The significance of the relative potencies of noradrenaline and α-methylnoradrenaline for the mode of action of α-methyldopa

It is commonly agreed that the hypotensive action of α-methyldopa is mediated through an interference with the sympathetic system, but the site of action has not been established. Opinions differ on the function of the peripheral sympathetic nerves after treatment with α-methyldopa (Muscholl, 1966, Holtz & Palm, 1967; Sourkes & Rodriguez, 1967; Stone & Porter, 1967; Kopin, 1968). It has been proposed that the amines (α-methylnoradrenaline and α-methyldopamine) formed on metabolism of α-methyldopa take over the function of the normal transmitter noradrenaline in the brain (Carlsson & Lindqvist, 1962) and in the peripheral sympathetic nerves (Day & Rand, 1963; 1964).

The observation that α-methylnoradrenaline was less potent as a pressor agent than noradrenaline (Day & Rand, 1964) led to the hypothesis that the formation of such less active amines from α-methyldopa may act as "false transmitters". This theory was challenged by the experiments of Henning & van Zwieten (1968) and Henning (1969a, b). Moreover, Brunner, Hedwall & others (1967) failed to find any hypotensive effect with α-methylnoradrenaline, even though the heart was depleted of noradrenaline by 50%, without a concomitant depletion in the brain. Furthermore, adrenergic neuronal function was only slightly impaired at the time of maximal fall in blood pressure (Henning & Svensson, 1968).

I have compared the potency of noradrenaline with that of α-methylnoradrenaline on blood pressure and heart rate of rabbits and rats, and both these parameters and also myocardial contractility and cardiac output in dogs.

Dogs of either sex (10 to 15 kg) were anaesthetized with pentobarbitone (35 mg/kg) and artificially ventilated with oxygen from a positive pressure respirator through a cuffed endotracheal tube. Arterial blood pressure was recorded by a Statham P23 Db pressure transducer and the heart rate by means of a cardiotachometer triggered by the electrical activity of the QRS complex of the electrocardiograph. The force of cardiac contraction was measured using a Walton-Brodie strain gauge arch (Boniface, Brodie & Walton, 1953) sutured to the right ventricle. Cardiac output was obtained by placing a well-fitting probe for a square wave electromagnetic flow meter (Carolina Medical Electronics) around the ascending aortic arch. Zero flow was obtained by clamping the aorta proximally. All the above-named parameters were recorded on a multi-channel Sanborn thermal recorder.

Albino rats (180 to 220 g) were pithed by the method of Shipley & Tilden (1947) and ventilated by a small animal respirator. Mean arterial pressure was recorded from a carotid artery by a Statham pressure transducer coupled to an Offner Dynograph penrecorder.

Rabbits weighing 2 to 3 kg were anaesthetized with 35 mg/kg of pentobarbitone. Systemic pressure was recorded as outlined for rats. Drugs (−)-noradrenaline bitartrate and (−)-α-methylnoradrenaline were diluted in normal saline and injected intravenously. Standard error of the mean (s.e.) and paired *t*-tests were used to analyse the results.

In dogs, noradrenaline and α-methylnoradrenaline at doses of 0·3, 0·6 and 1·2 μg/kg were equi-active in increasing blood pressure, force of cardiac contraction, cardiac output and in decreasing the heart rate reflexly. Table 1 gives a summary of these data.

Pressor responses to 10, 20, 30 and 40 ng of noradrenaline and α-methylnoradrenaline were equipotent on the blood pressure of pithed rats. This is shown in Table 2. In rabbits α-methylnoradrenaline (0·5, 1·0 and 2 μg/kg) appeared to be less potent than

noradrenaline, although it was only unequivocal at 0·5 and 2 μg/kg ($P < 0·01$ and $<0·05$ respectively).

The comparison of the potencies of α-methylnordrenaline and noradrenaline was determined by taking the responses to a number of doses of each amine. The results are shown in Table 3. In all the preparations tested, α-methylnoradrenaline and noradrenaline were equiactive with the exception of blood pressure responses in the rabbit where α-methylnoradrenaline was only marginally less potent.

Table 1. *Comparison of the cardiovascular effects of noradrenaline with α-methylnoradrenaline in dogs* (n = 9).

Dose	Drug	Blood pressure (mm Hg)		Contractility (g force)		Heart rate (beats/min)		Cardiac output ml/min)	
0·3 μg/kg	NA	+33±3	NS	+22·6±2·1	NS	−37±4	NS	+ 810±100	NS
	αMeNA	+39±4		+24·8±3·8		−37±6		+ 880±300	
0·6 μg/kg	NA	+54±4		+28·3±3·0		−43±7		+ 620±250	
	αMeNA	+43±3		+22·8±1·1		−43±8		+1000±100	
1·2 μg/kg	NA	+70±6		+36·7±8·5		−57±12		+1050±170	
	αMeNA	+61±5		+36·6±8·7		−64±3		+1100±200	

Table 2. *Comparison of pressor responses to noradrenaline and α-methylnoradrenaline in rats and rabbits.*

Dose	No. of animals	Mean increase in blood pressure mm Hg (±s.e.)		*P* value
Rats (ng)		Noradrenaline	α-Methylnoradrenaline	
10	10	29·1±2·7	28·1±2·7	NS
20	10	41·7±3·2	38·6±3·2	
30	10	50·1±5·4	53·1±2·8	
40	10	64·0±3·5	59·0±2·3	
Rabbits (μg/kg)				
0·5	6	49±2	39±3	<0·01
1	6	55±4	44±3	>0·05
2	6	74±5	52±5	<0·05

Table 3. *Relative potency of noradrenaline and -methylnoradrenaline.*

	Preparation	No. of experiments	Mean potency ratio
Dog	blood pressure		1·05
	heart rate		1·0
	cardiac output	9	0·8
	myocardial contractility		1·0
Rat (pithed)	blood pressure	10	1·03
Rabbit	blood pressure	6	1·3

It is known that α-methylnoradrenaline is taken up (Malmfors, 1965), stored in granules (Lundborg & Stitzel, 1967) in adrenergic nerve fibres and released by nerve stimulation (Muscholl & Maître, 1963). These findings indicate that the amine metabolites of α-methyldopa function as pseudo-transmitters.

Basic to this concept is that the new transmitter has less receptor activity than the natural substance. Day & Rand found α-methylnoradrenaline to be 2 to 8 times less potent than noradrenaline in increasing arterial blood pressure in several laboratory animal species. Brunner & others (1967) and Holtz & Palm (1967) also found α-methylnoradrenaline to have less pressor activity. In contrast, Muscholl & Maître (1963), Maître & Staehelin (1963) and Krzysztof (1967) found the two amines to be largely equipotent.

In my experiments, both amines were equipotent on all cardiovascular parameters in the dog and on the pressor responses in the rat over a wide dose range. Only in the rabbit, the pressor activity of α-methylnoradrenaline was slightly less than that for noradrenaline, the mean potency ratio being merely 1·3 which is in marked contrast to the eightfold difference obtained by Day & Rand (1964) in this species.

Despite these conflicting results, sufficient evidence from the present experimental findings and those of other workers (Henning, 1969a,b; Henning & van Zwieten, 1968) has been obtained to conclude that the replacement of noradrenaline by α-methylnoradrenaline at peripheral sympathetic nerve terminals does not substantially contribute to the hypotensive action of α-methyldopa.

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