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May 28, 1971

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A comparison of adrenergic α-receptors by the use of *NN*-dimethyl-2-bromo-2-phenylethylamine (DMPEA)

There has been much discussion of the possible subclassification of the α- and β-categories of adrenergic receptors (cf. *inter alia*, van Rossum, 1965; Lands, Arnold & others, 1967; Patil, 1969; Bristow, Sherrod & Green, 1970; Furchgott, 1970; Brittain, Jack & Ritchie, 1970; Patil, Patil & Krell, 1971; Triggle, 1971). Evidence in support of such subclassification comes from the discovery of tissue selective agonists and antagonists, the comparative sequences of activities of agonists and antagonists in various tissues and by the use of isomer activity ratios (Patil, 1969; Patil & others, 1971) in which the activities of *R* and *S* isomers of catecholamines are compared in a number of tissue systems experimentally controlled to minimize the influence of non-receptor catecholamine processes. This latter method has the theoretical advantage also in that problems of diffusion and access to the receptor, which may complicate comparisons between structurally dissimilar molecules, should be minimized. According to this procedure, the α-receptors of six tissues, including rabbit aorta and rat vas deferens, are not distinguishably different.

This finding agrees with our previous limited report (Moran, Triggle & Triggle, 1969) that the kinetics of recovery of response of the rabbit aorta and rat vas deferens to noradrenaline from irreversible antagonism by *NN*-dimethyl-2-bromo-2-phenylethylamine (DMPEA) were identical. This procedure would appear to afford another potential probe of comparative α-receptor structure, sharing the advantages of the isomer ratio technique, since recovery from an established blockade is measured and the product of the presumed receptor hydrolysis ($Ph{\cdot}CHOH{\cdot}CH_2{\cdot}NMe_2$) is inactive.

Table 1 presents our data, together with brief experimental details, for four α-receptor containing tissues. The results with rabbit aorta and rat vas deferens confirm our previous findings (Moran & others, 1969) and those with the guinea-pig and rabbit vas deferens extend them and show differences in the kinetics of recovery of α-receptor response.

It has been argued elsewhere (Belleau, 1958; Triggle, 1965, 1971) that the recovery of response from alkylation by DMPEA is consistent with a spontaneous intramolecular (direct nucleophilic or general base catalysed) hydrolysis of a β-dialkylaminocarboxylate ester. For such a reaction a decreased rate would be anticipated on shifting to a less polar environment since this would hinder charge production.

Table 1. *Recovery of response to noradrenaline after α-receptor blockade by DMPEA.*

Tissue	DMPEA (concn M)	% Blockade (initial)	Time (min) for 50% recovery of resp. (mean ±s.e.)	*n*
Rabbit aorta[a,b]	10^{-5}M/5′	95	23·8 ± 2·4	10
Rat vas deferens[b,c,d]	10^{-5}M/5′	96	23·0 ± 0·9	14
Guinea-pig vas deferens[b,e] ..	10^{-5}M/5′	95	75·0 ± 6·0	6
Rabbit vas deferens[c,e]	2×10^{-5}M/5′	86	124 ± 11·2	6

[a] Responses were recorded isometrically in Krebs-bicarbonate solution with Grass FT. 03C force-displacement transducers and Grass polygraph (Model 5D).
[b] Responses at various times were determined with a maximum challenging concentration of noradrenaline. Cumulative dose-response curves with the rat vas gave the same kinetics.
[c] Tissues were set up for recording isotonic contractions in Krebs bicarbonate by the method described previously (Moran & others, 1969). First order kinetics of recovery were observed for at least 70% of the recovery of response. Huković's solution (Huković, 1961) was used with the guinea-pig vas to minimize spontaneous contractions.
[d] Isotonic and isometric recording yielded identical data which have been pooled.
[e] Responses were followed by cumulative dose-response curves with noradrenaline.

The comparatively small decreases in rate shown in Table 1 may, therefore, represent an increasingly hydrophobic binding site for DMPEA.

Extension of this conclusion to the noradrenaline binding site of the α-receptor hinges upon the question of identity of binding sites for the agonist and antagonist. For the series of antagonists related to DMPEA several lines of evidence (Chapman & Graham, 1967; Moran & Triggle, 1970; Triggle, 1971) suggest at least a partial identity. Hence, the structural differences reflected in the data of Table 1 may reflect differences at or very close to the noradrenaline binding site of the α-receptor.

This work was supported by a grant from the National Institutes of Health (NS 09573).

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June 16, 1971

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