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THE SELECTIVE ANTIMUSCARINIC ACTION OF STERCURONIUM

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1 The antimuscarinic activity of stercuronium, a competitive neuromuscular blocking drug, has been compared in the anaesthetized guinea-pig, guinea-pig atria, bladder and ileum, rabbit atria and the sympathetically innervated rabbit ear artery preparation using carbachol (CCh) as agonist.

2 In the anaesthetized guinea-pig, stercuronium (0.2 and 2.0 μmol/kg) produced significantly greater inhibition ($P < 0.05$) of the bradycardia than of the vasodepressor response produced by CCh, the difference being 2 fold at the low dose and 5.8 fold at the higher dose.

3 In guinea-pig atria the negative chronotropic response to CCh was inhibited to a similar degree to the negative inotropic response by stercuronium, whereas in bladder and ileum stercuronium was 17 fold less active as an antimuscarinic drug.

4 The affinity of stercuronium for the prejunctional muscarinic receptor on sympathetic nerve endings in the rabbit ear artery was similar to that for the muscarinic receptor mediating negative inotropic responses to CCh in the rabbit left atrium, and 2.3 fold less than the affinity for the muscarinic receptors in guinea-pig atria.

5 A similar trend was observed with gallamine, another neuromuscular blocking drug, when results obtained in the rabbit ear artery preparation were compared to previously reported data. Also, the affinity of gallamine for muscarinic receptors mediating relaxation of the cat anococcygeus muscle was found to be similar to that for prejunctional muscarinic receptors in the rabbit ear artery.

6 It is suggested that stercuronium and gallamine have a greater affinity for cardiac receptors and the inhibitory muscarinic receptors on sympathetic nerve endings than for muscarinic receptors mediating contraction of bladder and ileum.

Introduction

Stercuronium and gallamine are two competitive neuromuscular blocking drugs which also exert an antimuscarinic effect at doses comparable to those producing neuromuscular blockade (Riker & Wescoe, 1951; Marshall, 1973). Furthermore, the antimuscarinic action appears to be cardioselective. In the anaesthetized cat, bradycardia produced by vagal stimulation or methacholine is inhibited by doses of these antagonists which have no effect on the vasodepressor response to methacholine (Riker & Wescoe, 1951; Marshall, 1973).

Gallamine has been shown to be over 10 fold less effective as an antimuscarinic agent in guinea-pig ileum or bladder than in guinea-pig atria (Clark & Mitchelson, 1976) and Rathbun & Hamilton (1970) estimated the affinity of gallamine for muscarinic receptors in the rat and cat heart *in vivo* to be 100 and 1000 fold greater respectively than the affinity for muscarinic receptors in guinea-pig isolated ileum. Stercuronium is about 5 times more potent than gallamine as an antimuscarinic compound in guinea-pig atria (Li & Mitchelson, 1978a) and similarly produces a non-linear Arunlakshana-Schild plot (A-S plot, Arunlakshana & Schild, 1959) for this tissue (Li & Mitchelson, 1978a, b).

This paper is concerned with the effect of stercuronium on a range of muscarinic receptors to determine the extent of the cardioselectivity and to compare its effectiveness with that of gallamine.

Methods

Anaesthetized guinea-pig

Guinea-pigs (400 to 800 g) were anaesthetized by an intraperitoneal injection of urethane (25% w/v) solution (6 ml/kg). Blood pressure was recorded on a Grass polygraph via a cannula connected to a Statham pressure transducer P23DC and heart rate was determined via a tachometer triggered from the QRS complex of the ECG. Artificial respiration was administered through a tracheal cannula with a Palmer small animal respirator using a stroke volume of 6 ml at a rate of 35 strokes per min. Drugs were

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administered via a cannula in the external jugular vein.

The lower end of the anterior tibialis muscle was isolated and connected to a Grass force-displacement transducer (FT.03). After sectioning, the sciatic nerve was placed on platinum electrodes and stimulated at supramaximal voltage with pulses of 5 ms duration at a frequency of 0.1 Hz. Drugs were injected into the jugular vein and washed in by 0.2 ml of saline (0.9% w/v NaCl solution). For determination of the effects of stercuronium, the drug was injected intravenously and the changes in tibialis muscle contractility, blood pressure and heart rate were measured. A second dose was injected only after the muscle had recovered its original contractility.

