Salmefamol: inhibitor or stimulant of gastric acid secretion?

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β_2-Adrenoceptor agonists have been shown to inhibit pentagastrin-induced gastric acid secretion in both dog (Curwain, Holton & Spencer, 1972; Daly & Stables, 1977) and rat (Lundell & Svensson, 1974). We have investigated the action of a drug of this type, salmefamol, on gastric acid secretion and mucosal blood flow (MBF) in 4 conscious dogs with well-established Heidenhain pouches and also in a rat isolated stomach preparation. The results showed the expected inhibition of secretion in the dog but there was a stimulation of acid output by salmefamol in the *in vitro* preparation.

Submaximal doses of either pentagastrin (2μg kg^{-1} h^{-1}) or bethanechol chloride (1μg kg^{-1} min^{-1}) were infused i.v. in saline (1 ml/min) in the dogs until a plateau of acid secretion was obtained. MBF was estimated by radioactive aniline clearance (Curwain & Holton, 1973). Salmefamol (0.2 or 0.8 μg kg^{-1} min^{-1} i.v. for 30 min) was tested against each secretagogue in each of the 4 dogs. The control rates of acid secretion and MBF were taken as the mean values for the 4 successive 15 min periods immediately before giving salmefamol. The means of the 2 successive 15 min samples giving the lowest rate of acid secretion were used as test values. Secretory rate was profoundly decreased (between 33 and 98%, mean 76%) in each of the 8 experiments. Changes in MBF were variable but in each experiment the ratio of blood flow to secretion increased.

The isolated stomachs from rats (35–50 g) were set up as described for the guinea pig by Holton & Spencer (1976) and were stimulated with either bethanechol chloride (1.7×10^{-5}M) or pentagastrin (2×10^{-5}M). The acid output was measured over four 15 min periods. The drug was then washed out and the tissues incubated for 1 h with salmefamol (10^{-5}M) before a second dose of the same stimulant was added in the presence of salmefamol. The results are expressed as the percentage increase above the spontaneous secretory rate in the absence of drugs.

The mean increase in acid output due to the pentagastrin alone was 185 ± 4.7% and 299 ± 15.6% in the presence of pentagastrin and salmefamol (s.e., $n = 3$). The values for bethanechol were 276 ± 88% and 356 ± 72% ($n = 3$) respectively. The results do not show any evidence of inhibition of the secretory response. Paired t tests indicated that the increase in the response in the presence of salmefamol was significant both for bethanechol ($P<0.05$) and pentagastrin ($P<0.02$). Salmefamol alone (10^{-5}M) increased the rate of acid secretion by 231 ± 19% ($n = 6$).

The concentration dependence of this salmefamol-stimulated acid secretion and the action upon it of various established inhibitors of acid output is being investigated.

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Comparative assay of histamine H_2-receptor antagonists using the isolated mouse stomach

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There is still insufficient evidence about the nature of the interaction between H_2-receptor antagonists and histamine on gastric acid secretion to argue that the inhibition of physiologically-induced acid secretion is due to blockade of histamine receptors. Bunce & Parsons (1976), using isolated rat stomachs, found a pA_2 value for metiamide equivalent to that measured in atrial and uterine tissues but the slope of the Schild plot of 0.73 was significantly different from unity. Apparently the necessary conditions for simple competitive inhibition were not met. To assess the significance of this finding we have assayed the activity of burimamide, metiamide and cimetidine on the isolated, lumen-perfused whole mouse stomach preparation (Angus & Black, 1978).

Each preparation was equilibrated with a single

Table 1 pA_2 and n values (equivalent to the slope in the Schild plot) with 95% confidence limits for gastric acid secretion in the isolated mouse stomach. For comparison, previously reported pA_2 values for atria and uterus are also given (Black et al., 1972(a); 1973(b); Brimblecombe et al., 1975(c); Parsons et al., 1977(d).

		Gastric Secretion		*Atria*	*Uterus*
Antagonist	*Agonist*	pA_2(±95%CL)	n(±95%CL)	pA_2	pA_2
Burimamide	Histamine	4.59 (0.23)	0.98 (0.24)	5.11[a]	5.17[a]
Metiamide	Histamine	5.08 (0.32)	0.96 (0.22)	6.04[b]	6.12[b]
Metiamide	Dimaprit	5.23 (0.25)	1.17 (0.23)	6.19[d]	6.07[d]
Cimetidine	Histamine	5.14 (0.31)	0.99 (0.21)	6.10[c]	6.09[c]

agonist concentration with or without previous incubation with antagonist (up to 3×10^{-3}M). A single assay consisted of 90 stomachs, 15 preparations on each of 6 experimental days. Three-point dose-response curves were constructed for the control and for each of four dose-levels of antagonist. The stomachs on any one day were randomly allocated to the 15 treatments so that a complete block was done each day. The antagonist was added to the bath 20 min after setting up the preparation and a further 40 min later the agonist was added. Responses were taken as $\log_e$ (peak $[H^+]$ nmol/min) to balance the effect of experimental error at the different response levels. The data were analyzed by fitting linear equations to all 90 observations generally following the iterative technique of Waud (1975) with the use of a PDP-11 computer and GLIM statistical package.

Table 1 shows the pA_2 values and n values (equivalent to the slope in the Schild plot) together with 95% confidence limits. For each study, the n value was not significantly different from unity suggesting that simple competitive inhibition was present. The pA_2 values were significantly lower than the values reported previously for atria and uterus. (Black, Duncan, Durant, Ganellin & Parsons, 1972; Black, Duncan, Emmett, Ganellin, Hesselbo, Parsons & Wyllie, 1973; Brimblecombe, Duncan, Durant, Emmett, Ganellin & Parsons, 1975). Approximately a 10-fold difference in potency was observed for metiamide and cimetidine and four-fold for burimamide. The pA_2 value for metiamide against dimaprit, the selective H_2-receptor agonist, (Parsons, Owen, Ganellin & Durant, 1977) was not significantly different from that found using histamine. Bunce & Parsons (1976) suggested that the low slope in their Schild plot for metiamide might be due to a loss of antagonist from the bath diffusing through the tissue into the lumen and out with the perfusate. We have detected a small amount of $[C^{14}]$-metiamide in the lumen perfusate (collected over 40 min) but this amounted to less than 0.1% of the bath $[C^{14}]$-metiamide content which is probably not sufficient to distort the assay.

Our findings show that the pA_2 values for the three H_2-antagonists were significantly lower than the estimates from atria and uterus. Perhaps there is an uptake mechanism for histamine which all the antagonists also block or there is a different sub-set of receptors. However, Sjostrand, Ryberg & Olbe (1977) have reported pA_2 values for metiamide and cimetidine of 4.82 and 5.82 respectively using isolated sheets of guinea pig mucosa and so it would seem prudent to reserve judgement about the significance of our results until the measurements have been repeated using different techniques.

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