The interaction of WB4101, and other α-adrenoceptor antagonists, on 5-hydroxytryptamine receptors

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Previous studies in which high concentrations of α-adrenoceptor antagonists have been applied to rat isolated vas deferens have shown that spontaneous spiked contractions were induced (Drew 1977; Doggerell & Paton 1978). The mechanism by which these contractions were produced was not evaluated. The potent α-adrenoceptor blocking drug WB4101 (Mottram & Kapur 1975; Greenberg et al 1976) has also been observed to induce spiked contractions in rat vas deferens and the present study was undertaken to investigate this phenomenon in an attempt to establish the mechanism by which α-adrenoceptor antagonists induce the spontaneous contractions in rat isolated vas deferens.

Male rats, 200–300 g, were killed by a blow to the head. The vasa were excised, stripped of extraneous material and suspended in organ baths containing Mg-free Krebs solution (composition (g litre^{-1}): NaCl, 6·923; $CaCl_2$, 0·285, $NaHCO_3$, 2·1; KCl, 0·354; KH_2PO_4, 0·162 and glucose 2·0), maintained at 37 °C and aerated with a mixture of 5% CO_2 in oxygen. It has previously been reported (Hughes et al 1975; Jenkins et al 1977) that contractile responses are enhanced in Mg-free Krebs solution, and previous work on this tissue has been carried out in Krebs solution of this composition (Kapur & Mottram 1978). Isometric contractions were recorded with Devices 2 oz strain gauge transducers and two channel recorder. All drugs were freshly prepared in Krebs solution.

α-Adrenoreceptor antagonists at concentrations in excess of those required for α-blockade were administered to vasa and left in contact with the tissues for periods of up to 1 h, after either a single or cumulative dose regime.

The α-blocking drugs investigated were: WB4101 (2-(N-[2,6-dimethoxyphenoxyethyl])aminomethyl-1,4-benzodioxane) (6×10^{-6} to 2×10^{-5}M), phentolamine (8×10^{-6} to 10^{-3}M), yohimbine (8×10^{-6} to 8×10^{-5}M), thymoxamine (8×10^{-6} to 6×10^{-5}M).

Phentolamine failed to produce a contractile response, whilst WB4101, yohimbine and thymoxamine all produced dose-dependent spontaneous contractions of the vas deferens (Fig. 1). The onset of action following the administration of these drugs was immediate though the maximal height of the spiked contraction took some 15 min to develop. Contractions continued for over 1 h after administration.

Contractions elicited by WB4101 (4×10^{-5}M) were challenged by a series of antagonists. Atropine and phenoxybenzamine had no effect on the spiked contractions, at any dose. Mepyramine (2×10^{-4}M), pimozide (10^{-4}M), and chlorpromazine (2×10^{-4}M), produced a blockade, but at far higher concentrations than those normally required. The only effective

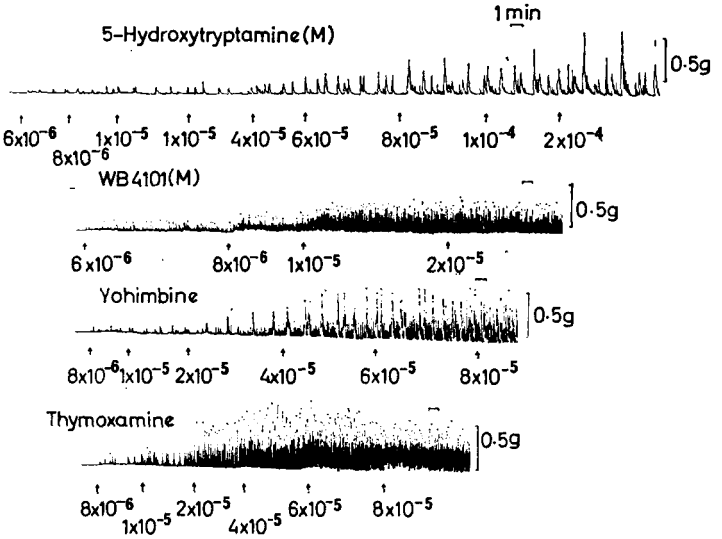

FIG. 1. Cumulative dose-response relationships for the α-adrenoceptor antagonists, WB 4101, yohimbine and thymoxamine and the agonist 5-hydroxytryptamine on rat vas deferens. Vertical calibration 0·5 g, horizontal calibration 1 min.

