPGE_2$ was 4·4 times more active than PGE_2 and 16·8 times more active than $PGF_{2\alpha}$. Thus the rank order of potency of the prostaglandins as inhibitors of acid secretion is the same as for stimulation of Na^+ output (Fig. 2). A more detailed evaluation of the effect of acid secretion on the stimulation of gastric non-parietal

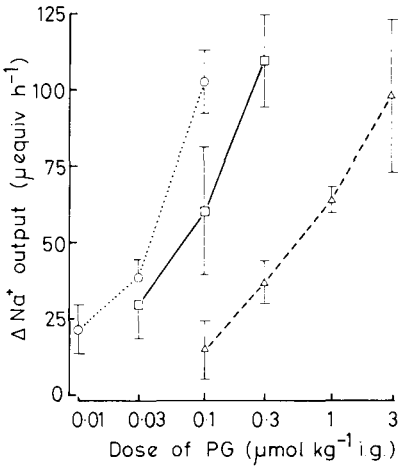

FIG. 2. A comparison of the activities of prostaglandins as stimulants of gastric Na^+ output in the anaesthetized rat. Key: □ prostaglandin E_2; ○ 16,16-dimethyl prostaglandin E_2; △ prostaglandin $F_{2\alpha}$. Na^+ output is expressed as the increase in secretion above the corresponding mean basal level. Vertical lines show s.e. mean. Each point is the mean of 4–6 observations.

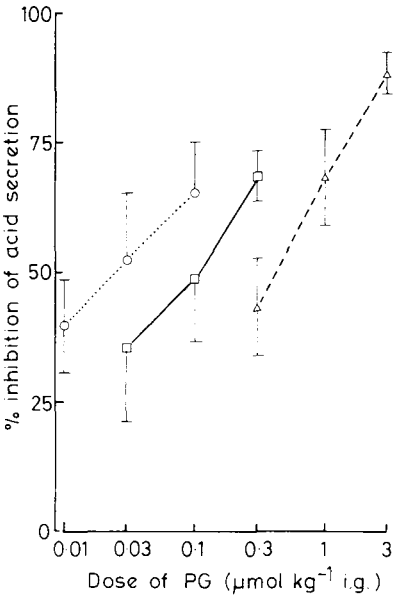

FIG. 4. A comparison of the activities of prostaglandins as inhibitors of gastric H^+ output in the anaesthetized rat. □ prostaglandin E_2; ○ 16,16-dimethyl prostaglandin E_2; △ prostaglandin $F_{2\alpha}$. Vertical lines show s.e. mean. Each point is the mean of 4–6 observations.

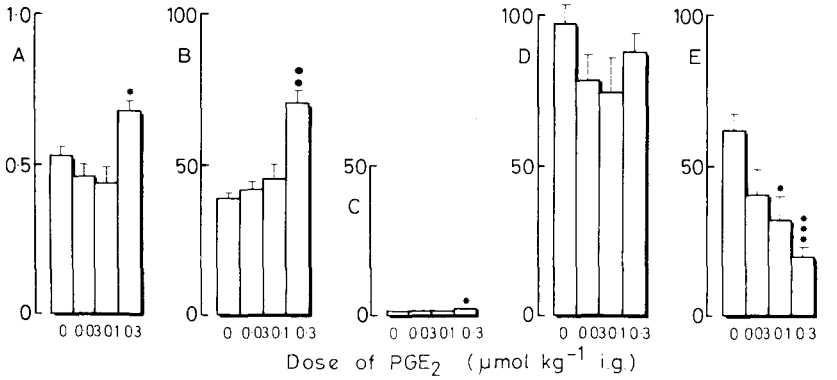

FIG. 3. The effect of intragastric prostaglandin E_2 on secretory volume and net ion outputs in the stomach of the anaesthetized rat during stimulation of gastric acid secretion by histamine infusion. Histamine was infused at a rate of 100 μg kg^{-1} min^{-1} i.v. Vertical lines show s.e. mean. Each point is the mean of 4–6 observations. $^*P < 0{\cdot}05$, $^{**}P < 0{\cdot}01$, $^{***}P < 0{\cdot}001$ compared with corresponding control. Key: A, volume (mL h^{-1}); B, Na^+; C, K^+; D, Cl^-; E, H^+ (μequiv h^{-1}).

