ACETYLCHOLINE ANTAGONISM OF ADRENERGIC BLOCKING DRUGS

by

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INTRODUCTION

The literature contains indications that adrenaline antagonists inhibit muscarinic actions of acetylcholine, however, this is generally regarded as a weak and unspecific effect, and a quantitative evaluation has rarely been carried out. Employing the isolated guinea pig atrium and ileum, this study shows that phenoxybenzamine is a potent and specific atropine-like agent. Chlorpromazine is less potent than phenoxybenzamine, and other adrenaline antagonists - phentolamine, prosympal, and yohimbine - are even less potent than chlorpromazine.

The work originated from observations that phenoxybenzamine reverses the effect of vagal stimulation on the isolated guinea pig atrium so that stimulation instead of inhibition occurs (Benfey and Greeff, 1961). In addition, phenoxybenzamine was found to inhibit the effect of vagal stimulation on the heart of the spinal dog (Benfey, 1962).

It may be pointed out here that the adrenaline antagonists used in this study antagonize only certain actions of adrenaline. Thus they fail to inhibit sympathomimetic stimulation of the heart and sympathomimetic inhibition of the intestinal tract. In fact, it has been shown that phenoxybenzamine potentiates the effect of sympathetic

nervous stimulation on the isolated rabbit atrium (Hukovic, 1959), facilitates the induction of arrhythmias (automaticity) in the isolated papillary muscle of the cat (Dresel and Duncan, 1961) and potentiates the chronotropic and inotropic actions of noradrenaline on the isolated guinea pig atrium (Benfey and Greeff, 1961). On the other hand, dichloroisoproterenol antagonizes all these sympathomimetic actions.

HISTORICAL REVIEW

1. 2-Hakogenoalkylamines.

The 2-halogenoalkylamines have a very low aqueous solubility, except in the presence of high acidity, and undergo quite rapid decomposition in neutral aqueous solutions to form readily soluble alcohol derivatives, which have no adrenergic blocking action. They may be prepared as stable stock solutions in acidified propylene glycol or alcohol. The chemical structure of two agents of this group, Dibenamine and phenoxybenzamine, is shown in Fig. 1. The adrenergic blocking action of the first of these, Dibenamine, was discovered by Nickerson and Goodman in 1947.

In regard to the anti-acetylcholine action of 2-halogenoalkylamines, Furchgott (1954) reported that Dibenamine inhibited the vasoconstrictor action of acetylcholine on the isolated rabbit aorta. The blockade was 99% effective and lasted a long time. When he incubated the tissue with Dibenamine in the presence of high concentrations of acetylcholine, the inhibition of acetylcholine was only 80%. When he treated the preparation with Dibenamine in the presence of atropine, the inhibition was only 84%. Incubation with adrenaline, histamine, 5-hydroxytryptamine or antagonists of histamine