For determination of the effect of antagonists on the cardiovascular responses to carbachol (CCh), a range of concentrations of agonist was injected and reproducible responses obtained at least in duplicate for determination of the dose-response relationship. After a dose of antagonist was injected, a dose-response curve to CCh was obtained again within the next 30 min.

Guinea-pig and rabbit atria

Right and left atria were isolated from guinea-pigs and left atria from rabbits. Atria were mounted under a resting tension of 0.5 g in an organ bath having a capacity of 10 ml (guinea-pig) or 30 ml (rabbit) and containing McEwen's solution (McEwen, 1956) at 32°C and gassed with a mixture of 95% O_2 and 5% CO_2. Left atrial preparations were stimulated electrically by square wave pulses with a voltage twice threshold at a frequency of 3 Hz and a pulse duration of 2 ms; right atrial preparations were allowed to beat spontaneously.

Contractions were recorded with a force–displacement transducer (FT.03) connected to a polygraph. CCh was allowed to remain in contact with the atria until the full response was obtained (negative inotropic response in left atrium, negative chronotropic response in right atrium). This was usually 90 s for guinea-pig and 120 to 180 s for rabbit atria. Cycle time (time between additions of agonist) was 5 min (guinea-pig) or 8 min (rabbit).

Guinea-pig ileal longitudinal muscle

Ileal longitudinal muscle was isolated as described by Paton & Zar (1968) and a 3 to 4 cm length of tissue was mounted under 1 g tension in McEwen's solution at 32°C, and gassed with a mixture of 95% O_2 and 5% CO_2. Agonists were added to the bath at 5 min intervals and remained in contact with the tissue until the full response was obtained (1 to 2 min).

Guinea-pig bladder

Bladders from guinea-pigs were bisected longitudinally and set up under 1 g tension. A contact time of 3 to 4 min was used for the agonist with a dose cycle of 7 to 10 min. Other details are similar to those described under guinea-pig atria.

Perfused rabbit ear artery

The proximal section of the central ear artery was removed from the ears of rabbits (1.5 to 4 kg) as described by de la Lande & Rand (1965). The isolated artery was cannulated at both ends and perfused at 2 to 6 ml/min with McEwen's solution gassed with a mixture of 95% O_2 and 5% CO_2 and maintained at 37°C while mounted on a plastic holder in a 25 ml organ bath filled with McEwen's solution. The perfusate passed out of the artery via the second cannula and did not enter the organ bath fluid. The perfusion pressure was recorded on a polygraph with a Statham pressure transducer P23DC. The periarterial sympathetic nerves were stimulated via coaxial platinum electrodes every 3 min with pulses of 30 to 80 V and 1 to 2 ms duration at a frequency of 2 Hz for 10 or 20 s.

After an equilibration period of 30 min when stable perfusion pressures and responses to electrical stimulation had been obtained, a cholinomimetic was added to the bath 2 min before a stimulation period and remained in contact with the tissue for a further 2 to 3 periods of stimulation to ensure the maximal effect of the cholinomimetic had been obtained. The preparation was then washed by changing the organ bath solution and control responses were re-established. A second concentration of the cholinomimetic was then added and the procedure repeated to obtain a dose-response curve to the agonist, each concentration of agonist being tested at least in duplicate.

Cat anococcygeus muscle

Anococcygeus muscles were isolated from kittens killed by ether as described by Gillespie & McGrath (1974) and mounted in Krebs solution, containing ascorbic acid (1 mM), under a resting tension of 1 g at 32°C and gassed with a mixture of 95% O_2 and 5% CO_2. The composition of the Krebs solution was (mM): NaCl 94.1, $NaHCO_3$ 25, NaH_2PO_4 0.90, KCl 4.7, $MgSO_4$ 0.45, $CaCl_2$ 2.5 and glucose 11.1.

