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An inhibitory effect of histamine on the rat anococcygeus muscle

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The rat anococcygeus muscle contracts in response to noradrenaline, 5-hydroxytryptamine (5-HT), acetylcholine and carbachol (Gillespie 1972). It is also contracted by high doses of histamine. However, the responses to histamine showed tachyphylaxis after a single dose. In a similar preparation in the cat (Gillespie & McGrath 1974) and the rabbit (Creed et al 1977), histamine-induced contractions were abolished by mepyramine suggesting an action on histamine H_1-receptors. It was also observed that metiamide, an H_2-receptor antagonist (Black et al 1973) potentiated histamine-induced contractions in the rabbit anococcygeus which might suggest the presence of histamine H_2-receptors in this species. This communication, reports the inhibitory effect of histamine on the rat isolated anococcygeus muscle.

Adult male rats (ca. 250 g) were killed by a blow on the head and then bled. The two anococcyeus muscles were removed according to Gillespie (1972) and suspended in a 20·0 ml organ bath containing aerated Tyrode solution (NaCl 137; KCl 2·7; $CaCl_2$ 1·8; $MgCl_2$ 0·9; NaH_2PO_4 0·3; $NaHCO_3$ 11·9 and glucose 5·6 mmol litre^{-1}) at 37 °C. Isotonic contractions (under a tension of 0·5 g) were recorded. Drugs used were: histamine acid phosphate; dimaprit; mepyramine maleate; impromidine; cimetidine; metiamide; acetylcholine chloride; carbachol; (−)-noradrenaline bitartrate and 5-hydroxytryptamine creatinine sulphate. All drug concentrations refer to the base.

The muscle has no intrinsic tone, hence inhibitory effects of histamine and two selective H_2-receptor agonists—dimaprit (Parsons et al 1977) and impromidine (Durant et al 1978) were tested against agonist-induced contractions in the presence of mepyramine (1 μM) to block H_1-receptors. In preliminary experiments when noradrenaline, carbachol and ACh were used as agonist, very high concentrations of histamine ($\geqslant 10^{-3}$ M) were needed to demonstrate an inhibitory effect. However, much lower doses (approx. 2×10^{-5} M) of histamine produced an inhibitory effect against 5-HT. In all subsequent experiments therefore, inhibitory effects were tested against 5-HT induced concentrations. Histamine ($4{\cdot}5 \times 10^{-5}$–$7{\cdot}2 \times 10^{-4}$ M) consistently produced a concentration-dependent inhibition of 5-HT-induced contractions of the muscle (Fig. 1). In individual experiments, the threshold inhibitory concentration varied between $2{\cdot}5$–$4{\cdot}5 \times 10^{-5}$ M. In all experiments, recovery from the inhibitory effect of low concentrations of histamine was rapid. However at high concentrations of histamine ($\geqslant 3{\cdot}6 \times 10^{-4}$ M) the percentage recovery ranged from 45–70% despite repeated washing for 1 h. Impromidine ($2{\cdot}3 \times 10^{-6}$–$3{\cdot}7 \times 10^{-5}$ M) and dimaprit (4×10^{-5}–$1{\cdot}2 \times 10^{-3}$ M) produced qualitatively similar responses to histamine (Fig. 1). The only difference was in the potency. As shown in Table 1, impromidine was approximately ten times more potent than histamine which in turn was about four times as potent as dimaprit.

Cimetidine (4×10^{-5}–8×10^{-5} M), an antagonist at H_2-receptors (Brimblecombe et al 1975) had little or no effect (Fig. 2) on the inhibitory effect of histamine in this preparation. Metiamide, another H_2-receptor antagonist (Black et al 1973) was also not effective, rather it appeared to be an agonist in this preparation, having about half the potency of histamine (See Table 1).

The above results show that the inhibitory effect of histamine on the rat anococcygeus muscle appears to be agonist specific. While consistent inhibitory effects were obtained against 5-HT as the agonist, much higher concentrations of histamine, which produced a maximum of less than 36% inhibition, were needed when noradrenaline, carbachol or acetylcholine was used as the agonist. Burnstock et al (1978) demonstrated an inhibitory response to ATP in the rat anococcygeus muscle only with high concentrations of ATP when noradrenaline and 5-HT were used to raise tone. Also, relatively high concentrations of ATP were required to relax the rabbit anococcygeus when phenylephrine was used to raise tone (San San Wai & Coupar 1976). Histamine stimulates two types of receptors; H_1-receptors (Ash & Schild 1966) and H_2-receptors (Black et al 1972). In the present study, the H_1-receptor was blocked with mepyramine. It would thus appear that

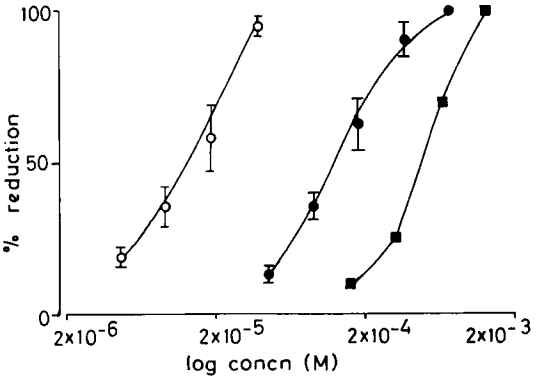

FIG. 1. The inhibitory effect of impromidine (○) histamine (●) and dimaprit (■) on 5-HT-induced contractions of the rat anococcygeus muscle. All agonists were added 2 min before 5-HT. Each point on the graph represents mean ± s.e. of 4, 10 and 6 experiments for impromidine, histamine and dimaprit respectively.