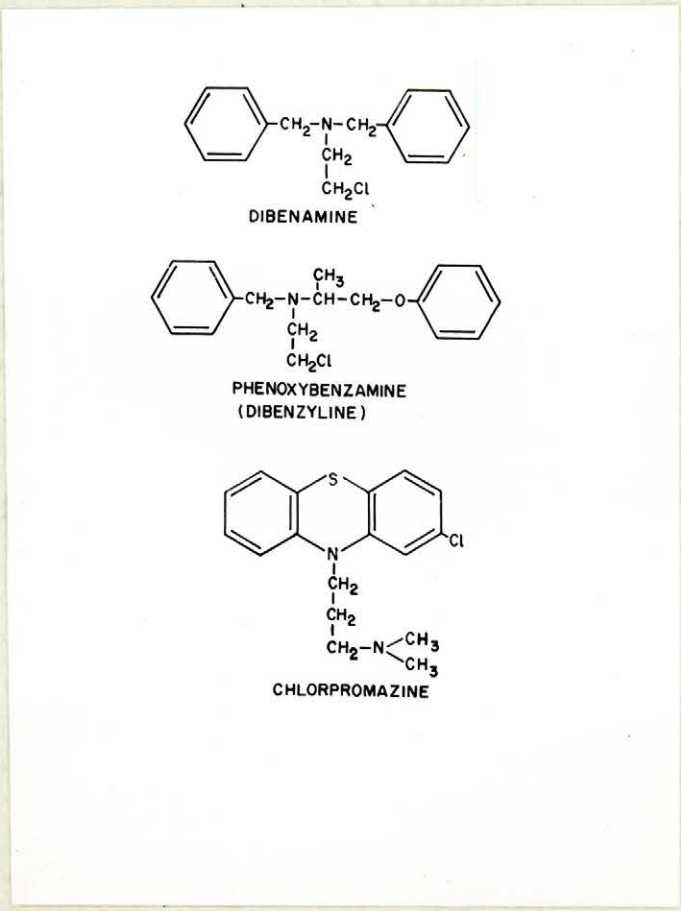

DIBENAMINE
PHENOXYBENZAMINE
(DIBENZYLINE)
CHLORPROMAZINE

Fig. 1

and 5-hydroxytryptamine did not diminish the effect of Dibenamine. Thus Furchgott concluded that Dibenamine exerts a specific and prolonged blockade of cholinergic receptors which is less effective if the receptors are occupied by acetylcholine or by the short-acting antagonist, atropine.

In addition, Furchgott (1954) reported that Dibenamine produces a prolonged blockade of both the stimulating effect of acetylcholine on isolated strips of smooth muscle from rabbit stomach and the inhibitory effect of acetylcholine on isolated rat atria. Furchgott concluded, "Thus it would appear that Dibenamine is an effective parasympathetic blocking agent, although it is considerably less potent as such than as a sympathetic blocking agent."

Graham (1960) measured the acetylcholine antagonism of a new series of 2-halogenoalkylamines on the guinea pig ileum. He found that their potency was weak and not related to their adrenergic blocking activity.

Trendelenburg (1962) reported that phenoxybenzamine reduced the action of acetylcholine on the nictitating membrane of the cat slightly, in contrast to its potent anti-adrenaline effect.

Finally, Innes (1962) reported that phenoxybenzamine inhibits the contractions of isolated strips of cat spleen due to acetylcholine.

2. Chlorpromazine.

The pharmacological actions of this drug were first described extensively by Courvoisier et al. (1953). These authors found that chlorpromazine inhibited the negative chronotropic effect of peripheral vagal stimulation in the anesthetized dog.

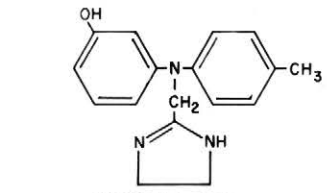
Kopera and Armitage (1954) reported that chlorpromazine has weak anti-acetylcholine actions on the salivary secretion of the cat and on the isolated guinea pig ileum.

Ahmed and Marshall (1962) determined the cholinergic blocking potency of chlorpromazine in the isolated guinea pig ileum. They found that $10^{-5.61}$M chlorpromazine inhibits the effects of acetylcholine 90%.

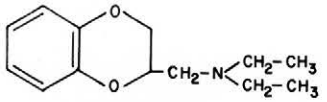
3. Phentolamine.

The adrenergic blocking action of this imidazoline derivative (structure in Fig. 2) was first described by Meier et al., in 1949.

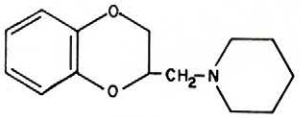
Leimdorfer (1953 a) found that, in dogs in pentobarbital anesthesia, phentolamine alleviated the initial hypotensive phase of nicotinic action. Furthermore, Leimdorfer, 1953 b) phentolamine inhibited the effects of peripheral vagal stimulation on the blood pressure and heart rate of these dogs and converted cardiac arrhythmias induced by high amounts of methacholine to normal rhythm.



PHENTOLAMINE
(REGITINE)



PROSYMPAL
(883F)



PIPEROXAN
(933F)

Fig. 2

4. Prosympal

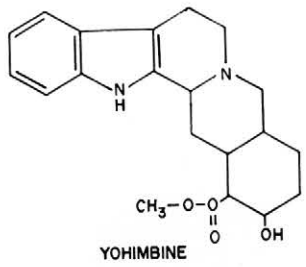
The adrenergic blocking action of the synthetic benzodioxanes, prosympal (883 F) and piperoxan (933 F) was first described by Fourneau and Bovet (1933).

De Vleeschhouwer (1935) found that they inhibit the effect of peripheral vagal stimulation on the heart of anesthetized dogs.