Although preparations developed spontaneous tone the amount of relaxation produced by carbachol was small and only occurred at high concentrations (see Results). In order to increase the degree of relaxation produced by carbachol the tone of the muscle was increased further by addition of noradrenaline to the preparation in concentrations sufficient to produce 80% of the maximal response to the amine. After the

tone of the anococcygeus muscle became constant in the presence of the amine, the responses to cumulative concentrations of carbachol were then obtained. Twenty minutes was allowed for washout and recovery before determination of a second dose-response curve.

Estimation of dose-ratios

Responses of isolated tissue to cholinomimetics were obtained in duplicate within the range of 20 to 80% of maximal responses in guinea-pig atria, bladder and ileum and in rabbit atria, 10 to 70% in rabbit ear arteries and 10 to 90% in cat anococcygeus muscle and anaesthetized guinea-pig experiments. A regression line was fitted by the least squares method through the linear portion of the dose-response curve for determination of the EC_{50} value.

The effects of antagonists were determined by initially incubating the tissue for 20 to 30 min in the presence of the antagonists to establish equilibrium conditions and then repeating the procedure as described above in the presence of the antagonists. Dose-ratios were calculated as the EC_{50} in presence of antagonist/EC_{50} in the absence of antagonist. All statistical comparisons were made by means of Student's t test (two-tailed) unless otherwise noted.

Drugs

The following drugs were used: acetylcholine chloride, atropine sulphate, hexamethonium bromide, homatropine hydrobromide, methacholine chloride, (±)-noradrenaline hydrochloride (Sigma); carbamyl choline (carbachol, Koch-Light); gallamine triethiodide, urethane (May & Baker); mecamylamine hydrochloride (Merck, Sharp and Dohme); stercuronium iodide (Gist-Brocades).

Results

Anaesthetized guinea-pig

The dose of stercuronium required to produce 50% inhibition of contractions of the tibialis muscle elicited by stimulation of the sciatic nerve was 66 nmol/kg (40–88, 3) (geometric mean dose, 95% confidence limits, n).

Stercuronium (0.02 to 2 μmol/kg) did not alter heart rate but there was a slight increase in blood pressure with doses of 0.02 and 0.2 μmol/kg and a fall in blood pressure to 71.4 ± 12.7% (3) [mean ± s.e. mean (n)] of the control value with a dose of 2 μmol/kg.

Stercuronium (0.2 and 2 μmol/kg) caused parallel shifts in the dose-response curve for the vasodepressor response and bradycardia produced by CCh. The dose-ratios obtained with stercuronium at either dose level for the inhibition of CCh-induced bradycardia were higher and significantly different ($P < 0.05$) from those obtained for inhibition of the depressor response to CCh (Table 1).

Experiments were conducted also with a competitive antagonist homatropine, for comparison. In doses of 0.28 and 2.8 μmol/kg homatropine did not affect heart rate or blood pressure of the guinea-pig but caused parallel shifts of the dose-response curves to CCh and there was no significant difference in the dose-ratios obtained with homatropine for the inhibition of either response at any one dose level of the antagonist (Table 1).

Table 1 Dose-ratios obtained with stercuronium (0.2 and 2 μmol/kg) and homatropine (0.28 and 2.8 μmol/kg) as inhibitors of the vasodepression and bradycardia produced by carbachol (CCh)

Drug	*Dose* (μmol/kg)	*Response to CCh*	*Geometric mean dose-ratio (95% confidence limits)* (n)	P*
Stercuronium	0.20	Vasodepression	2.32 (1.25–4.30) (5)	<0.05
		Bradycardia	4.38 (2.70–7.90) (5)	
	2.00	Vasodepression	5.78 (1.31–25.4) (3)	<0.05
		Bradycardia	28.7 (9.94–82.6) (3)	
Homatropine	0.28	Vasodepression	2.72 (1.34–5.52) (3)	>0.05
		Bradycardia	1.90 (0.95–3.78) (3)	
	2.80	Vasodepression	24.7 (7.36–82.9) (3)	>0.05
		Bradycardia	13.9 (0.25–779) (3)	

* Significance of the difference between dose-ratios obtained with the one dose of antimuscarinic for vasodepression and bradycardia produced by carbachol.