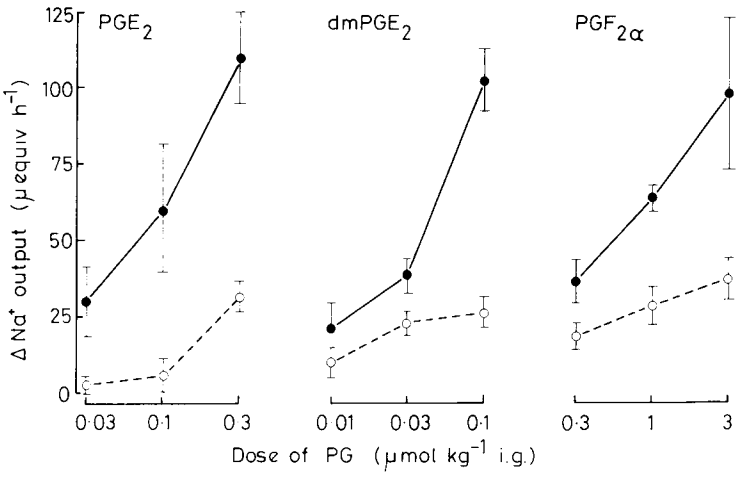

FIG. 5. A comparison of the effect of prostaglandins on gastric Na^+ output under control conditions (●) and during stimulation of gastric acid secretion by histamine infusion (○, 100 μg kg^{-1} min^{-1} i.v.). Na^+ output is expressed as the increase in secretion above the corresponding mean basal level. Vertical lines show s.e. mean. Each point is the mean of 4–6 observations.

secretion by prostaglandins is made in Fig. 5. These results show that, compared with controls, during histamine infusion each prostanoid was a relatively weak stimulant of gastric Na^+ output.

This effect of intraluminal acid on the output of non-parietal juice in response to prostaglandins was further investigated by instilling exogenous acid into the gastric lumen. In the experiments with PGE_2 described in Fig. 3, the mean acid concentration in the stomach ranged between 78·4 and 21·5 mM and therefore the effect of 50 mM HCl (in 175 mM mannitol/25 mM theophylline) was determined. Under control conditions (no prostaglandin) the output of Na^+ during acid instillation was 38·6 ± 4·9 μequiv h^{-1} and this was not significantly different from the Na^+ output obtained in the absence of acid (27·4 ± 6·1 μequiv h^{-1}, $P = 0{\cdot}18$).

The results obtained with PGE_2 are shown in Fig. 6 where a comparison is also made with the results presented in Fig. 5. In the presence of exogenous HCl, PGE_2 was a relatively weak stimulant of gastric non-parietal secretion, and a similar result was obtained with PGE_2 in the presence of endogenous HCl stimulated by histamine infusion.

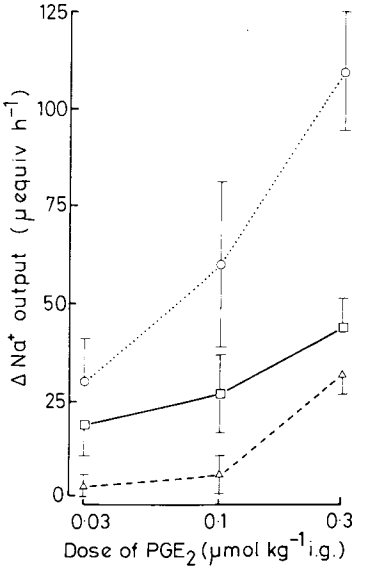

FIG. 6. The effect of intraluminal acid on gastric Na^+ output stimulated by prostaglandin E_2 in the anaesthetized rat. ○ control (no acid); □ exogenous 50 mM HCl; △ endogenous acid stimulated by histamine infusion (100 μg kg^{-1} min^{-1} i.v.). Na^+ output is expressed as the increase in secretion above the corresponding mean basal level. Vertical lines show s.e. mean. Each point is the mean of 4–6 observations.

DISCUSSION

The present results confirm previous observations that E prostaglandins stimulate gastric non-parietal secretion in the rat (Bolton et al 1978; Main & Melarange 1980; Van Kolfschoten et al 1983; Tao & Wilson 1984), and that $dmPGE_2$ is more potent that PGE_2 as a secretagogue (Bolton et al 1978; Tao & Wilson 1984). The effect of $PGF_{2\alpha}$ on gastric non-parietal secretion in the rat has not been reported previously; the compound was effective but much weaker than the E prostaglandins and similar

observations have been made in the cat (Gascoigne & Hirst 1981), dog (Konturek et al 1983) and frog (Garner & Heylings 1979).

