AN ESTIMATE OF THE MUSCARINIC GANGLION BLOCKING POTENCY OF ATROPINE

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Summary: The mechanism and potency of the blocking action of atropine on the ganglionic muscarinic receptors was investigated in chloralose anaesthetised cats. Atropine blocked competitively the stimulant action on the nictitating membrane of muscarine and 4-(m-chlorophenylcarbamoyloxy)-3-butynyltrimethyl ammonium chloride (McN-A-343) when injected intraarterially into the blood supply of the superior cervical ganglion. The "pA2" values of atropine with muscarine and McN-A-343 as the agonists were 9.6 and 9.4 respectively.

Key Words: muscarinic ganglionic blockade atropine

INTRODUCTION

In view of the interest evinced in the muscarinic ganglion receptors from time to time (4, 8, 9, 10, 11, 12) and the well known competitive blocking action of atropine at non-neural muscarinic receptors the mechanism and potency of blocking action of atropine at the ganglionic muscarinic receptors was investigated.

MATERIALS AND METHODS

Cats of either sex weighing 2 - 3.5 kg were anaesthetised with chloralose (70 mg/kg, intravenously) after preliminary ethyl chloride anaesthesia. A polyethylene tube of a fine bore was inserted into the common carotid artery through the superior thyroid artery. The tip of the polyethylene tube in the artery was coaxed in the direction of flow of blood. Into the other end of the tube was inserted a 21 gauge needle attached to a three-way stopcock. All the drugs were administered into the common carotid artery through the three-way stopcock and were followed by 0.5 ml of normal saline every time. The external carotid artery was occluded for 15 sec at the time of administration of the drugs. Contractions of the nictitating membrane were recorded on smoked drum with isotonic lever (10-fold magnification) subjected to 3.5 g tension. Contractions of both the membranes were recorded simultaneously. 4-(m-chlorophenyl-carbamoyloxy)-3-butynyltrimethyl ammonium chloride (McN-A-343) and muscarine were used as the agonists and were administered at intervals of 15-20 min.
to avoid tachyphylaxis. Atropine was used in 4 doses and 3 experiments were set up for each dose. After eliciting a control panel of agonist responses atropine was given and 15 min later response to a dose of an agonist was obtained. After recovery, effect of another dose of atropine was recorded. It was possible to record the effects of only two doses of atropine with one membrane since reproducible control responses could not, in general be elicited subsequently. Since responses of both the membranes were recorded in the same animal, it was possible to obtain the effect of four doses of atropine in one experiment. The effect of atropine lasted for 20 min.

RESULTS AND DISCUSSION

Muscarine (5.8 x 10^{-4} M - 5.8 x 10^{-8} M) and McN-A-343 (6 x 10^{-8} M - 8 x 10^{-7} M) when administered intraarterially through the lingual artery into the blood supplying the superior cervical ganglion elicited dose-related contractions of the nictitating membrane. Atropine (3.4 x 10^{-10} M - 3.4 x 10^{-9} M) competitively antagonized the maximal responses and flattened the dose-response curves of the cat nictitating membrane to muscarine (injected intra-arterially into the blood supply of the superior cervical ganglion); abscissa, log M of muscarine; ordinate, percentage of maximal contraction.

![Dose-response curves](image1.png)

**Fig 1:** Dose-response curves of the contractile responses of the cat nictitating membrane to muscarine (injected intra-arterially into the blood supply of the superior cervical ganglion); abscissa, log M of muscarine; ordinate, percentage of maximal contraction. ---O indicates control dose-response curve; ---X indicates dose-response curves after 8.5 x 10^{-10} M, 1.7 x 10^{-9} M and 3.4 x 10^{-9} M respectively of atropine. Contractions were recorded 15 min after injection of atropine into the blood supply of the superior cervical ganglion.

![Dose-response curves](image2.png)

**Fig 2:** Dose-response curves of the contractions elicited by muscarine (3.4 x 10^{-10} M - 3.4 x 10^{-9} M) intra-arterially into the blood supply of the superior cervical ganglion; abscissa, log M of muscarine; ordinate, percentage of maximal contraction. --- indicates competitive antagonism (Fig. 1, 3). The "pA" values were determined (7) to identify the blocking activity of absolute concentrations of atropine that the concentration at the injection (3, 8). Thus the values were used for the purpose of (dose ratios). The dose ratio is the "pA" values.
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...10-8 M - 8 x 10-7 M) and supplying the sup-

...ne (3.4 x 10^-16 M - 3.4 x 10^-9 M) caused parallel shifts to the right (without suppression of the maximal responses and flattening of the curves) of the dose-response curves indicating...

...competitive antagonism (Fig. 1, 2). Although parallel shifts of agonist dose-response curves suggested competitive antagonism the data were further analysed according to Arunlakshana and Schild (2). The in vivo equivalents of pA2 values for atropine were determined to quanti-...

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Fig. 2: Dose-response curves of the contractile responses of the cat nictitating membrane to McN-A-343 (injected intra-arterially into the blood supply of the superior cervical ganglion); abscissa, log M of McN-A-343; ordinate, per cent of maximal contraction. - - - - - - indicates control dose-response curve; × - × ; 0 ---- O and indicate dose-response curves after 3.4 x 10^-16 M, 8.5 x 10^-16 M, 1.7 x 10^-9 M and 1.4 x 10^-8 M respectively of atropine. Contractions were recorded 15 min after injection of atropine into the blood supply of the superior cervical ganglion.

competitive antagonism (Fig. 1, 2). Although parallel shifts of agonist dose-response curves suggested competitive antagonism the data were further analysed according to Arunlakshana and Schild (2). The in vivo equivalents of pA2 values for atropine were determined to quantify the blocking activity of atropine. Since the experiments were performed in vivo the absolute concentrations of atropine at the site of action were unknown. It was, therefore, assumed that the concentration at the site of action was proportional to the dose of the atropine injected (3, 8). Thus the values determined have been referred to as “pA2” values. For this purpose the log of (dose ratio-1) was plotted against the negative log M of atropine (pA2 plots). The dose ratio is the ratio of doses of agonist in the presence and absence of antagonist (7). The “pA2” values of atropine determine from these plots by regression analysis

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Fig. 2: Dose-response curves of the contractile responses of the cat nictitating membrane to McN-A-343 (injected intra-arterially into the blood supply of the superior cervical ganglion); abscissa, log M of McN-A-343; ordinate, per cent of maximal contraction. - - - - - - indicates control dose-response curve; × - × ; 0 ---- O and indicate dose-response curves after 3.4 x 10^-16 M, 8.5 x 10^-16 M, 1.7 x 10^-9 M and 1.4 x 10^-8 M respectively of atropine. Contractions were recorded 15 min after injection of atropine into the blood supply of the superior cervical ganglion.
The corresponding slope values of pAₐ plots were -1.11 ± 0.06 and -1.16 ± 0.8 respectively. These slope values were not significantly different (p > 0.05) from the theoretical value of unity for competitive antagonism (2). The present study confirms the blocking action of atropine at the cat superior cervical ganglion against peripherally acting muscarinic (4, 12, 16) agonists. The “pA₂” values of atropine determined in the present study are very close to the pA₂ value of 9.0 reported for the guinea pig ileum by Arunlakshana and Schild (2). A competitive reversible antagonist would have the same Kᵦ (dissociation constant) or pA₂ value in different tissue preparations if it reacts with closely similar receptors (1, 5, 6, 13, 14). On this basis it is possible to identify receptors in different tissues... Thus the smooth muscle muscarinic receptors seem to be identical with the neural muscarinic receptors of the superior cervical ganglion.

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REFERENCES