Guinea-pig atria and rabbit atria

Stercuronium (1 to 300 μM) causes parallel shifts of the concentration-response curves for the negative inotropic response to a number of cholinomimetics including CCh and acetylcholine (ACh) in guinea-pig atria (Li & Mitchelson, 1978a, b). As stercuronium causes greater inhibition of the bradycardia than of the vasodepression produced by CCh, the effectiveness of stercuronium on the negative chronotropic response to the agonist was also determined.

Stercuronium (3 μM) produced parallel shifts of concentration-response curves for the negative chronotropic response to CCh and similar dose-ratios to those obtained for the negative inotropic response (Table 2).

In rabbit atria stercuronium (10 μM) was 2.5 fold less effective than in guinea-pig atria as an inhibitor of negative inotropic responses to CCh (Table 2).

Guinea-pig ileal longitudinal muscle

Stercuronium (10 or 100 μM) or homatropine (10 or 300 μM) produced parallel shifts of the concentration-response curves to CCh with no depression of maximal responses to the agonist. The dose-ratios obtained with stercuronium were not affected by the presence of mecamylamine (25 μM) (Figure 1, Table 3). Slopes of the A–S plots based on the 2 data points obtained for homatropine and stercuronium were 1.0 and 1.1 respectively.

In guinea-pig atria responses to ACh are inhibited by stercuronium less than those to CCh and the A–S plot has a lower slope (Li & Mitchelson, 1978b). In ileum, responses to ACh were not inhibited to a significantly different extent by stercuronium although the slope of the A–S plot (0.7) was significantly less ($P < 0.05$) than the theoretical slope of 1 expected for a competitive antagonist (Figure 1).

Guinea-pig bladder

The antimuscarinic action of stercuronium (10 μM) in bladder was similar to that in ileum and the mean dose-ratio obtained with carbachol as agonist was not affected by the presence of mecamylamine (25 μM) throughout the experiment (Table 3).

Rabbit ear artery

The effect of the antimuscarinic drug was investigated also on prejunctional muscarinic receptors on noradrenergic nerves in the rabbit ear artery.

Stercuronium (10 and 100 μM) did not alter the responses of the ear artery to electrical stimulation but caused parallel rightward shifts of the concentration-response curves for the inhibitory effects of carbachol on responses to electrical stimulation at 2 Hz (Figure 2). Stercuronium (10 μM) produced a similar degree of inhibition of responses to CCh in the ear artery as in the rabbit atria, the dose-ratio obtained for the ear artery preparation being 21.6 (15.3 to 30.5) (8) (mean, 95% confidence limits, *n*).

Gallamine (10 and 100 μM) and homatropine (10 and 100 μM) were also investigated in this preparation and produced similar effects to stercuronium (Figure 2). Slopes of the A–S plots based on the dose-ratios obtained with the two concentrations of each antagonist were 0.86 (gallamine), 0.88 (homatropine) and 0.69 (stercuronium) (Figure 3).

Cat anococcygeus muscle

In preliminary experiments it was found that CCh in

Table 2 Dose-ratios obtained with stercuronium (Sterc) (3 or 10 μM) in guinea-pig or rabbit atria with carbachol (CCh) as agonist

Response to CCh	*Tissue*	*Conc of Sterc (μM)*	*Geometric mean dose-ratio (n) (95% confidence limits)*
Negative inotropic	Guinea-pig left atrium	3	17.0 (3) (12.6–22.9)
		10	48.8 (12)* (40.7–58.7)
	Rabbit left atrium	10	19.2 (4) (16.8–21.8)
Negative chronotropic	Guinea-pig right atrium	3	15.3 (5) (11.1–21.0)

* Li & Mitchelson (1978b).

