theophylline remained unaltered. Theophylline elevates endogenous cyclic AMP in pancreatic β-cells, thus producing liberation of calcium from intracellular bound pools, with resultant insulin release (Brisson, Malaisse-Lagae & Malaisse, 1972). It seems unlikely, therefore, that cyproheptadine interferes with either cyclic AMP generation or with intracellular calcium metabolism. Although increasing the extracellular calcium concentration by an additional 6.0 mEq/l did not itself stimulate insulin release, it partially reversed the inhibition of glucose mediated release caused by cyproheptadine. Taken together, these results suggest that cyproheptadine inhibits the uptake of calcium by the β-cell without affecting its intracellular metabolism.

I am grateful to Dr M.E. Kitler for the statistical analysis of the data.

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## Effects of dibutyryl cyclic AMP and phosphodiesterase inhibitors on acid secretion by mouse stomach *in vitro*

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Kimberg (1974) has reviewed the evidence about the involvement of cyclic AMP in histamine- or pentagastrin-stimulated gastric acid secretion *in vivo* in the rat. In the present investigation quantitative studies on the effects of dibutyryl cyclic AMP on gastric acid secretion have been carried out *in vitro* in the presence and absence of metiamide, a specific histamine $H_2$-receptor antagonist. The effects of a potent phosphodiesterase inhibitor, a triazolopyrimidine 2-amino-6-methyl-5-oxo-4-*n*-propyl-4,5-dihydro-*s*-triazolo(1,5-a) pyrimidine (ICI 63197) on the acid secretory responses to histamine and pentagastrin have also been examined.

As the stomach wall of immature mouse is very thin, an isolated whole mouse stomach was considered suitable for *in vitro* studies. Mice (Charles River) of either sex, 2-6 weeks old, were anaesthetized with ether. The stomach was washed with warm saline by way of incisions made at the pyloric and cardiac regions. A glass bead was introduced into the lumen to reduce dead space. The oesophagus was ligated and polythene cannulae were tied into the pyloric sphincter and the cardiac region. The isolated stomach was placed in an organ bath at 37°C containing a buffered solution (Davenport, 1951) gassed vigorously with 95% $O_2$ + 5% $CO_2$. The stomach lumen was perfused at 1 ml/min with unbuffered solution gassed with 100% $O_2$. The lumen perfusate was passed over a flow-type glass micro-electrode and pH changes were continuously recorded. The results were expressed as peak acid secretion $[H^+]$ μM.

Basal secretion usually reached a steady level after incubation for forty minutes. Dibutyryl cyclic AMP(db cyclic AMP) regularly stimulated acid secretion in a dose-dependent manner. Since tachyphylaxis to repeated exposure to db cyclic AMP was sometimes observed, only results for acid secretory response to the first dose of db cyclic AMP have been used for statistical analysis. The results show that in the presence of db cyclic AMP $10^{-4}$, $2.5 \times 10^{-4}$, $5 \times 10^{-4}$, and $10^{-4}$ M, hydrogen ion concentrations rose from a mean ± s.e. mean basal level of 35.3 ± 4.2 ($n = 19$) μM to 73.9 ± 10.9(3), 87.8 ± 9.5(7), 114.8 ± 10.4(3) and 299 ± 29.1(6) respectively.

Paired 't' tests on results from four experiments showed that within preparations, there was no

significant difference between the acid secretory responses to db cyclic AMP ($2.5 \times 10^{-4}$ M) in the absence and presence of metiamide (up to $5 \times 10^{-4}$ M). Student's 't' test on results from different preparations also indicated that metiamide did not inhibit acid secretion induced by db cyclic AMP ($n = 5$ for db cyclic AMP, $2.5 \times 10^{-4}$ M, and for metiamide up to $5 \times 10^{-4}$ M + db cyclic AMP $2.5 \times 10^{-4}$ M). In contrast to db cyclic AMP, histamine or pentagastrin did not regularly stimulate acid secretion. However, marked stimulation of acid secretion by histamine or pentagastrin could be obtained in the presence of phosphodiesterase inhibitors. The order of effectiveness was triazolopyrimidine > theophylline > caffeine. In preparations treated with histamine 20 min after triazolopyrimidine ($10^{-4}$ M) was added, sustained and dose-related responses to histamine ($10^{-5}$ to $10^{-3}$ M) could be obtained. In the presence of triazolopyrimidine ($10^{-4}$ M), $[H^+]$ secretion to a submaximal dose of pentagastrin ($2 \times 10^{-6}$ M) was about 80 $\mu$M as compared to that of about 100 $\mu$M in response to a submaximal dose of histamine ($2.5 \times 10^{-4}$ M). Triazolopyrimidine on its own caused slight stimulation of acid secretion by the isolated mouse stomach.

The present results are in agreement with the findings of Fromm, Schwartz & Quijano (1975), who showed that marked stimulation of acid secretion in the isolated rabbit gastric mucosa by db cyclic AMP was not inhibited by metiamide. The exact mode of action of phosphodiesterase inhibitors on the acid secretory responses to histamine and pentagastrin is not clear. In view of the evidence that triazolopyrimidine greatly potentiated the increase in cyclic AMP levels induced by biogenic amines in mouse cerebral slices (Nahorski & Rogers, 1975), the present results support the hypothesis that cyclic AMP may be involved in histamine or pentagastrin-induced acid secretion by the mouse stomach *in vitro*.

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## The effects of intravenous secretin on the small intestinal vasculature of the cat

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Secretin, administered intravenously or intra-arterially, increases superior mesenteric arterial blood flow in the anaesthetized cat (Ross, 1970; Fasth, Filipsson, Hulten & Martinson, 1972). Since other gastrointestinal hormones such as glucagon and pentagastrin, when infused intravenously in low doses, alter capillary filtration coefficient in the cat small intestine (Richardson, 1975), the effects of intravenous secretin on the resistance, capacitance, and vascular exchange function of this tissue have been examined.

Eight cats (2.66-3.87 kg) were anaesthetized with α-chloralose (70 mg/kg i.v.) after halothane induction, and loops of sympathetically-innervated jejunum (62.6 ±18.4 g, mean ± s.d.) prepared for the measurement of blood flow, changes in tissue volume, and capillary filtration coefficient (CFC), by a modification (Richardson, 1974) of the plethysmographic technique of Folkow, Lundgren & Wallentin (1963).

Under control conditions, the systemic arterial mean pressure (BP) was 151.4 ± 4.2 (mean ± s.e. mean) mmHg, the heart rate (HR) 174.6 ± 10.0 beats/min, and the superior mesenteric venous outflow (SMVF) 55.7 ± 7.8 ml $min^{-1}$ 100 $g^{-1}$, giving a calculated jejunal vascular resistance (JVR) of 3.15 ± 0.57 mmHg $ml^{-1}$ min 100 g. The CFC, measured as the continuous volume increase resulting from raising the superior mesenteric venous pressure by 10 cm $H_2O$ for 1 min was 0.060 ± 0.009 ml $min^{-1}$ $mmHg^{-1}$ 100 $g^{-1}$ ($n = 5$).

Natural secretin (Boots) was infused intravenously in a dose of 0.1 U $kg^{-1}$ $min^{-1}$ (Crick-Harper-Raper Units; 1 U = 62.5 ng) to five preparations, resulting in a significant (paired 't'-test; $P < 0.05$) increase in CFC of 38.8 ± 9.2% from 0.060 ± 0.009 to 0.083 ± 0.012 ml $min^{-1}$ $mmHg^{-1}$ 100 $g^{-1}$. The jejunal volume (JV) rose by 0.27 ± 0.06 ml/100 g at the start of the infusion