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Is thymoxamine a specific α-adrenoceptor blocking agent?

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Thymoxamine is a competitive α-adrenoceptor blocking agent with fewer unwanted actions than other α-adrenoceptor blocking drugs. It has some antihistaminic activity (Birmingham & Szolcsanyi, 1965) but is otherwise considered to be specific. In this study using the guinea-pig isolated vas deferens-hypogastric nerve preparation, it is shown that thymoxamine has activity which appears to be independent of α-adrenoceptor blockade.

The guinea-pig vas deferens was stimulated via the nerve at a rate of 20 Hz for 7 s every 2 min, using supramaximal voltage and a pulse width of 0·5 ms. The preparation was bathed in McEwen's Ringer (1956) maintained at 31±1° C and aerated with a mixture of 95% O_2 and 5% CO_2. Figure 1 shows the effects of thymoxamine in these conditions. Appreciable reduction in the size of response was produced in concentrations of 5–125 ng/ml. A similar situation existed when the transmurally stimulated vas was used (Birmingham & Wilson, 1963). In these concentrations,

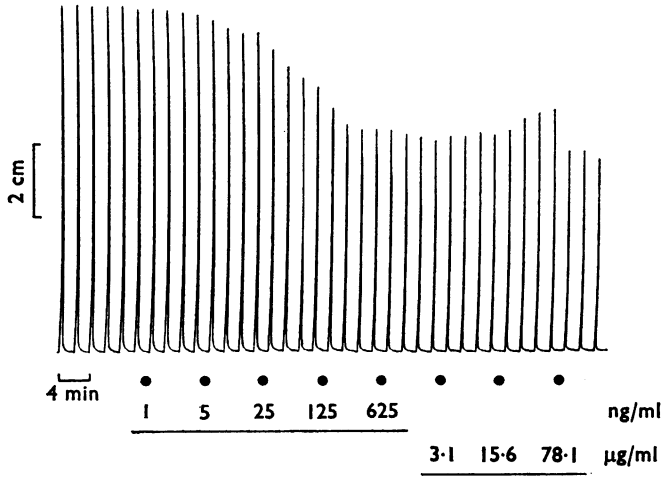

FIG. 1. Cumulative concentration-effect curve for thymoxamine on the guinea-pig isolated vas deferens stimulated via the hypogastric nerve.

phentolamine, another α-adrenoceptor blocking agent, had no effect on the size of contraction, so it was of interest to investigate if the effect of thymoxamine was due to α-adrenoceptor blockade.

Phenylephrine, a compound thought to act exclusively on α-adrenoceptors (Goodman & Gilman, 1970), increases the contractions of the vas deferens in response to nerve stimulation. α-Adrenoceptor blockade antagonizes this effect and thus displaces the concentration-effect curve for phenylephrine to the right. Although 25 ng/ml thymoxamine reduced the contraction size by 16%, it did not significantly antagonize phenylephrine ($P > 0.05$); however, antagonism was apparent with higher concentrations of thymoxamine. This indicates that thymoxamine has pharmacological actions distinct from α-adrenoceptor blockade. These actions are detectable at extremely low concentrations of the drug and therefore throw doubt on its specificity as an α-adrenoceptor blocking agent. The nature of these actions is being investigated.

I thank D. W. Snowdon for preparing the figure and William Warner & Co. Ltd. for supplying thymoxamine.

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Effects of sympathomimetic amines on rabbit platelet aggregation *in vitro*

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Adrenaline and noradrenaline can produce aggregation of blood platelets and potentiate aggregation induced by adenosine diphosphate; this action is thought to be mediated at sympathomimetic receptors on the platelet membrane (Mills & Roberts, 1967). We have studied the effects of several directly and indirectly acting sympathomimetic compounds to establish the structural specificity of the receptors involved in aggregation and the preceding morphological change of platelets.

Velocities of the morphological change and aggregation were measured in 1 ml volumes of rabbit citrated platelet-rich plasma at 37° C (Michal & Born, 1971). Drugs were dissolved in buffered saline pH 7 and added in volumes not exceeding 20 μl so that the final concentrations were 10^{-8}–2×10^{-3} M.

(−)-Adrenaline (2×10^{-6} M) and (−)-noradrenaline (2×10^{-4} M) caused platelets to aggregate but the morphological change needed only about 1/10 of these concentrations. None of the other catecholamines examined caused aggregation or shape change in concentrations up to 2×10^{-3} M except dopamine, which at 2×10^{-4} M caused platelets to change shape. None of seventeen non-catecholamines aggregated platelets but tyramine (2×10^{-3} M), amphetamine (10^{-4} M), mephentermine (2×10^{-4} M) and phenylethylamine (2×10^{-4} M) induced the morphological change.

Most of the compounds accelerated platelet aggregation caused by low concentrations of ADP but (+)-isoprenaline (2×10^{-4} M) and (±)-orciprenaline (2×10^{-3} M)