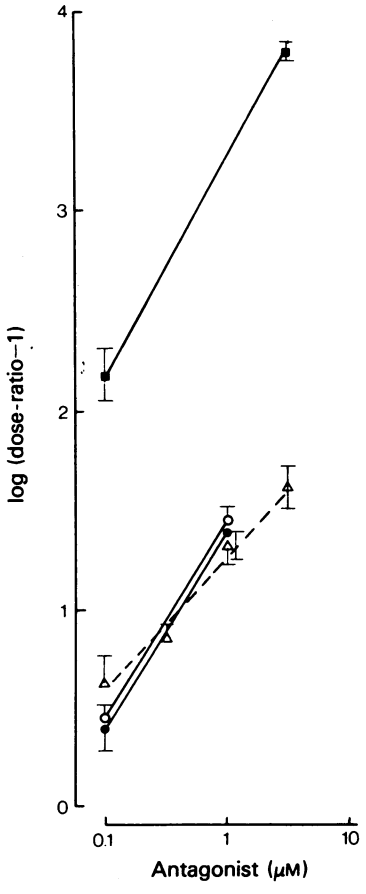

Figure 1 Arunlakshana-Schild plots of log (dose-ratio −1) versus log concentration of antagonist for the effect of homatropine on responses to carbachol (■) (n = 3) and for the effect of stercuronium on responses using carbachol (○) (n = 6), carbachol plus mecamylamine (25 μM) (●) (n = 6) or acetylcholine (△----△) (n = 3 to 5) in guinea-pig ileal longitudinal muscle.

low concentrations (1 to 10 μM) produced contraction of preparations while relaxation or biphasic responses of contraction followed by relaxation occurred with higher concentrations (up to 2 mM). The contraction was abolished by hexamethonium (20 μM) and was not affected by atropine whereas the relaxation was inhibited by atropine. To increase the magnitude of the relaxation response to CCh and inhibit the contractile phase, preparations were contracted by noradrenaline and responses to CCh obtained in the presence of hexamethonium (20 μM). Atropine (10 nM) or gallamine (30 μM) caused parallel shifts of the concentration–response curve to CCh. The geometric mean dose-ratio [95% confidence limits (n)] obtained using atropine was 19.1 [5.12–71.3 (6)] and with gallamine was 7.50 [2.29–24.6 (6)].

Discussion

Stercuronium was found to be a more effective antagonist of cardiac post-junctional muscarinic receptors in the guinea-pig than of other types of muscarinic receptors. Thus *in vivo* stercuronium was significantly more effective in inhibiting the bradycardia induced by CCh than the vasodepressor response. Marshall (1973) found the vasodepressor response to methacholine in the cat was unaffected by stercuronium in doses which inhibited the bradycardia and similar findings have been made with gallamine (Riker & Wescoe, 1951) although no quantitative data were reported in either case. In the guinea-pig the relative effectiveness of stercuronium in inhibiting the two types of response to CCh was dose-dependent. With a dose of stercuronium of 0.2 μmol/kg there was a 2 fold difference in the dose-ratios whereas with a 10 fold higher dose the difference was 5.8 fold. Resting blood pressure was lowered by the higher dose of stercuronium but this should reduce the sensitivity of the animal to vasodepressor agents and thus enhance any antimuscarinic activity of stercuronium. In con-

Table 3 Dose-ratios obtained with stercuronium (10 μM) using carbachol (CCh) as agonist in the ileum and bladder of the guinea-pig

Tissue	*Mecamylamine* (25 μM)	*Geometric mean dose-ratio* (n) (*95% confidence limits*)
Ileum	−	3.90 (6) (2.73–5.57)
	+	3.59 (6) (1.86–6.92)
Bladder	−	3.92 (3) (2.13–7.19)
	+	3.95 (3) (1.68–9.26)

