Carotid arterial blood level measurements suggest that phenolphthalein may be systemically bioavailable from the EHC. Thus, in intact but not in bile-duct-cannulated rats there is a secondary plasma peak of radioactivity 5-6 h after the intravenous administration of [^{3}H]-phenolphthalein. This peak coincides with the absorption of the aglycone from the intestine following the bacterial hydrolysis of phenolphthalein glucuronide (see Figure 1a).

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The effects of cyproheptadine pretreatment on insulin release from isolated pancreatic islets

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Cyproheptadine, an antiserotonin-antihistaminic agent with a chemical structure similar to the tricyclic antidepressants (Stone, Wenger, Ludden, Stavorski & Ross, 1961) inhibits glucose-mediated insulin release by an immediate and direct effect on the rat pancreatic islet of Langerhans (Richardson, McDaniel & Lacy, 1975).

The present studies describe the effects of different secretogogues on insulin release from cyproheptadine-pretreated rat islets. Approximately 200 islets were isolated from two 200-300 g ten week old male albino rats (OFA Sandoz SPF strain) by the collagenase technique (Lacy & Kostianovsky, 1967). An equal number of islets were placed in each of two perfusion chambers and perifused at 37° C and pH 7.40 with Krebs Ringer bicarbonate containing 5.6 mM D-glucose at a rate of 1 ml/min as described previously (Lacy, Walker & Fink, 1972). After 45 min, the test islets were exposed to 100 μM cyproheptadine hydrochloride monohydrate for five minutes. Subsequently both chambers were stimulated with an insulin secretogogue for a further 60 min as indicated in the Table. The perfusate was collected at 1- or 5-min intervals throughout the study. The insulin content was determined by radioimmunoassay (Wright, Makulu, Vichick & Sussman, 1971) and expressed as (μU/islet)/minute. All data was subjected to complete statistical analysis.

Cyproheptadine pretreatment completely abolished tolbutamide- or glucose-evoked insulin release. Conversely the responsiveness of islets to

Table 1 The effects of cyproheptadine pretreatment on insulin release from perifused islets

Mean rate of secretion with 5.6 mM D-glucose (μU/islet)/min ± s.e.		*Insulin secretogogue added*	*n*	*Mean rate of secretion after addition of secretogogue $\mu\mu$/islet per min ± s.e. mean*		**P*	*% Inhibition*
Control	*Test*			*Control*	*Test*		
0.59 ± 0.04	0.54 ± 0.09	1.1 mM tolbutamide	3	1.37 ± 0.08	0.48 ± 0.09	< 0.001	100.0
0.47 ± 0.21	0.78 ± 0.29	11.1 mM D-glucose	3	2.67 ± 0.65	0.72 ± 0.22	< 0.01	100.0
0.73 ± 0.15	0.67 ± 0.08	11.1 mM D-glucose + 6.0 mEq/1. Ca^{++}	3	3.17 ± 0.37	0.96 ± 0.15	< 0.001	88.5
0.53 ± 0.35	0.49 ± 0.24	5.0 mM theophylline	4	1.19 ± 0.44	1.17 ± 0.33	NS	0.0

* Control versus test values after addition of secretogogue
NS = not significant

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.

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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}, 2.5×10^{-4}, 5×10^{-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