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Effects of McN-A-343 on responses induced by sympathetic nerve stimulation in the rabbit isolated ear artery

M. J. RAND* and B. VARMA, *Department of Pharmacology, University of Melbourne, Parkville, Victoria* 3052, *Australia*

Acetylcholine and other cholinomimetic drugs affect the responses of isolated arterial preparations to sympathetic nerve stimulation. The responses may be enhanced or decreased depending on the frequency of stimulation and the concentration of drug (Malik & Ling, 1969a; Rand & Varma, 1970). Both of these effects are produced by the purely nicotinically acting drug DMPP (Malik & Ling, 1969b). We have investigated the effects of McN-A-343 [4(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride; *m*-$Cl.C_6H_4.NH.CO.O.CH_2.C:C.CH_2.N^+(CH_3)_3.Cl^-$), which was reported to stimulate only mucarinic receptors of ganglion cells (Roszkowski, 1961).

With low frequencies of stimulation (<5 Hz), vasoconstrictor responses induced by sympathetic nerve stimulation were reduced by infusion of McN-A-343, but the vasoconstrictor effects of noradrenaline were not affected. In the presence of atropine, McN-A-343 did not reduce responses induced by sympathetic nerve stimulation. Similar effects were observed with methacholine. These results suggest that cholinomimetic drugs may act muscarinically to impair the release of noradrenaline by sympathetic nerve impulses. Direct evidence for such an effect of acetylcholine has been produced by Löffelholz & Muscholl (1969). Amphetamine reversed the impairment of sympathetic nerve stimulation by acetylcholine (Malik & Ling, 1969a), McN-A-343 and methacholine, indicating a similarity between their effects and that of adrenergic neurone blocking drugs.

Enhancement of the effects of sympathetic nerve stimulation was produced by infusions of McN-A-343 when high frequencies of stimulation (>10 Hz) were used or when low frequencies were used in the presence of atropine. With high frequencies of stimulation, the responses were gradually decreased after prolonged infusion of high concentrations of McN-A-343 (2 μg/ml). In the presence of atropine, the effects of McN-A-343 in producing at first an increase and then a decrease in responses induced by high frequencies of stimulation were not altered qualitatively, but the effective concentrations were higher than in the absence of atropine. The enhancement of responses elicited by sympathetic nerve stimulation by McN-A-343 suggests either facilitation of noradrenaline release or blockade of reuptake of noradrenaline; since the effects of noradrenaline were only slightly increased, both factors may be involved. The secondary decrease may be due to reduction of transmitter reserve with a high frequency of stimulation.

Our interpretation of the findings is that McN-A-343 acts muscarinically on the adrenergic terminal axons innervating the rabbit ear artery to impair or to enhance

vasoconstrictor responses elicited by sympathetic nerve stimulation, the impairing effect being more susceptible to blockade by atropine than the enhancing effect. The mechanism of the effects may involve an interaction between McN-A-343 and the sites at which acetylcholine may act in mediating noradrenaline release by sympathetic nerve impulses.

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The uptake of adrenergic neurone blocking drugs

J. WILSON, *Department of Pharmacology and Therapeutics, St. Thomas's Hospital Medical School, London, S.E.*1

Boura & Green (1965) suggested that the concentrations of adrenergic neurone blocking drugs which accumulate in sympathetic nerves might be sufficient to block conduction in the nerve terminals. However, Rand & Wilson (1967) showed that, in a group of guanidine compounds, there was no direct relationship between the local anaesthetic activity of individual drugs and their potency as adrenergic neurone blocking drugs.

In the present experiments uptake of four compounds previously studied by Rand & Wilson (1967) has been measured in the rat's heart. These compounds have similar local anaesthetic activity but differ in their adrenergic neurone blocking activity. Thus, guanethidine and EM 311 (2-cyclohexylamino-2-methylethyl guanidine) are potent adrenergic neurone blocking drugs, while EM 97 (3-cyclohexylamino-*n*-propyl guanidine) and EM 336 (2-cyclohexylamino-2-ethylethyl guanidine) are virtually inactive in this respect. Figures for uptake are shown in Table 1. The reduction in uptake after pretreatment of the rats with dexamphetamine was taken as a measure of uptake into the sympathetic nerves. Uptake by the heart of

TABLE 1. *Uptake of guanidine derivatives into rat hearts and the effect of dexamphetamine (5 mg/kg intraperitoneally, 30 min before giving the guanidine derivative) on this uptake. Each figure is the mean result (±S.E.) obtained using twelve rats*

Drug	Concentration in heart (nmol/g)	Concentration in heart (nmol/g) after dexamphetamine pretreatment	Depression of uptake by dexamphetamine
Guanethidine 10 mg/kg	63·4±2·2	43·5±1·7	19·9
EM 311 10 mg/kg	60·4±2·8	44·9±2·2	15·4
EM 336 10 mg/kg	29·2±3·2	—	—
EM 336 20 mg/kg	52·1±1·8	56·0±2·0	0
EM 97 10 mg/kg	171·2±6·9	145·4±5·8	25·8