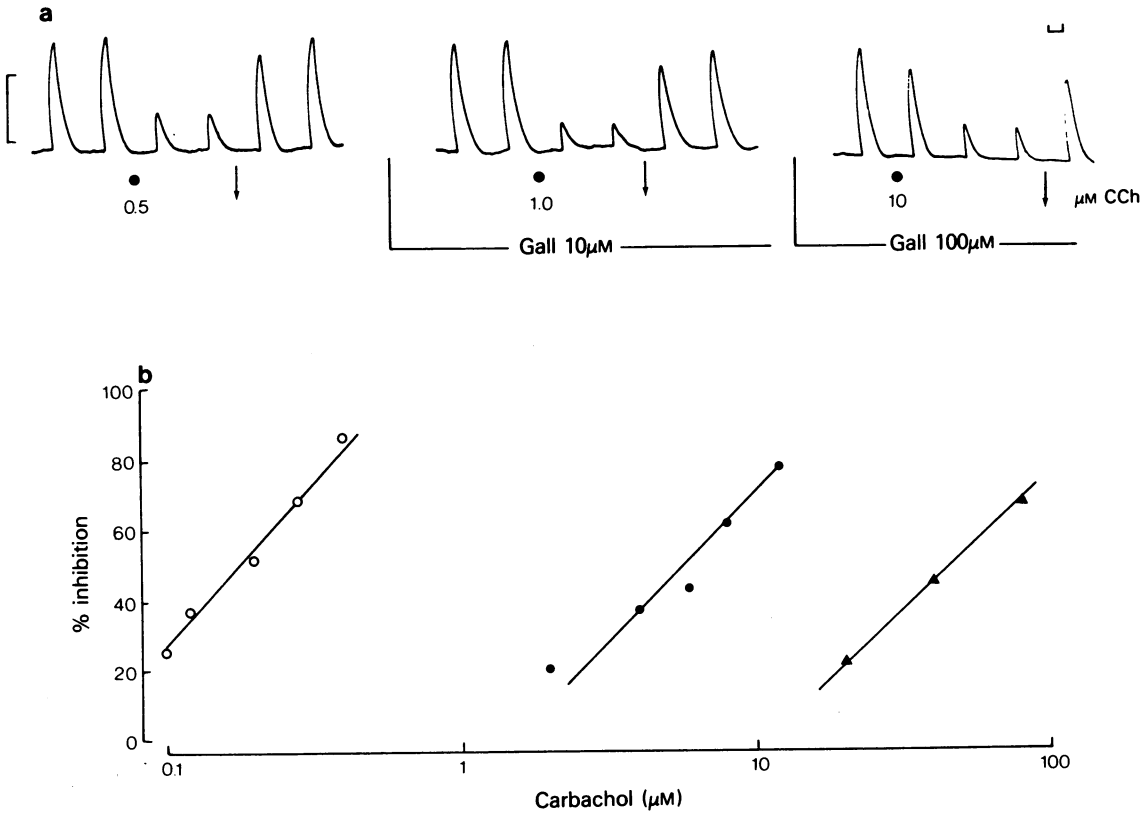

Figure 2 (a) Illustration of the effect of carbachol (CCh) on responses of the rabbit ear artery preparation to periarterial stimulation in the absence or presence of gallamine (Gall) 10 or 100 μM. Vertical bar on left of record indicates pressure change of 20 mmHg (2.6 kPa). Time mark, 1 min. CCh washed out at arrow. (b) Illustration of the concentration-response curve for CCh-induced inhibition of the response of the rabbit ear artery preparation to periarterial stimulation in one experiment in the absence (○) or presence of stercuronium 10 μM (●) or 100 μM (▲).

trast to the findings with stercuronium, homatropine was equi-effective in inhibiting the two types of response to CCh and exhibited a similar increase in dose-ratio with a 10 fold increase in concentration.

Differences were also found in the affinity of stercuronium for muscarinic sites in isolated tissues. In guinea-pig ileum and bladder the affinity of stercuronium was 16 to 17-fold less than that in atria. These results are comparable with those of Clark & Mitchelson (1976) who found that gallamine was 10 and 44 times less active in ileum and bladder respectively than in atria (Table 4) and those of Saxena & Bonta (1970) who found that pancuronium, another drug with cardioselective antimuscarinic activity, was 4.7 times less active as an antimuscarinic in ileum than in atria. The pK_B value for stercuronium obtained in the investigation of the prejunctional muscarinic receptors on sympathetic neurones of the rabbit ear artery, was also significantly different from that in guinea-pig atria ($P < 0.001$) or ileum ($P < 0.001$) and a similar pattern was observed with gallamine. In contrast, the pK_B value of homatropine in the ear artery experiments did not differ significantly from the value obtained in the ileum although that in atria was significantly different ($P < 0.05$). Steinsland, Furchgott & Kirpekar (1973) found that atropine had a similar affinity for presynaptic inhibitory muscarinic receptors in the rabbit ear artery to that for post-junctional excitatory muscarinic receptors in the rabbit aortic strip (Carrier & Ahlquist, 1976) and rabbit jejunum (Furchgott & Bursztyn, 1967).