* Correspondence.

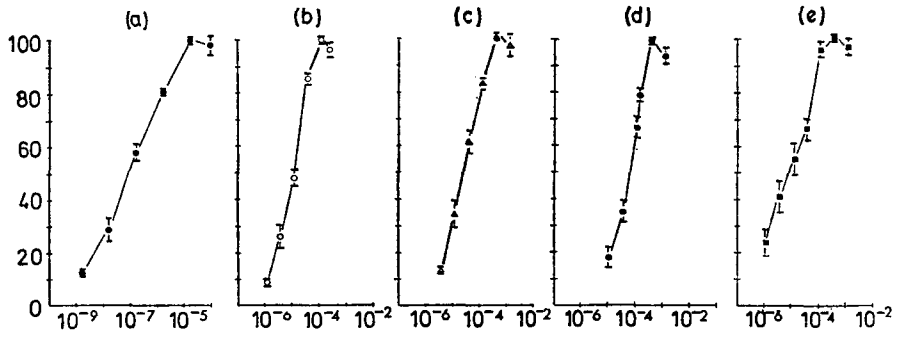

FIG. 2. Dose-percentage response (ordinate) curves for the drugs producing contractions of the isolated rat fundus strip. Each point is the mean ± s.e. of 4–6 experiments. Abscissa: drug dose (M). (a) 5-HT, (b) LB101, (c) yohimbine, (d) guabexane, (e) thymoxamine.

antagonist against the spiked contractions produced by WB4101 was the 5-HT antagonist, cyproheptadine (Stone et al 1960) which completely abolished contractions at a concentration of 10^{-5}M.

Cumulative dose-response relationships for a series of agonists (histamine, dopamine and 5-hydroxytryptamine) on the vas deferens showed that histamine failed to produce contractions of the tissue up to a concentration of 10^{-3}M, dopamine produced a sustained noradrenaline-like contraction, confirming a previous observation by Simon & Van Maanen (1976), whilst 5-HT produced spiked contractions of the vas deferens, like those produced by the α-blocking drugs under investigation.

The results of studies on the rat vas deferens indicate that WB4101 and other α-blocking drugs, in high concentrations, produce sustained spiked contractions of the tissue which are immediate in onset but require time to achieve maximal height. Results suggest that these compounds may be acting by a direct stimulation of 5-hydroxytryptamine receptors, which have previously been shown to exist in the rat vas deferens (Jurkiewicz et al 1969).

The rat fundus strip was chosen to evaluate the effect of the α-blocking drugs under investigation on a tissue rich in 5-HT receptors. The preparation was set up using the method of Vane (1957) and dose-response curves plotted for 5-HT and each of the drugs (Fig. 2). Unlike the spiked contractions produced in the rat vas deferens, contractions of the fundus were sustained. The 5-HT antagonist cyproheptadine at 2×10^{-5}M produced an equal degree of antagonism against both 5-HT and WB4101.

Whether 5-HT receptors are specific, particularly peripherally, seems open to question. Woodruff (1971) has proposed a composite dopamine/5-HT receptor, whilst Cook & MacLeod (1978) suggest that in rabbit portal vein histamine and 5-HT share a common receptive site. The results of the present study appear to be more in accord with the suggestion of Apperley et al (1976) that 5-HT receptors and α-adrenoceptors, although distinct entities, have features in common. We therefore suggest that certain structurally related antagonists of α-adrenoceptors are able to interact as agonists on 5-HT receptors which are located not only in rat fundus strip, but also, perhaps in a different form, in the rat vas deferens.

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