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Haloperidol inhibits contractions of the vas deferens

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Although the vasa deferentia of several mammalian species contain very high concentrations of noradrenaline (Sjöstrand, 1965; Blakeley, Dearnaley & Harrison, 1970), it is not agreed whether noradrenaline functions as a motor transmitter or whether an as yet unidentified substance performs this function. In the rat and guinea-pig, for example, Ambache and colleagues (Ambache & Zar, 1971; Ambache, Dunk & others, 1972) have provided evidence that adrenoceptor blocking agents do not diminish nerve-mediated contractions of isolated vasa although they do prevent the contractions produced by exogenously applied noradrenaline and by indirectly acting sympathomimetics such as tyramine. Other groups have also noted a large discrepancy between the doses of phentolamine which block noradrenaline and those which reduce electrically-induced contraction (Jones & Spriggs, 1975; Jenkins, Marshall & Nasmyth, 1976). These results have been attributed to a failure of phentolamine to reach a sufficiently high concentration in the narrow extracellular spaces of vasa to inhibit the effects of very high concentrations of synaptically released noradrenaline (Furness, 1974; Jones & Spriggs, 1975).

The present experiments were undertaken to examine the effects of the largely unionized catecholamine antagonist haloperidol on vasa of mice, rats and guinea-pigs. Adult animals were killed by a blow on the head and a vas deferens was immediately removed and placed in cold Krebs solution. The connective tissue and blood vessels were carefully cut away from the vas, which was then suspended in a 25 ml organ bath at 36° containing Krebs solution of the following composition (mM): NaCl, 118; KCl 4·75; $CaCl_2$ 2·54; $MgSO_4$ 1·19; $NaHCO_3$ 25; KH_2PO_4 0·93; glucose 11. The solution was aerated with a mixture of 5% carbon dioxide in oxygen. Contractions were recorded by an isotonic transducer. Stimulation of the intramural nerves was achieved by a pair of ring electrodes around the tissue. The electrodes were 15 mm apart and had diameters of 3 mm. Preparations were usually stimulated to contract with trains of 10 pulses at 50 Hz every 15 or 30 s. The stimuli were of 1 ms duration and were delivered by a Devices Digitimer unit and stimulus isolators.

Drugs were made up in Krebs solution and were usually injected into the bath in volumes of 0·1 ml. The only exceptions were for the higher doses of haloperidol applied to rat and guinea-pig vasa. Haloperidol solutions were made from ampoules of haloperidol for injection (Serenace, Searle). This preparation also contains dextrose and lactic acid, but these were found to have no effect on contractions of vasa. The antagonist was left in contact with vasa for 2 min.

The results are summarized in Fig. 1. Sample records of the effects of haloperidol on electrically-induced and noradrenaline-induced contractions are shown in

Fig. 1A and B, and the results from 15 mouse vasa are summarized in the concentration-response curves of Fig. 1C. It is apparent that the doses effective in reducing noradrenaline responses in this species are closely similar to those causing reduction of nerve-mediated contractions. There was no significant difference between any of the pairs of points ($P < 0{\cdot}001$; n = 15; Student's *t*-test).

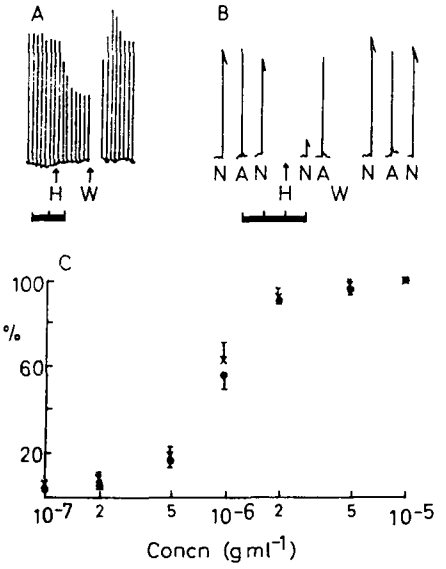

FIG. 1. A. Record of the electrically-induced contractions of a mouse isolated vas deferens. At H, haloperidol was added to a final bath concentration of 1 μg ml^{-1}. The preparation was washed at W. Time: min. B. Contractions of the same preparation as in A produced by bath concentrations of 10 μg ml^{-1} of noradrenaline (N) and ATP (A). Again, at H haloperidol was added to a concentration of 1 μg ml^{-1}, and the preparation washed at W. The same result was also obtained by adding haloperidol before each of the agonists separately. Time: min. C. Concentration-response curves for the inhibitory effect of haloperidol (g ml^{-1}) on electrically-induced (●) and noradrenaline-induced (×) contractions of 15 mouse vasa. The points represent the mean and standard error of the mean. Ordinate—% reduction in twitch.

Eight rat vasa and 4 guinea-pig vasa were also used. The overall sensitivity to haloperidol of the vasa from these species was some 10 to 20 times less than for mouse vasa. There was also an approximately 2-fold difference in the concentrations of haloperidol causing antagonism of nerve-mediated contractions and noradrenaline contractions in these preparations.

As illustrated in Fig. 1B contractions of the vasa produced by adenosine triphosphate (ATP) at a bath concentration of 10 μg ml^{-1} were completely unaffected by haloperidol even at doses causing complete abolition of electrical and noradrenaline contractions. The doses of haloperidol being used here were not therefore producing a non-specific depression of the target tissue.

As haloperidol is usually considered to be an antagonist mainly at dopamine receptors, this compound was also tested on the vasa. However, dopamine did not cause contraction of vasa from any of the species used, at concentrations up to 50 μg ml^{-1}. On the other hand, a response of the rat vas deferens to dopamine has been reported (Birmingham, Paterson & Wojcicki, 1970; Simon & Van Maanen, 1976).

The similar susceptibility of electrical and noradrenaline induced contractions to haloperidol, using doses which did not affect ATP, supports the idea that noradrenaline is the motor transmitter released by sympathetic nerves to the vas deferens. The effectiveness of haloperidol in reducing motor transmission compared with phentolamine, for example, remains to be explained, but could be due to a relative ease of penetration to the transmitter sensitive surface, perhaps due to the uncharged nature of the haloperidol molecule.

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