Furchgott (1972) considered receptors to be different if the affinity constants or dissociation constants for an antagonist differ by a minimum of 3 fold, pro-

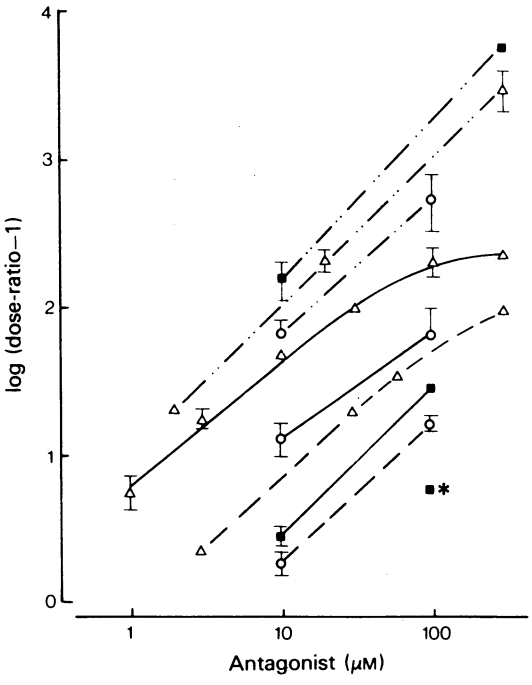

Figure 3 Arunlakshana-Schild plot of log (dose-ratio −1) versus log concentration of antagonist for homatropine (—·—), stercuronium (——), and gallamine (----) in ileum (■), atria (△) and rabbit ear artery preparations (○). Data for homatropine, stercuronium and gallamine on the atria obtained from Li & Mitchelson (1978a). * Data point for gallamine in ileum obtained from Clark & Mitchelson (1976). Where standard errors are not shown they lie within the dimensions of the symbol.

viding experiments were conducted with special precautions, such as the elimination of the uptake or metabolism of agonists and blockade of alternative receptor sites. The affinity constants of stercuronium and gallamine obtained in the ileum and bladder with carbachol as agonist differed more than 3 fold from those in the atria and on sympathetic nerve endings in the ear artery, suggesting differences in muscarinic receptor conformation at the various sites. Use of CCh as the agonist avoids the complications of hydrolysis by cholinesterases and the involvement of nicotinic receptors is unlikely, although stercuronium can inhibit (Marshall, 1973) and CCh can stimulate these receptors. Mecamylamine did not affect the degree of inhibition produced by stercuronium in the ileum or bladder and a similar finding has been reported in atria (Li & Mitchelson, 1978b). The effectiveness of stercuronium in the presence of mecamylamine in the rabbit ear preparation was not evaluated but in this tissue any activation of nicotinic receptors by CCh in the concentrations employed to establish dose-ratios in the presence of stercuronium is most unlikely as very high concentrations of CCh (>0.25 mM) are required to produce sympathomimetic effects by activation of nicotinic receptors in the ear artery (Steinsland & Furchgott, 1975).

The difference in the affinity of stercuronium for the prejunctional muscarinic site in the rabbit ear artery and that in guinea-pig atria, although statistically significant, was small in magnitude and would not be different by Furchgott's (1972) criterion. A small species variation may possibly account for the difference as the affinity of stercuronium for muscarinic receptors in rabbit atria was similar to that in the rabbit ear artery. In general, gallamine exhibited a similar pattern of affinity to stercuronium, being more active at muscarinic sites mediating inhibition although there was a greater difference between its affinity for cardiac muscarinic receptors and those in the ear artery. The general trend in the affinity of gallamine was supported by the findings in the cat anococcygeus muscle (Table 4) where activation of muscarinic receptors causes relaxation of smooth muscle. Comparison of the affinity constants obtained for either homatropine or atropine showed that they are of a similar order to those previously reported in a variety of tissues (Table 4) and confirmed by numerous investigators, indicating that tissue selectivity does not occur for atropine-like compounds.

