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EFFECT OF IMPROMIDINE (SK&F 92676) ON THE ISOLATED PAPILLARY MUSCLE OF THE GUINEA-PIG

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Impromidine was found to have a positive inotropic effect on the isolated papillary muscle from the guinea-pig. The dose-response curve to impromidine was shifted to the right by cimetidine and ranitidine. Impromidine was 35 times more potent than histamine but with a maximal response of only 81% that obtained with histamine. This difference, which was statistically significant ($P < 0.005$), suggested that impromidine acts as a partial agonist at the histamine H_2-receptors of the papillary muscle as has been observed in other tissues.

Introduction Impromidine is the newest member of the family of the histamine H_2-receptor selective agonists that includes 5(4)-methylhistamine (Black, Duncan, Durant, Ganellin & Parsons, 1972; Bertaccini, Impicciatore, Vitali & Plazzi, 1972), 5(4)-methyl-N-methylhistamine (Bertaccini, Impicciatore & Vitali, 1976) and dimaprit (Parsons, Owen, Durant & Ganellin, 1977). Impromidine was found to be devoid of agonist activity on H_1-receptors and to be extremely potent on H_2-receptors acting as a full agonist in all the *in vivo* preparations tested so far and in the guinea-pig atrium but as a partial agonist on the rat isolated uterus and stomach (Durant, Duncan, Ganellin, Parsons, Blakemore & Rasmussen, 1978; Parsons & Sykes 1980) and also in guinea-pig isolated gastric cells (Lewin, Grelac, Cheret, Rene & Bonfils, 1979). In a previous investigation (Bertaccini, Coruzzi & Vitali, 1978) the papillary muscle of the guinea-pig was found to be useful for the study of H_2-receptor agonists and antagonists. We therefore decided to investigate the action of impromidine on this preparation and to study not only its degree of potency in comparison with histamine but also possible differences in the 'efficacy' of the two compounds.

Methods The technique described in a previous paper (Bertaccini *et al.*, 1978) was followed. Guinea-pigs of 300 to 400 g were killed, and the hearts rapidly removed. The papillary muscles were carefully dissected from the left ventricles and immersed in an organ bath filled with nutrient fluid (NaCl 153.98, $NaHCO_3$ 5.95, KCl 5.62, $CaCl_2$ 2.16 and glucose 5.55 mM) kept at 37°C and bubbled with 95% O_2 and 5% CO_2. A resting tension of 0.8 g was maintained in all the experiments and the preparation was driven electrically through platinum electrodes by square-wave pulses of 2 Hz frequency, 1 ms in duration and a voltage approx. 20% above threshold. Isometric contractions were recorded by a transducer and a microdynamometer. After an equilibration time of about 60 min the inotropic force was considered steady (control force of contraction was approximately 340 mg throughout the whole experiment). Cumulative dose-response curves with impromidine and histamine were constructed increasing the threshold doses by a factor of 3, each concentration being in contact for 1 to 2 min (Van Rossum, 1963). After completion of the dose-response curve, the preparation was washed every 10 min until the developed tension returned to the control (pre-drug) level. When antagonists were used, they were added to the bath 15 min before the administration of the agonist. The following drugs were used: histamine hydrochloride (Fluka); impromidine and cimetidine kindly supplied by the Smith Kline and French Laboratories (Welwyn Garden, Herts); ranitidine (Glaxo, Verona).

Results Impromidine had a positive inotropic effect on the papillary muscle of the guinea-pig starting from very low threshold concentrations (3×10^{-10} M). The effect was dose-related up to concentrations of 3×10^{-7} M which caused the maximum response and tachyphylaxis was never observed. The ED_{50} was 1.42×10^{-8} M (0.71–2.13 95% fiducial limits, $n = 30$). Also histamine induced a remarkable increase in the inotropic force confirming our previous results (Bertaccini *et al.*, 1978). The dose-response curve to the amine was linear over the range of 10^{-7} to 10^{-6} M with a threshold concentration of 10^{-8} M and the maximum response at 10^{-5} M. The ED_{50} of histamine was 0.51×10^{-6} M (0.36–0.67 95% fiducial limits, $n = 32$) showing that impromidine is approximately 35 times as active as histamine on the papillary muscle. Figure 1 shows the dose-response curves of the two compounds and indicates that apart from the difference in potency there is also a modest difference in the 'efficacy' of the two compounds: the maximum response to impromidine was 81.2% in comparison with that of histamine. The absolute values expressed as difference in tension between basal levels and the response to the agonists were 0.64 ± 0.03 g for histamine and 0.52 ± 0.01 g for impromidine. The difference between these values was highly significant as

