An inhibitory histamine H_2-receptor in the mouse vas deferens

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Histamine (0.3–30 μM) produced a concentration dependent inhibition of the twitch response of the mouse vas deferens (0.2 Hz, 2.0 ms, 256 mA) with an ID_{50} of 4.8 μM. Histamine acts on H_1- and H_2-receptors. Therefore selective agonists and antagonists were used to characterize which histamine receptor was present in the mouse vas deferens.

The selective agonist at histamine H_1-receptors, 2-pyridylethylamine (Durant, Ganellin & Parsons, 1975) produced a weak inhibition of the twitch with an ID_{50} of about 1 mM. Dimaprit, a highly specific agonist at histamine H_2-receptors (Parsons, Owen, Ganellin & Durant, 1977), was much more effective with an ID_{50} of 14.5 μM, about a third of the potency of histamine. This is within the range of the activity of dimaprit on other H_2-receptors (Parsons *et al.*, 1977).

Mepyramine, 1.0 μM, which is an antagonist at H_1-receptors did not alter the histamine concentration-inhibition curve in the vas deferens. However, the selective competitive H_2-receptor antagonist cimetidine (Brimblecombe, Duncan, Durant, Emmett, Ganellin & Parsons, 1975) 10 μM shifted the histamine curve to the right by half a log unit.

These results show that the inhibitory effect of histamine on the stimulated vas deferens is mediated by an H_2-receptor.

Inhibition of the twitch response can be produced by drugs acting at pre-synaptic receptors as, for example, clonidine which stimulates pre-synaptic α-adrenoceptors in the vas deferens (Marshall, Nasmyth, Nicholl & Shepperson, 1978). Agonists at pre-synaptic receptors are more effective at low rather than at high frequencies of stimulation (Langer, 1977). The inhibition of the twitch by histamine, 10 μM, was greater at low frequencies than at high frequencies but was almost as marked at 5.0 Hz as at 0.2 Hz (both over 70%). With frequencies of 10 Hz and 16 Hz there was a decrease in the effect of histamine (45% and 25% respectively). This fall off is not as marked as that produced by clonidine (Marshall *et al.*, 1978).

The possibility that stimulation of the histamine H_2-receptor could inhibit the overflow of noradrenaline was investigated. Vasa were pretreated for 45 min with [7-^{3}H]-(−)-noradrenaline (100 ng/ml, sp.act. 54 mCi/mg), washed and the overflow from 6 vasa collected. The bath contents were assayed for noradrenaline and its metabolites using alumina and Dowex columns (Graefe, Stefano & Langer, 1973).

The fractional noradrenaline release (Dubocovich & Langer, 1976) after stimulation at 1.0 Hz, 2.0 ms for 2 min was $8.15 \times 10^{-4} \pm 0.75$ (mean ± s.e. mean). When histamine 1.0 μM or 10 μM was added 30 s prior to stimulation the fractional release of noradrenaline was not significantly altered at $7.7 \times 10^{-4} \pm 1.23$ and $8.09 \times 10^{-4} \pm 1.82$ respectively.

In conclusion, therefore, histamine inhibits the twitch response to electrical stimulation of the mouse vas deferens via a histamine H_2-receptor. This receptor, unlike the pre-synaptic α-adrenoceptor, does not mediate the reduction in twitch height by reducing the overflow of noradrenaline.

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