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COMPARISON OF THE AGONIST ACTIVITY OF IMPROMIDINE (SK&F 92676) IN ANAESTHETIZED RABBITS AND ON THE RABBIT ISOLATED FUNDIC MUCOSA

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1 The actions of impromidine *in vivo* and *in vitro* have been compared on gastric acid secretion. In both preparations impromidine was more potent than histamine.

2 There were no statistically significant differences between the maximum responses to impromidine and histamine *in vivo* or *in vitro* although *in vitro* the maximum response to impromidine was only 67% of that to histamine. *In vivo* the maximum response to impromidine was significantly less than the maximum response to histamine plus mepyramine.

3 The results are discussed in the light of recent findings.

Introduction

Impromidine (SK&F 92676) has been reported to be a potent and specific agonist for histamine H_2-receptors (Durant, Duncan, Ganellin, Parsons, Blakemore & Rasmussen, 1978). *In vitro* it acts as a partial agonist on the rat uterus (Durant *et al.*, 1978) and stomach (Parsons & Sykes, 1980), eliciting only 80% and 50% of the maximum responses to histamine respectively. *In vivo* studies have shown it to be between 16 and 27 times more potent than histamine in stimulating gastric acid secretion and to have a maximum response equal to, or, in the case of the Heidenhain pouch dog, greater than that to histamine (Durant *et al.*, 1978). We have investigated this apparent difference in the agonist activity *in vivo* and *in vitro* of impromidine on gastric acid secretion in anaesthetized rabbits and in rabbit isolated mucosa preparations.

Methods

Experiments were performed on male New Zealand White rabbits; the methodology for the *in vivo* and *in vitro* studies has been fully described by Curwain & Turner (1981b) and Curwain & Turner (1981a) respectively.

Results

Anaesthetized rabbits (see Figure 1a)

Intravenous infusion of histamine ($3-50 \times 10^{-9}$ mol kg^{-1} min^{-1}) caused a dose-related increase in acid secretion, the mean maximum secretory rate was $99.36 \pm 18.38 \times 10^{-6}$ mol H^+/min (s.e.mean). In the presence of mepyramine (2.49×10^{-6} mol kg^{-1} min^{-1}) the maximum acid secretory response to histamine was significantly potentiated ($P < 0.01$) to $153 \pm 9 \times 10^{-6}$ mol H^+/min; at the other doses of histamine studied, mepyramine had no significant effect ($P > 0.1$ in both cases).

Impromidine ($0.6-200 \times 10^{-12}$ mol kg^{-1} min^{-1}) caused a dose-related increase in acid secretion. The maximum secretory rate obtained was $102 \pm 8 \times 10^{-6}$ mol H^+/min (s.e.mean) which is not significantly different from the maximum response to histamine alone but which is significantly less than the maximum response obtained to histamine in the presence of mepyramine ($P < 0.01$). Due to the adverse effects of high doses of impromidine a maximum response was not obtained. However, from the observed means a maximum response was calculated to be $114 \pm 7.05 \times 10^{-6}$ mol H^+/min (100–128, 95% confidence limits). The calculation was carried out using the logistic function which is a more general form of the hyperbola

$$V = \frac{V_m \times A^p}{A^p + ED^p_{50}}$$

but which makes no assumption of slope ($p = 1$ hyperbola), and the least squares. Analysis of data using this function is described by Waud (1976) and its applicability to gastric secretory studies is described by Knight, McIsaac, Rennie, Flannery & Fielding (1980). A curve is fitted to the data using iterative techniques to calculate the parameters,

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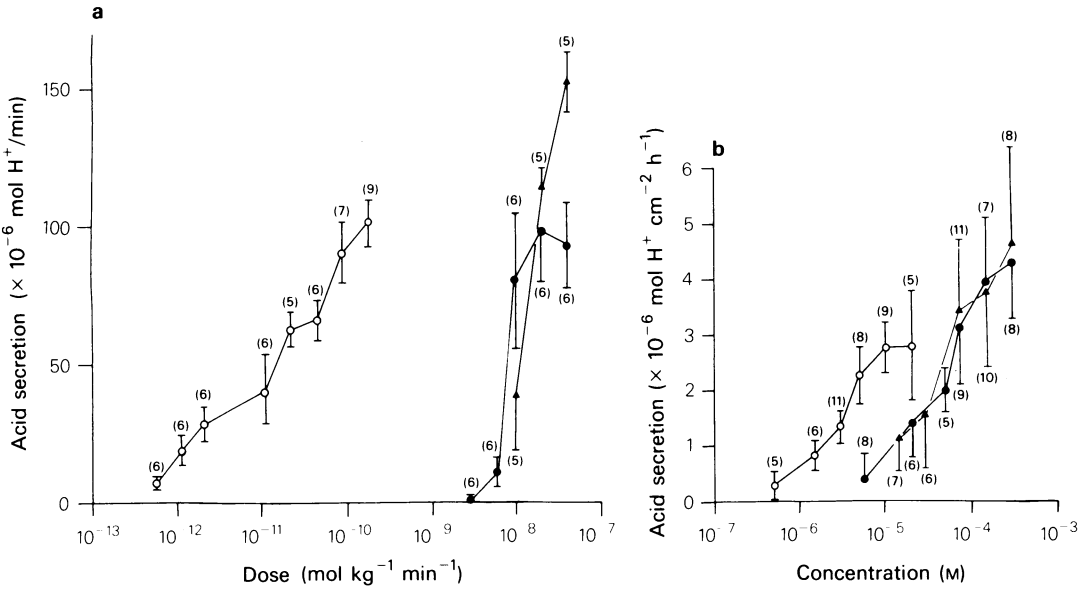