In atria, the effect of cholinomimetics is to increase potassium permeability, shorten the action potential and cause hyperpolarization of the muscle membrane (Rand & Stafford, 1967). Vanhoutte & Verbeuren (1976) have suggested that in the periarterially stimulated rabbit ear artery, ACh-induced reduction in noradrenaline release is associated with hyperpolarization of the nerve ending. Further, Fozard & Muscholl (1972) have suggested that the muscarinic receptor mediating inhibition of atrial tension or inhibition of the release of noradrenaline in rabbit heart resembles the inhibitory muscarinic receptor on ganglia, rather than that causing ganglionic excitation. It is therefore of interest that Gardier and co-workers (Gardier, Ganansia, Delannois & Hamelberg 1974; Gardier, Tsevdos & Jackson 1978) found gallamine and pancuronium enhanced transmission at the ganglion by selective blockade of the muscarinic site associated with hyperpolarization.

In guinea-pig atria several differences have been noted between the antimuscarinic activity of competitive antagonists such as atropine or homatropine and those of stercuronium (Li & Mitchelson, 1978b) or gallamine (Clark & Mitchelson, 1976) which was attributed to the neuromuscular blocking drugs acting as allosteric antagonists of the metaffinoid type (Ariëns, Simonis & Van Rossum, 1964; Van den Brink, 1977).

Table 4 Comparison of the pK_B values (negative log of the dissociation constants) obtained with various antimuscarinic drugs in different tissues

Tissue	*Stercuronium* pK_B	Δ	*Gallamine* pK_B	Δ	*Homatropine* pK_B	Δ	*Atropine* pK_B	Δ
Guinea-pig								
Atria (force)	6.68 ± 0.03†† (12)	1.0	5.74† (6)	1.0	7.01 ± 0.04†† (7)	1.0	9.21 ± 0.01††† (6)	1.0
Atria (rate)	6.68 ± 0.05 (5)	1.0	5.83† (6)	1.3	—			
Ileal longitudinal muscle	5.45 ± 0.06 (6)	17.0	4.73† (3)	10.2	7.16 ± 0.14 (3)	1.4	9.26 ± 0.05* (4)	1.1
Bladder	5.46 ± 0.09 (3)	16.6	4.10† (3)	43.7	—			
Rabbit								
Atria	6.26 ± 0.02 (4)	2.6	—		—			
Ear artery	6.31 ± 0.07 (8)	2.3	5.16 ± 0.08 (5)	3.8	6.77 ± 0.07 (9)	1.7	9.10 ± 0.01** (10)	1.3
Cat								
Anococcygeus muscle	—		5.25 ± 0.20 (6)	3.1	—		9.20 ± 0.22 (6)	1.0

Values shown are the mean ± s.e. mean (n). Also shown (Δ) are the antilogs of the difference between the pK_B value obtained in the guinea-pig atria with those in other tissues. The pK_B values for stercuronium were calculated from dose-ratios obtained with concentrations of 10 μM or lower, for gallamine 100 μM (ear artery) or 30 μM (anococcygeus muscle), using the relationship $K_B = B\ (\text{dose-ratio} - 1)^{-1}$ where B is the concentration of antagonist.
† Clark & Mitchelson (1976). Estimated from dose-ratios quoted with gallamine 0.11 mM.
†† Li & Mitchelson (1978b).
††† Madden & Mitchelson (1975).
* Barlow, Berry, Glenton, Nikolaou & Soh (1976).
** Steinsland *et al.* (1973).

In atria, stercuronium and gallamine produce a non-linear A–S plot which flattens at high concentrations of antagonist (Figure 3). The results obtained in the ear artery are suggestive of a similar effect although in ileum the A–S plot had a slope of unity, similar to competitive antagonists (Figure 3).

In conclusion, both stercuronium and gallamine exhibit selectivity for certain muscarinic sites, the order of selectivity being guinea-pig atria, rabbit atria and ear artery, cat anococcygeus muscle and guinea-pig ileum and bladder, whereas homatropine has a similar affinity at all of the sites examined. These findings suggest that differences exist in the binding of the neuromuscular blocking drugs and of atropine-like drugs at various muscarinic receptors.

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