5. Yohimbine

This is an alkaloid whose structure is shown in Fig. 3. Its adrenergic blocking action was first shown by Raymond-Hamet (1925).

Ross (1936) found that yohimbine and piperoxan weakly inhibited the contractile response to acetylcholine of the nictitating membrane of cats under Dial anesthesia. There was a moderate inhibition of the stimulant effects of calcium and potassium and a strong effect on the action of adrenaline.



YOHIMBINE

Fig. 3

METHODS

The isolated guinea pig atrium was prepared by the method of Greeff, Benfey and Bokelmann(1959), but the Tyrode solution contained 10 mg/l of the ganglion-blocking drug, pempidine, to prevent nicotinic effects of high concentrations of acetylcholine. The bath had a capacity of 100 ml and was kept at 28° C unless the room temperature exceeded this value (as in summer). The bath fluid had the following composition:

sodium chloride, 0.8%
potassium chloride, 0.02%
calcium chloride, 0.02%
sodium bicarbonate, 0.1%
sodium monophosphate, 0.005%
dextrose, 0.1%.

The bath was aerated with 5% carbon dioxide in oxygen. The contractions of the atrium were recorded isotonically using a spring lever, with a tension of 1 gm and a magnification of 11.5.

Acetylcholine was added every 10 minutes throughout the experiment and left in the bath for one minute. The heart rate was counted with a stop watch.

Increasing concentrations of acetylcholine produced progressively greater negative inotropic and chronotropic

effects, as illustrated in Fig. 4. The mean dose-response curve for acetylcholine in 32 experiments on the atrium was compared with the curve obtained from a similar number of experiments on the guinea pig ileum (Fig. 5). The two curves were of a similar order of magnitude and slope.

After determining the dose-response curve, antagonists were added to the bath immediately after its change so that the preparation remained in contact with the drug continuously. When the effect of acetylcholine decreased its concentration was increased to obtain approximately 50% inhibition of contractions.

After two hours the drugs were discontinued and the preparation was allowed to recover. As the effect of acetylcholine increased its concentration was reduced. Acetylcholine was given for two hours after withdrawal of the antagonists.

The potency of the antagonists was calculated in terms of the dose ratio by comparing effects of acetylcholine in the presence of antagonist with the initial dose-response curve. The dose ratio (Gaddum et al., 1955) is the ratio of the concentration of the agonist which has a given effect in the presence of antagonist to the concentration of the agonist which has the same effect in the absence of antagonist.

The guinea pig ileum was suspended in 50 ml Tyrode solution containing 10 mg/l of pempidine which was aerated with air. This solution differed from that used for the

