A dose of PG $F_2\alpha$ (500 ng – 2 μg), which was necessary to produce a 9% increase in resistance in normal animals (248 ± 10 to 271 ± 11 cms H_2O l^{-1} s), produced a 38% increase following β-adrenoceptor blockade (411 ± 10 to 567 ± 36 cm H_2O l^{-1} s) (10 tests in 4 animals; $P < 0.001$). However, following vagal section and in the presence of β-adrenoceptor blockade, there was only an 18% increase in respiratory resistance following an identical dosage of PG $F_2\alpha$ (346 ± 31 to 410 ± 35 cm H_2O l^{-1} s; $P < 0.001$).

Histamine induced broncho-constriction (2–10 μg), in marked contrast to PG $F_2\alpha$, produced less increase in respiratory resistance following bilateral cervical vagotomy. The potentiated increase in resistance produced by histamine in animals treated with propranolol persisted after the vagi were cut.

In conclusion, we suggest that prostaglandin $F_2\alpha$ initiates a vago-sympathetic reflex which modifies airway tone. This is shown by (1) its greater bronchoconstrictor action in vagotomised animals and (2) a potentiation of broncho-constriction with β-adrenoceptor blockade only when the vagi were intact.

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Differential inhibition by PGE_1, PGE_2 and endoperoxide analogue U46619 of secretion from the rat isolated gastric mucosa stimulated by histamine, pentagastrin and methacholine

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Prostaglandins of the E-series inhibit secretory responses to various stimuli including histamine, pentagastrin and vagal stimulation *in vivo* (Nezamis, Robert & Stowe, 1971). We have investigated the direct effects of these agents and the endoperoxide analogue U46619 (Bundy, 1975) on the rat isolated gastric mucosa stimulated by various secretogogues.

Paired mucosae were obtained from each rat (Main & Pearce, 1978a). Drugs were added to the serosal bathing solution and four responses were obtained in each preparation (30 min contact) separated by 60 min washout periods. Randomly allocated to control and test groups, one preparation was used to monitor time-dependent changes in responses and the other treated with inhibitor for 30 min preceding the second response.

In the presence of PGE_2 (2×10^{-6} M) the response to histamine (H, 5×10^{-5} M, $n = 7$) was reduced to 20 ± 6% (mean ± s.e. mean) of that in the parallel controls. The third and fourth responses recovered to 38 ± 7% and 92 ± 13% respectively. In contrast, PGE_2 did not inhibit the response to pentagastrin (P, 1.8×10^{-8} M, $n = 5$) during contact, but decreased the third response to 52 ± 10%. Prolonged contact with PGE_2 (2×10^{-6} M, 240 min, $n = 4$) caused progressive inhibition of P, decreasing to 53 ± 15% and 24 ± 7% at the third and fourth responses. A higher concentration (2×10^{-5} M, $n = 4$) caused a fall to 18 ± 6% at the third response. PGE_2 (2×10^{-6} M) had no immediate effect on methacholine (M, 5×10^{-7} M, $n = 6$), although the third response was reduced to 41 ± 14%. When added 15 min after H or M, PGE_2 (2×10^{-6} M, $n = 6$ for all groups) decreased the response to H at 30 min but had no effect on M over the same period. Responses to dibutyryl cyclic-AMP were unaffected.

Similar effects were observed with PGE_1 (2×10^{-6} M, $n = 4$) and U46619 (2×10^{-5} M, $n = 3$). Second responses to H were reduced to 19 ± 11% and 11 ± 6%, while no inhibition of P was observed until the third response (62 ± 19% and 37 ± 15%, respectively).

These results show that PGE_2, E_1 and U46619 are qualitatively similar in their inhibitory effect on acid secretion and confirm that the latter substance is less potent (Frame & Main, 1977). In a concentration which caused immediate inhibition of histamine, PGE_2 had only a delayed effect on pentagastrin. This differential effect has not been reported for the rat (Main & Whittle, 1973) or other species *in vivo*. In this *in vitro* preparation, metiamide (10^{-5} M), which abolishes responses to histamine, only partially inhibits pentagastrin (Main & Pearce, 1978b), although *in vivo* it has similar activity against both secretogogues.

Our results suggest that the inhibitory effect of PGE_2 on different secretogogues *in vivo* may be due largely to an action on histamine sensitization of parietal cells to other stimuli. However, the delayed inhibition of pentagastrin and methacholine suggests that PGE_2 has an additional mechanism of action.

J.B.P. is an M.R.C. student. We thank S.K. & F. Ltd., for metiamide and Upjohn for prostaglandins.

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Calcium dependence of basal and secretagogue-induced acid secretion in the isolated rat stomach

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Extracellular calcium appears to be an important factor in the control of both basal and secretagogue-induced acid secretion in amphibian (Jacobson, Schwartz & Rehm, 1965; Kasbekar, 1974) and mammalian (Black & Welch, 1977; Main & Pearce, 1977) gastric mucosa preparations. In the present study the role of extracellular calcium in the control of acid secretion has been studied using the rat isolated stomach (Bunce & Parsons, 1976).

Control experiments were carried out using solutions (both serosal and mucosal) which contained calcium (2.5 mM). Acid secretion was stimulated repeatedly by the addition of a secretagogue to the serosal solution. Five repeated doses of histamine (30 μM), gastrin (0.1 μM) and acetylcholine (1 mM), or four repeated doses of dibutyryl cyclic adenosine 3′,5′-monophosphate (dbcAMP, 0.1 mM) were used. The acid response to an agonist was calculated as peak response above basal. Calcium was removed from both the serosal and mucosal solutions, and the acid output under these conditions was compared with corresponding data from separate control experiments.

In Ca^{2+}-free conditions there were no significant changes in basal acid secretion or in the acid secretory responses to gastrin or dbcAMP. Removal of calcium caused an increase in histamine-stimulated acid output from a maximum value under control conditions of 62.5 ± 12.4 ($n = 6$) nmol H^+/min to a maximum of 151.3 ± 28.4 ($n = 6$, $P = 0.008$) nmol H^+/minute. Removal of calcium caused a decrease in acetylcholine-stimulated acid output from a maximum value under control conditions of 73.1 ± 8.5 ($n = 6$) nmol H^+/min to a minimum value of 4.5 ± 2.0 ($n = 8$, $P = 0.002$) nmol H^+/minutes. This reduction in the acid response to acetylcholine was readily reversed on adding calcium to the extracellular bathing solutions. Increasing the concentration of magnesium in the external media from 1.2 to 20.0 mM did not affect acetylcholine-stimulated secretion.

The removal of calcium caused an increase in histamine-stimulated acid secretion without affecting the acid response to dbcAMP, and since there is evidence that histamine causes an increase in cAMP levels in the gastric mucosa, this result might suggest that a mechanism involved with the metabolism of cAMP is sensitive to calcium. On possible explanation of the increased acid response to histamine under Ca^{2+}-free conditions is that gastric mucosal adenylate cyclase is inhibited by relatively high concentrations of calcium (2.5 mM). The inhibition of adenylate cyclase by calcium has been reported previously in brain (Bradham, Holt & Sims, 1970). The results provide no evidence that histamine, gastrin or acetylcholine share a common pathway in stimulating acid secretion. In addition, the present experiments indicate that the acid response to acetylcholine might be accompanied by an influx of calcium into the parietal cell.