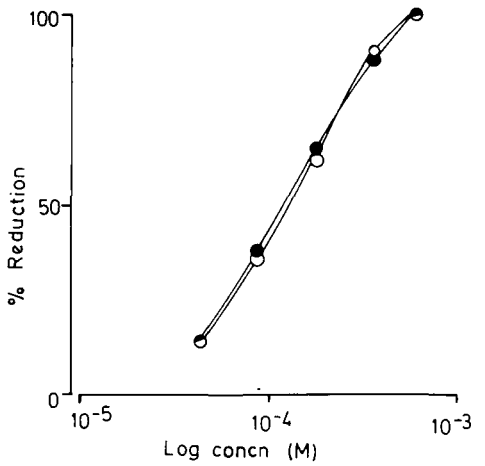

FIG. 2. The inhibitory effect of histamine on 5-HT-induced contractions of the rat anococcygeus muscle in the absence (○) and also in the presence of 8×10^{-6} M cimetidine (●). Cimetidine was allowed to equilibrate with the tissue for 30 min. Each point on the graph represents the mean of 7 experiments.

the inhibitory effect of histamine was probably mediated via H_2-receptors. This is supported by the observation that selective H_2-receptor agonists—impromidine and dimaprit produced inhibitory effects qualitatively similar to that of histamine. However, even though the rank order of potency of the H_2-receptor agonists i.e. *impromidine > histamine > dimaprit is similar to that* observed on other preparations e.g. the rat uterus, it is apparent that typical H_2-receptors are probably not involved in this action of histamine because (1) unusually high concentrations of histamine, with a threshold at about 5×10^{-5} M were needed to produce an effect; (2) the inhibitory effect was resistant to blockade by cimetidine which blocks H_2-receptors in other preparations and (3) metiamide, another H_2-receptor antagonist, was itself an agonist in the preparation. These results suggest the presence of metiamide and cimetidine-resistant H_2-receptors in the rat anococcygeus muscle. Eyre & Chand (1979) produced evidence to suggest the existence of a third type of histamine receptor which is resistant to blockade by available H_2-receptor antagonists. According to these authors, the new receptor could be functionally similar to H_2-receptors since it is activated by selective H_2-receptor agonists but differed in its insensitivity to H_2-receptor antagonists. They

Table 1. Inhibitory effects of some histamine H_2-receptor agonists on the rat anococcygeus muscle.

Agonists[a]	'n'	EC50 (concentration producing 50% reduction in height of contractions)
Histamine	9	$1{\cdot}4 \pm 0{\cdot}3 \times 10^{-4}$ M
Dimaprit	6	$4{\cdot}8 \pm 1{\cdot}1 \times 10^{-4}$ M
Impromidine	4	$1{\cdot}5 \pm 0{\cdot}2 \times 10^{-5}$ M
* Metiamide[b]	6	$2{\cdot}7 \pm 0{\cdot}8 \times 10^{-4}$ M

[a] agonists were added 2 min before the addition of 5-HT.
[b] metiamide, an H_2-receptor antagonist also inhibited 5-HT-induced contractions.

therefore proposed a subclassification of histamine H_{2A}-receptors into H_{2A} (blocked by metiamide) and H_{2B} (metiamide resistant). The present findings add support since selective H_2-receptor agonists are effective but the effects of these agonists were not antagonized by metiamide and cimetidine.

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REFERENCES

Ash, A. S. F., Schild, H. O. (1966) Br. J. Pharmacol. Chemother. 27: 427–439

Black, J. W., Duncan W. A. M., Durant, G. J., Ganellin, C. R., Parsons, M. E. (1972) Nature (London) 236: 385–390

Black, J. W., Duncan, W. A. M., Emmett, J. C., Ganellin, C. R., Hesselbo, T., Parsons, M. E., Wyllie, J. H. (1973) Agents Actions, 3: 133–137

Brimblecombe, R. W., Duncan, W. A. M., Durant, G. J., Emmett, J. C., Ganellin, C. R., Parsons, M. E. (1975) J. Int. Med. Res. 3: 86–92

Burnstock, G., Cocks, T., Crowe, R. (1978) Br. J. Pharmacol. 64: 13–20

Creed, K. E., Gillespie, J. S., McCaffery, H. (1977) J. Physiol. 273: 121–135

Durant, G. J., Duncan, W. A., Ganellin, C. R., Parsons, M. E., Blackemore, R. C., Rasmussen, A. C. (1978) Nature (London) 276: 403–405

Eyre, P., Chand, N. (1979) Agents Actions 9: 1–3

Gillespie, J. S. (1972) Br. J. Pharmacol. 45: 404–416

Gillespie, J. S., McGrath, J. C. (1974) Ibid. 50: 109–118

Parsons, M. E., Owen, D. A. A., Genellin, C. R., Durant, G. J. (1977) Agents Actions 7: 31–37

San San Wai, Coupar, I. M. (1976) Clin. Exp. Pharmacol. Physiol. 3: 141–145