In recent years, the HCO_3^- content of gastric non-parietal secretion has attracted intense interest because of the possibility that the 'mucus-bicarbonate barrier' is part of the gastric defence mechanism against damage induced, or at least aggravated by, intraluminal acid (Allen & Garner 1980). However, experiments in the dog (Bolton & Cohen 1978; Miller et al 1983) and cat (Smeaton & Hirst 1984) have shown that HCO_3^- is present at low concentration in non-parietal juice and that Na^+ and Cl^- are the main ions secreted in response to prostaglandin stimulation. In the present study, H^+ and HCO_3^- secretions were measured by acid/base titration and therefore it is not possible to quote absolute values for the outputs of these ions. Nevertheless it is clear that, as in the other species mentioned above, HCO_3^- is a relatively minor component of the non-parietal juice stimulated by prostaglandins in the rat. This result in the rat, however, contrasts with findings in the guinea-pig where equimolar amounts of Na^+ and HCO_3^- were secreted by the stomach in response to carbachol stimulation (Garner & Flemstrom 1978). The physiological role of this secretion of a NaCl-rich fluid is not entirely clear. Thomson (1981) has postulated that the presence of an unstirred water layer on the surface of the gastrointestinal mucosa may afford protection by impeding the access to the mucosa of noxious substances in the lumen. Indeed, Moody & Zalewsky (1981) have suggested that stimulation of gastric NaCl secretion by prostaglandins, which increases the thickness of the unstirred water layer, serves as an important protective mechanism to wash noxious substances from the mucosal surface. However, it must be pointed out that Robert et al (1985) found that cytoprotective doses of $dmPGE_2$ did not prevent the entry of ethanol into the gastric mucosa.

The inhibition of gastric acid secretion by E prostaglandins in the rat has been described previously: intragastric administration of PGE_2 at doses between 3–5 $\mu mol\ kg^{-1}$ and $dmPGE_2$ between 0·3–0·5 $\mu mol\ kg^{-1}$ inhibited acid output (Bolton et al 1978; Tao & Wilson 1984). These latter doses are slightly higher than those used in the present study (PGE_2, 0·03–0·3 $\mu mol\ kg^{-1}$ i.g.; $dmPGE_2$ 0·01–0·1 $\mu mol\ kg^{-1}$ i.g.). The effect of intragastric administration of $PGF_{2\alpha}$ on gastric acid secretion in the rat has not been reported previously but, as for E prostaglandins, the doses of $PGF_{2\alpha}$ that stimulated gastric non-parietal secretion also inhibited gastric acid secretion; thus the prostaglandins exhibited the same rank order of potency as stimulants of Na^+ output and as inhibitors of H^+ output. This inhibition of acid secretion cannot be attributed solely to the stimulation of HCO_3^- output by prostaglandins. For example, PGE_2 at 0·3 $\mu mol\ kg^{-1}$ stimulated a maximum possible HCO_3^- output of 25·6 $\mu equiv\ h^{-1}$ (19·8 + 5·8 $\mu equiv\ h^{-1}$; assuming no inhibition of basal acid output by PGE_2), whereas acid output was inhibited from 61·8 to 19·6 (i.e. by 42·2) $\mu equiv\ h^{-1}$. The comparison made in the latter point of discussion should, however, be considered with some caution since during stimulation of acid secretion by histamine, the output of Na^+, and therefore probably HCO_3^- also, stimulated by prostaglandins was low. Indeed, such an effect of intraluminal acid on gastric non-parietal secretion indicates that only a small proportion of the inhibitory effect of prostaglandins on acid secretion was attributable to HCO_3^- output.