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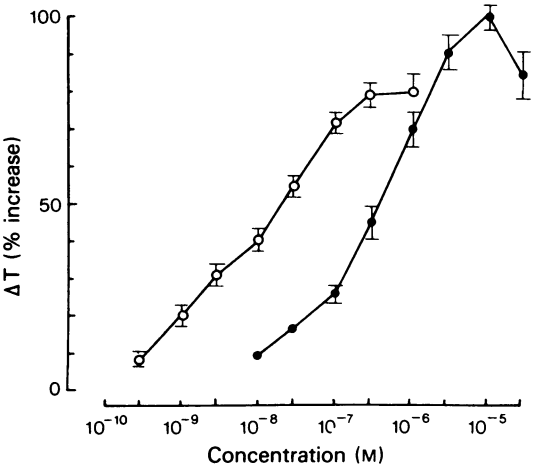

Figure 1 Inotropic effect of impromidine (○) and of histamine (●) on the isolated papillary muscle of the guinea-pig. On the ordinate scale: % increase of the isometric tension (ΔT) in comparison with basal levels; on the abscissa scale: molar concentrations of the two compounds. Each value represents the mean of the values obtained from 32 experiments. Vertical lines are standard errors.

assessed by Student's t test ($P < 0.005$). That the action of histamine was mediated through activation of H_2-receptors has already been demonstrated on the basis of competitive antagonism shown by cimetidine (Bertaccini *et al.*, 1978). In the present study both cimetidine and the new H_2-receptor blocker, ranitidine, shifted the dose-response curve of impromidine to the right: the pA_2 values of cimetidine against impromidine and histamine were 6.71 ± 0.19 and 6.41 ± 0.09 respectively; those of ranitidine were 7.04 ± 0.13 and 6.60 ± 0.19 respectively. Changing the agonist did not significantly alter the pA_2 values for either antagonist ($P > 0.4$ in the case of cimetidine and $P > 0.05$ in the case of ranitidine) showing that they interact with the same receptor (Arunlakshana & Schild, 1959).

Discussion Our experiments showed that impromidine is endowed with a striking stimulatory effect on the H_2-receptors of the isolated papillary muscle of the guinea-pig. This effect was competitively inhibited by cimetidine and ranitidine: surprisingly these H_2-receptor blockers had approximately the same potency, whereas under other experimental conditions ranitidine was 4.5 times as potent as cimetidine on the guinea-pig atrium (Bradshaw, unpublished) and was 5 to 12 times as potent as cimetidine in inhibiting gastric secretion *in vivo* (Domschke & Domschke, 1980). The potency of impromidine was, on a molar basis, 35 times that of histamine although the maximum response was only 81% that of the biogenic amine, the difference being statistically significant: this confirmed previous observations according to which impromidine may act as a partial agonist on H_2-receptors. The value of 81% found in our study is higher than that found by Parsons & Sykes (1980) on the rat isolated stomach and by Lewin *et al.* (1979) on the activation of adenylate cyclase in guinea-pig isolated parietal cells (about 50% in both studies); however, it is quite close to that found by Durant *et al.* (1978) in rat isolated uterus (80.2%). It is of interest that on the papillary muscle other H_2-receptor agonists such as 5-(4)-methylhistamine and dimaprit produced the same maximal response as histamine although having a different degree of potency (Bertaccini *et al.*, 1978). It is difficult to explain the difference between histamine and impromidine as far as the 'efficacy' is concerned. One possibility is that this situation represents a special feature of the measuring system and could represent only an artifact connected with the *in vitro* experimental conditions as pointed out by Angus & Black (1979); another explanation might be the possible heterogeneity of the histamine H_2-receptor population with sub-types of the classical receptors on which impromidine shows less intrinsic activity than on others. The existence of such subtypes of H_2-receptors has already been suggested in several investigations (Bertaccini, Molina, Vitali & Zappia, 1979; Chand, Eyre & de Roth, 1979; Coruzzi, Bongrani & Bertaccini, 1979; Fjalland, 1979). Further experiments using impromidine as a tool to stimulate the H_2-receptors in different tissues of various animal species and in different experimental conditions will clarify this problem.

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