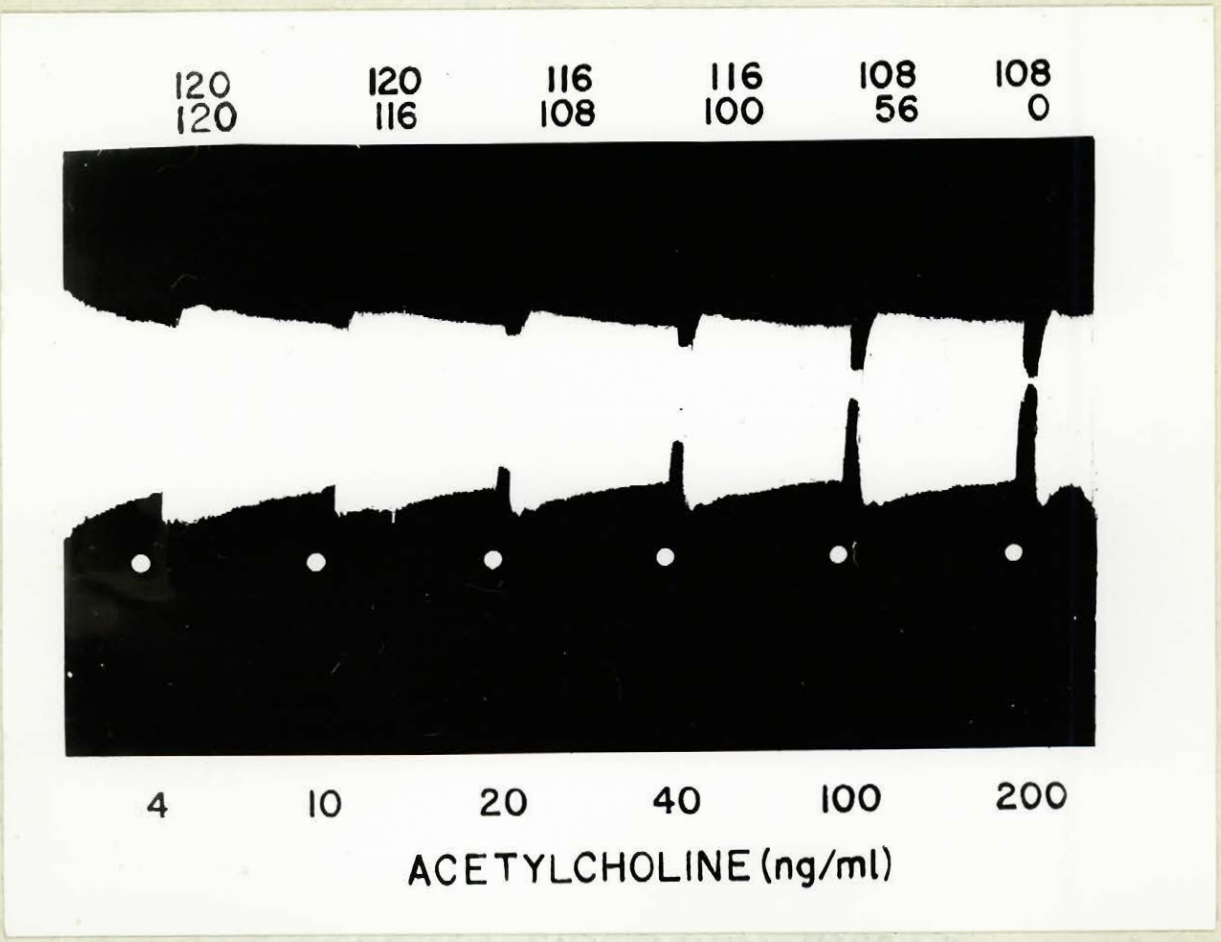


Fig. 4. Effect of acetylcholine on contractions and rate of the isolated guinea pig atrium. Acetylcholine was added every 10 minutes and remained in contact for one minute after which the bath was changed. The numerals at the top of the record show the atrial rate.

