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IMPROMIDINE (SK&F 92676) ACTS AS A PARTIAL AGONIST ON THE ISOLATED WHOLE STOMACH OF THE RAT

M. PARSONS & C. SYKES

The Research Institute, Smith Kline and French Research Limited, Welwyn Garden City, Hertfordshire

The present secretory studies on the isolated stomach of the rat provide evidence that impromidine acts as a partial agonist at the histamine H_2-receptors. It was found to be 100 times more potent than histamine but with a maximal response only 50% that obtained with histamine.

Introduction Impromidine (SK&F 92676) is a highly potent specific histamine H_2-receptor agonist (Durant, Duncan, Ganellin, Parsons, Blakemore & Rasmussen 1978). *In vivo* studies have shown that it is 17 to 22 times more potent than histamine as a gastric acid secretagogue and has a maximal response equal to or greater than that obtained with histamine. However, impromidine acts as a partial agonist on the isolated uterus of the rat, having a greater affinity for H_2-receptors than histamine but producing a maximal response only 80% that of histamine. *In vitro* studies on gastric secretion have now been carried out on the isolated stomach of the rat.

Methods Fed, immature rats weighing between 35 and 40 g were anaesthetized with pentobarbitone (3 mg i.p.), and the stomachs cannulated as described by Bunce & Parsons (1976). The stomach was rapidly removed and placed in an organ bath containing 10 ml Krebs-Henseleit solution at 37°C gassed with 95% O_2 and 5% CO_2. The lumen of the stomach was perfused with unbuffered Krebs-Henseleit solution and the changes in H^+ ion activity of the effluent perfusate recorded continuously. The basal secretion was allowed to stabilise both under control conditions and in the presence of metiamide before the secretory responses to histamine and impromidine were investigated. The responses to the gastric secretagogues were calculated as the amount of acid secreted at peak response minus the preceding basal level, and expressed as (H^+) mol $\times 10^{-8}$/min. The following drugs were used: histamine acid phosphate (BDH Ltd), pentobarbitone (Sagatal, May & Baker Ltd). Impromidine (SK&F 92676) and metiamide were synthesized in our own laboratories.

Results The dose-response curve to impromidine was linear over the range of 10^{-7} M to 10^{-6} M with a threshold concentration of 3×10^{-8} M (Figure 1). An approximate ED_{50} for impromidine was calculated to be 3×10^{-7} M. The dose-response curve obtained for histamine was linear over the range 10^{-5} M to 10^{-4} M and had a threshold concentration of 10^{-6} M. The calculated ED_{50} for histamine was 3×10^{-5} M showing that impromidine is approximately 100 times more potent than histamine on this preparation. However, the maximal response to impromidine was 6.5×10^{-8} mol/min, which was only half that obtained with histamine (12.2×10^{-8} mol/min).

In order to establish that impromidine interacts with histamine H_2-receptors, two-point dose-response curves to impromidine were constructed in the absence and presence of 3×10^{-5} M metiamide. A control dose-response curve was established, and then each stomach was equilibrated in Krebs-Henseleit solution containing the appropriate concentration of metiamide for 1 h, and a second curve constructed. Metiamide (3×10^{-5} M) produced a parallel displacement of the impromidine dose-response curve to the right with a calculated mean dose-ratio of 10 ($n = 10$).

Discussion Impromidine is a potent stimulant of acid secretion in the rat *in vitro* having some one hundred times the activity of histamine on a molar basis. This compares with a potency of 16.8 times that of histamine in the anaesthetized rat *in vivo*. The reason for this difference between the *in vivo* and *in vitro* result is not clear.

That its stimulant action is the result of activation of histamine H_2-receptors is indicated by the inhibitory action of the specific H_2-receptor antagonist, metiamide. The dose-ratio of 10 produced by 3×10^{-5} M metiamide agrees closely with the value obtained against histamine (Bunce & Parsons 1976). However, the reduced maximal response for impromidine as compared to histamine suggests that it is acting as a partial agonist as seen on the rat uterus preparation (Durant *et al.*, 1978). This means that although the compound has a high affinity for H_2-receptors, it has a relatively low efficacy.

Since impromidine behaves as a partial agonist *in vitro*, it should antagonize a maximal response to histamine. However, this cannot be easily tested *in vitro* since the secretory response to histamine shows

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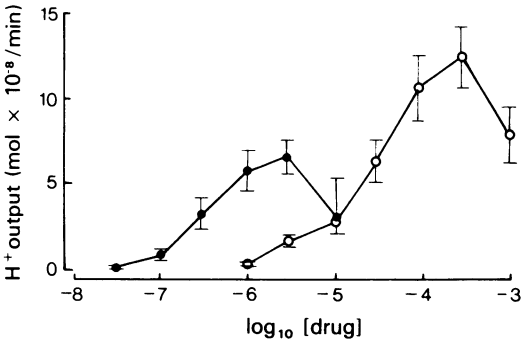

Figure 1 Sequential dose-response curves to impromidine (●) and histamine (○) constructed on 10 separate preparations of the rat isolated whole stomach. Vertical lines represent s.e. mean.

marked fade even when the agonist is infused into the organ bath (Parsons & Bunce 1979). *In vivo* studies in the anaesthetized rat have shown that there is no significant difference between the maximal secretory responses to impromidine and to histamine (R. C. Blakemore, personal communication).

These *in vitro* gastric secretory results agree well with results obtained by Lewin and co-workers (Lewin, Grelac, Cheret, Rene & Bonfils, 1979). They studied the activation of adenylate cyclase by impromidine and histamine in guinea-pig isolated parietal cells, and found that the ED_{50} for impromidine was 5×10^{-7} M compared to 5×10^{-5} M for histamine. Thus, impromidine was approximately one hundred times more potent than histamine on this preparation. However, as in the present studies, the maximal response was only 50% that obtained with histamine.

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