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.

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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.

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β-Adrenoceptor agonist stimulation of acid secretion in rat isolated stomach

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β-Adrenoceptor agonists inhibit pentagastrin-induced acid secretion from gastric pouches in conscious dog (Curwain, Holton and Spencer, 1972; Daly & Stables, 1977) and rat (Lundell and Svensson, 1974). Salmefamol, a β_2-adrenoceptor agonist inhibits bethanechol-induced acid secretion (Canfield, Curwain, King & Price, 1978) whilst in high doses the related drug, salbutamol will inhibit histamine-stimulated secretion in the dog (Daly, Long & Stables, 1978). We have recently shown that salmefamol does not inhibit acid secretion stimulated by pentagastrin, histamine or bethanechol in the rat isolated stomach (Canfield *et al.*, 1978), but appears to act as a stimulant of secretion. The present results extend this finding to include salbutamol and isoprenaline and the action of various antagonists on this stimulation by β-adrenoceptor agonists of acid secretion in the isolated stomach.

The rat stomach preparations were set up as described for the guinea pig by Holton & Spencer, 1976. All drugs were applied to the serosal bathing fluid. When required the tissues were pre-incubated with an inhibitor for one hour before addition of the β-adrenoceptor agonist for a further 60–90 minutes. Each tissue was exposed to only one concentration of salmefamol, salbutamol or isoprenaline, and the acid output was measured over fifteen-min periods. The change in rate of secretion is expressed as the ratio of the rate at the plateau of response to the average rate in the two control periods in the same tissue immediately before exposure to the agonist. The average control secretion in one series was 3.39 ± 0.190 μmol H^+ $cm^{-2}h^{-1}$ (s.e. mean, $n = 36$).

Both salmefamol (0.2–20 μM) and isoprenaline (0.06–6 μM) caused a concentration-dependent increase in the rate of acid secretion. The mean maximum observed value for the secretory ratio with salmefamol was 1.90 ± 0.09 ($n = 21$) and with isoprenaline 2.33 ± 0.28 ($n = 12$). Although the full concentration response curve remains to be investigated, salbutamol (0.1–20 μM) also caused an increase in acid secretion.

The responses to isoprenaline (1.25 μM) or salmefamol (5 μM) were not reduced by atropine (10 μM), metiamide (100 μM) or practolol (20 μM). However, propranolol (20 μM) did cause a significant decrease in the secretory ratio for both salmefamol and isoprenaline (t-test $P < 0.01$ in each case; $n = 12$ and 10 respectively) and caused a shift in the salmefamol concentration—response curve to the right with no change in slope of the linear region.

These results confirm that β-adrenoceptor agonists stimulate acid secretion by the rat isolated stomach. This action appears not to involve either histamine or cholinergic receptors and may be mediated by β_2 receptors. The reasons for the difference in response between the isolated preparation and the intact animal remain to be investigated.

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