Figure 1 Dose-response curves to histamine (●), histamine plus mepyramine (▲) and impromidine (○) in the anaesthetized rabbit (a) and on the rabbit isolated fundic mucosa (b). Vertical bars represent s.e.mean. Figures in parentheses indicate number of experiments per point.

there usually being 4 cycles before a change of less than 1% is reached. Standard errors are then derived from the sum of squares of the deviation of the points from the calculated line (ESS) and the degrees of freedom. The 95% confidence limits of the calculated maximum response to histamine in the presence of mepyramine ($157 \pm 10.1 \times 10^{-6}$ mol H^+/min) are 137–177. Mepyramine (2.49×10^{-6} mol kg^{-1} min^{-1}) had no effect on the responses to impromidine.

Isolated fundic mucosa (see Figure 1b)

Histamine (6×10^{-6}–3×10^{-4}M) and impromidine (5×10^{-7}–2×10^{-5}M) elicited concentration-related increases in acid secretion with ED_{50} values of 5×10^{-5}M and 3.4×10^{-6}M respectively. Impromidine was, therefore, approximately 15 times more potent than histamine, the maximal response was only 67% of that to histamine but this latter difference was not statistically significant ($P > 0.2$). In contrast to the observations *in vivo*, in this preparation the response to histamine was unaffected by mepyramine (2.5×10^{-6}M).

Discussion

Impromidine, is a potent stimulant of gastric acid secretion *in vivo* in the rat, cat, dog (Durant *et al.*, 1978), and, as shown in the present study, the rabbit. In agreement with the previous workers we observed no difference in the maximum acid output stimulated by impromidine or histamine.

In our studies of acid secretion *in vitro*, impromidine is more potent than histamine on a molar basis, but the maximum response is only 67% of that obtained with histamine although this latter difference did not reach statistical significance. However, it suggests that, as in the rat uterus, it may be acting as a partial agonist. Parsons & Sykes (1980) have similarly shown on the rat isolated stomach that the maximum response to impromidine was only 50% of that to histamine. It seems, therefore, that as a stimulant of acid secretion *in vitro* impromidine has a lower efficacy than histamine.

We have recently shown that, in the anaesthetized rabbit, in addition to stimulating acid secretion by an action on H_2-receptors, histamine also exerts an inhibitory effect, probably gastric vasoconstriction, mediated by H_1-receptors (Curwain & Turner, 1981b). Thus in the rabbit one would expect that a selective H_2-receptor agonist, of equal efficacy to histamine, devoid of any H_1-receptor-mediated activity, should elicit a greater maximum secretory response than histamine. In addition, the maximum secretory response to histamine should be converted to that of the selective H_2-agonist in the presence of mepyramine. In the present experiments the maximum acid secretory responses to impromidine and

histamine show no significant difference. However, the maximum response to impromidine is only 66% of that to histamine plus mepyramine. These results clearly suggest that impromidine has a lower efficacy than histamine *in vivo* as well as *in vitro* and that in this experimental model it is behaving as a partial agonist. The potentiating effect of H_1-receptor antagonists on histamine-stimulated acid secretion has also been described in conscious rats (Bunce & Parsons, 1978) and conscious cats (Carter, Impicciatore & Grossman, 1978). In addition, the H_2-selective agonist dimaprit has been shown to produce a greater maximum acid secretory response than histamine alone in Heidenhain pouch dogs (Parsons, Owen, Ganellin & Durant, 1977) and in conscious cats (Carter *et al.*, 1978). We conclude that, in the stomach of the rabbit and possibly in other species, impromidine is not a full agonist at histamine H_2-receptors either *in vivo* or *in vitro*. Its greater potency must, therefore, be a result of a higher affinity for H_2-receptors than histamine. Furthermore, it seems clear from these observations that the agonist potency of selective H_2-agonists should be compared to the unrestricted acid secretory response to histamine seen in the presence of an H_1-antagonist rather than to histamine alone.

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