The present data in the rat show that intraluminal acid, both endogenously secreted and exogenously applied, failed to affect *basal* gastric non-parietal secretion significantly as measured by Na^+ output. This result contrasts with the findings in frog isolated gastric mucosa (Heylings et al 1984) and the canine Heidenhain pouch (Garner & Hurst 1981) where application of HCl to the mucosal surface stimulated non-parietal secretion as measured by HCO_3^- output. However, it must be pointed out that in the present work the rats were pretreated with indomethacin and this would reduce any acid-induced non-parietal secretion if mediated by endogenous prostaglandins (Flemstrom & Garner 1982). Nevertheless, it appears unlikely that intraluminal acid is an effective stimulant of gastric non-parietal secretion in the rat since its presence caused a marked inhibition of the Na^+ output induced by exogenous prostaglandins. Thus the present results obtained in the rat are not consistent with the view that intraluminal acid controls gastric non-parietal secretion through a positive feedback mechanism.

In summary, doses of E and F prostaglandins that inhibit gastric acid secretion also stimulate the secretion of a NaCl-rich fluid from the stomach of the anaesthetized rat, and the presence of intraluminal acid in the stomach diminishes the capacity of prostaglandins to stimulate this non-parietal secretion.

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REFERENCES

Allen, A., Garner, A. (1980) Gut 21: 249–262

Bolton, J. P., Cohen, M. M. (1978) Digestion 17: 291–299

Bolton, J. P., Palmer, D., Cohen, M. M. (1978) Am. J. Dig. Dis. 23: 359–364

Bunce, K. T., Clayton, N. M. (1987) Br. J. Pharmacol. 91: 23–29

Flemstrom, G., Garner, A. (1980) Acta Physiol. Scand. 110: 419–426

Flemstrom, G., Garner, A. (1982) Am. J. Physiol. 242: G183–G193

Flemstrom, G., Garner, A., Nylander, O., Hurst, B. C., Heylings, J. R. (1982) Ibid. 243: G348–G358

Garner, A., Flemstrom, G. (1978) Ibid. 234: E535–E541

Garner, A., Heylings, J. R. (1979) Gastroenterology 76: 497–503

Garner, A., Hurst, B. C. (1981) in: Harmon, J. W. (ed.) Basic mechanisms of gastrointestinal mucosal cell injury and protection. Williams & Wilkins, Baltimore, pp 273–289

Gascoigne, A. D., Hirst, B. H. (1981) J. Physiol. 316: 427–438

Hedges, A. R., Parsons, M. E. (1977) Ibid. 267: 181–194

Heylings, J. R., Garner, A., Flemstrom, G. (1984) Am. J. Physiol. 246: G235–G242

Hirst, B. H., Labib, L. A., Reed, J. D., Stephen, J. G. (1980) J. Physiol. 306: 51–63

Konturek, S. J., Tasler, J., Bilski, J., Kania, J. (1983) Am. J. Physiol. 245: G539–G546

Main, I. H. M., Melarange, R. (1980) in: Samulesson, B., Ramwell, P. W., Paoletti, R. (eds) Advances in prostaglandin and thromboxane research. Vol. 8, Raven Press, New York, pp 1519–1520

Makhlouf, G. M. (1981) in: Johnson, L. R. (ed.) Physiology of the gastrointestinal tract. Ch. 18, Raven Press, New York, pp 551–566

Miller, T. A., Henagan, J. M., Watkins, L. A., Loy, T. M. (1983) J. Surg. Res. 35: 105–112

Moody, F. G., Zalewsky, C. A. (1981) in: Harmon, J. W. (ed.) Basic mechanisms of gastrointestinal mucosal cell injury and protection. Williams & Wilkins, Baltimore, pp 373–389

Robert, A., Lancaster, C., Davis, J. P., Field, S. O., Sinha, A. J., Thornburgh, B. A. (1985) Gastroenterology 88: 328–333

Smeaton, L. A., Hirst, B. H. (1984) in: Allen, A., Flemstrom, G., Garner, A., Silen, W. (eds) Mechanisms of mucosal protection in the upper gastrointestinal tract. Raven Press, New York, pp 107–112

Tao, P., Wilson, D. E. (1984) Prostaglandins 28: 353–365

Thomson, A. B. R. (1981) in: Harmon, J. W. (ed.) Basic mechanisms of gastrointestinal mucosal cell injury and protection. Williams & Wilkins, Baltimore, pp 327–350

Van Kolfschoten, A. A., Hagelen, F., Hillen, F. C., Jager, L. P., Zandberg, O., Van Noordwijk, J. (1983) Dig. Dis. Sci. 28: 1127–1132

Whittle, B. J. R., Kauffman, G. L., Boughton-Smith, N. K. (1984) Eur. J. Pharmacol. 100: 277–283