Modulation by the muscarinic agonist McN-A-343 of release of noradrenaline from sympathetic neurones in the rabbit pulmonary artery

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McN-A-343 (4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethyl-ammonium chloride) is a powerful muscarinic agonist on sympathetic ganglion cells (Roszkowski, 1961). In this study its effect on the overflow of tritium released by electrical-field stimulation (225 mA; 300 and 1000 pulses; 0.5 msec; 3 Hz) was studied on the rabbit isolated pulmonary artery preloaded with (−)-[^{3}H]-noradrenaline ([^{3}H]-NA).

The time course of the effect of McN-A-343 and cocaine on overflow of tritium evoked by stimulation was examined. At 10^{-6}–3×10^{-5} M, McN-A-343 continuously enhanced the [^{3}H]-overflow up to 192% of control. At higher concentrations (10^{-4} and 3×10^{-4} M), McN-A-343 initially potentiated the overflow and thereafter inhibited it. Cocaine in the lower concentrations (10^{-6}–3×10^{-5} M) also enhanced the [^{3}H]-overflow evoked by stimulation, but to a lesser degree (maximally 126% of control) than that seen with McN-A-343. At higher concentrations (10^{-4} and 3×10^{-4} M), cocaine solely reduced the [^{3}H]-overflow.

The spontaneous outflow of tritium from pulmonary artery preloaded with [^{3}H]-noradrenaline ([^{3}H]-NA) consisted of [^{3}H]-NA (13%), [^{3}H]-dihydroxyphenyl ethyl glycol ([^{3}H]-DOPEG, 17%), [^{3}H]-dihydroxy mandelic acid ([^{3}H]-DOMA, 8%), [^{3}H]-O-methylated and deaminated metabolites ([^{3}H]-OMDA, 51%), and [^{3}H]-normetanephrine ([^{3}H]-NMN, 2%). This outflow was not altered by McN-A-343 (10^{-4} M). The time course of the effect of McN-A-343 on the pattern of [^{3}H]-NA and its [^{3}H]-metabolites evoked by field stimulation was examined. The overflow from untreated artery *during* stimulation consisted of [^{3}H]-NA (28%), [^{3}H]-DOPEG (10%), [^{3}H]-DOMA (4%), [^{3}H]-OMDA (52%), and [^{3}H]-NMN (6%). Initially McN-A-343 only decreased [^{3}H]-DOPEG. Subsequently the amount of [^{3}H]-NA and [^{3}H]-NMN was also reduced with a corresponding rise in [^{3}H]-DOMA and [^{3}H]-OMDA.

The ability of various drugs to influence the biphasic response (potentiation of stimulation-evoked [^{3}H]-overflow followed by inhibition) caused by a high concentration (10^{-4} M) of McN-A-343 was studied. Prior addition of either cocaine (3×10^{-5} M), atropine (3×10^{-7} M), methylatropine (10^{-5} M), hexamethonium (3×10^{-5} M) or the prostaglandin-synthetase inhibitor, suprofen (3×10^{-5} M) did not prevent the initial potentiation induced by McN-A-343. In the case of cocaine, the enhancement was continuously maintained. The other drugs either abolished or markedly reduced the subsequent inhibition normally caused by McN-A-343. However, the enhancement was not maintained, and [^{3}H]-overflow either returned to pre-drug (control) level or just below.

The ability of McN-A-343 (10^{-6}–3×10^{-4} M), cocaine (10^{-8}–3×10^{-4} M), and desmethylimipramine to reduce the neuronal uptake of [^{3}H]-NA (10^{-8} M) by rabbit isolated aorta was examined. Aorta was treated with pargyline (5×10^{-4} M) and U-0521 (3′,4′-dihydroxy-2-methylpropiophenone; 10^{-4} M) in order to inhibit monoamine oxidase and catechol-*O*-methyltransferase, respectively. McN-A-343 was a much weaker inhibitor of [^{3}H]-NA uptake than cocaine and desmethylimipramine.

It is concluded that McN-A-343 enhances the stimulation-evoked [^{3}H]-overflow by inhibition of the neuronal membrane pump and by facilitation of transmitter release. The enhancement is not mediated by muscarinic or nicotinic receptors and is prostaglandin-independent. McN-A-343 may possibly be transported by the membrane amine pump into an intraneuronal site of inhibitory action.

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Reference

ROSZKOWSKI, A.P. (1961). An unusual type of ganglionic stimulant. *J. Pharmac. exp. Ther.*, **132**, 156–170.

Catecholamine receptors in thoracic spinal cord

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The existence of bulbospinal catecholamine pathways which have a dense termination in the sympathetic intermediolateral cell column of the thoraco-lumbar cord is now well established (Dahlstrom & Fuxe, 1965; Coote & Macleod, 1974; Coote, Fleetwood-Walker & Martin, 1979). In the cat, noradrenaline, dopamine and adrenaline are found in this region, although adrenaline is present in extremely small amounts (Coote, Fleetwood-Walker & Martin, unpublished). To try to establish a transmitter role for these catecholamines in the cat thoracic spinal cord,