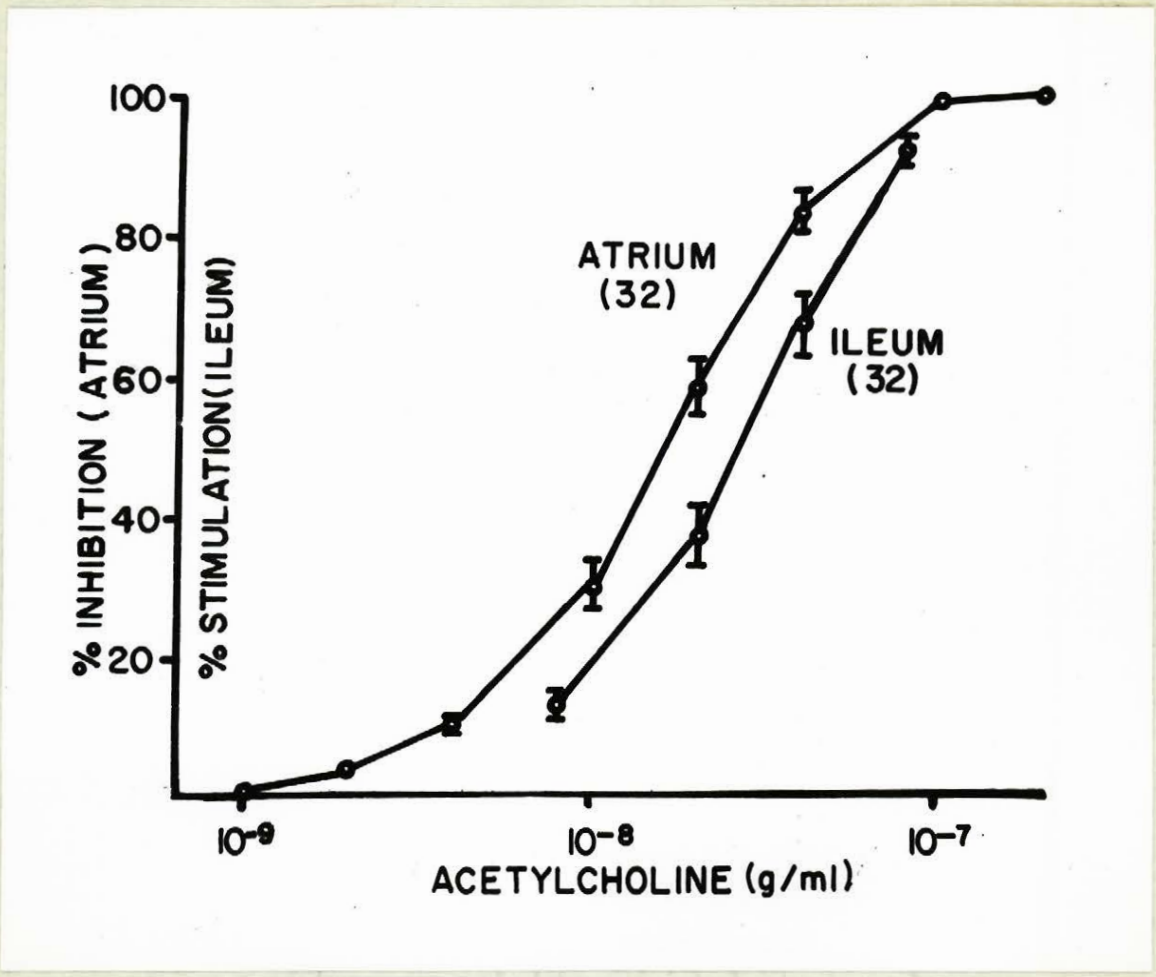


Fig. 5. Dose-response curves for acetylcholine in the isolated guinea pig atrium and ileum. The numerals in parentheses refer to the number of preparations. The vertical bars represent standard errors.

atrium by containing an additional 0.002% of magnesium chloride. The experiments were carried out at the summer room temperature of 29-35° C. The contractions of the gut were recorded with an isotonic lever. Throughout the experiment acetylcholine was added every three minutes and left in the bath until the maximum effect was obtained. The dose-response curve for acetylcholine was determined before and 60 minutes after adding the antagonist. The concentration of acetylcholine causing 50% of the maximum contraction was taken to calculate the dose ratio.

For the quantitative as well as qualitative evaluation of drug antagonism, Schild (1947) introduced the term pA. pA is the negative logarithm to base 10 of the molar concentration of an antagonistic drug which will reduce the effect of a multiple dose (x) of an active drug to that of a single dose. Thus pA_{10} is the negative logarithm of the molar concentration of antagonist which leads to an agonist dose ratio of 10. The pA has often found to depend on the time of contact of the antagonist with the tissue.

The following drugs were used. Atropine sulfate and pempidine tartrate. Phenoxybenzamine (Dibenzyline hydrochloride) was dissolved in 95% ethanol containing 0.005 ml concentrated HCl/ml. The amount of added solution did not exceed 0.02% of the bath fluid. The hydrochlorides of chlorpromazine (Largactil), phentolamine (Regitine), prosympal (883 F) and yohimbine were dissolved in water.

Reserpine (Serpasil) was injected in 1 mg/kg amounts subcutaneously on two days prior to the experiment. Amounts of acetylcholine refer to the bromide.

RESULTS

1. Atropine

Fig. 6 shows that, in the presence of atropine, the dose ratio of acetylcholine increased rapidly, reaching a maximum in 10-30 minutes. When atropine was withdrawn the dose ratio readily returned towards normal. The dose ratios for three concentrations of atropine are given in Table 1.

2. Phenoxybenzamine.

In the presence of phenoxybenzamine, the dose ratio of acetylcholine increased slowly without reaching a maximum in the two hours of contact (Fig. 7). When phenoxybenzamine was withdrawn the dose ratio declined very slowly. Values for the dose ratio are given in Table 2.

The highest concentration used (4.7×10^{-7}M, present for two hours) did not prevent complete inhibition of the atrium by suitable concentrations of acetylcholine, indicating surmountable ("competitive") blockade.

When phenoxybenzamine was added together with atropine there was the same immediate rise in the dose ratio and, when the two antagonists were withdrawn, the same rapid fall (Fig. 7). Thirty minutes after withdrawal

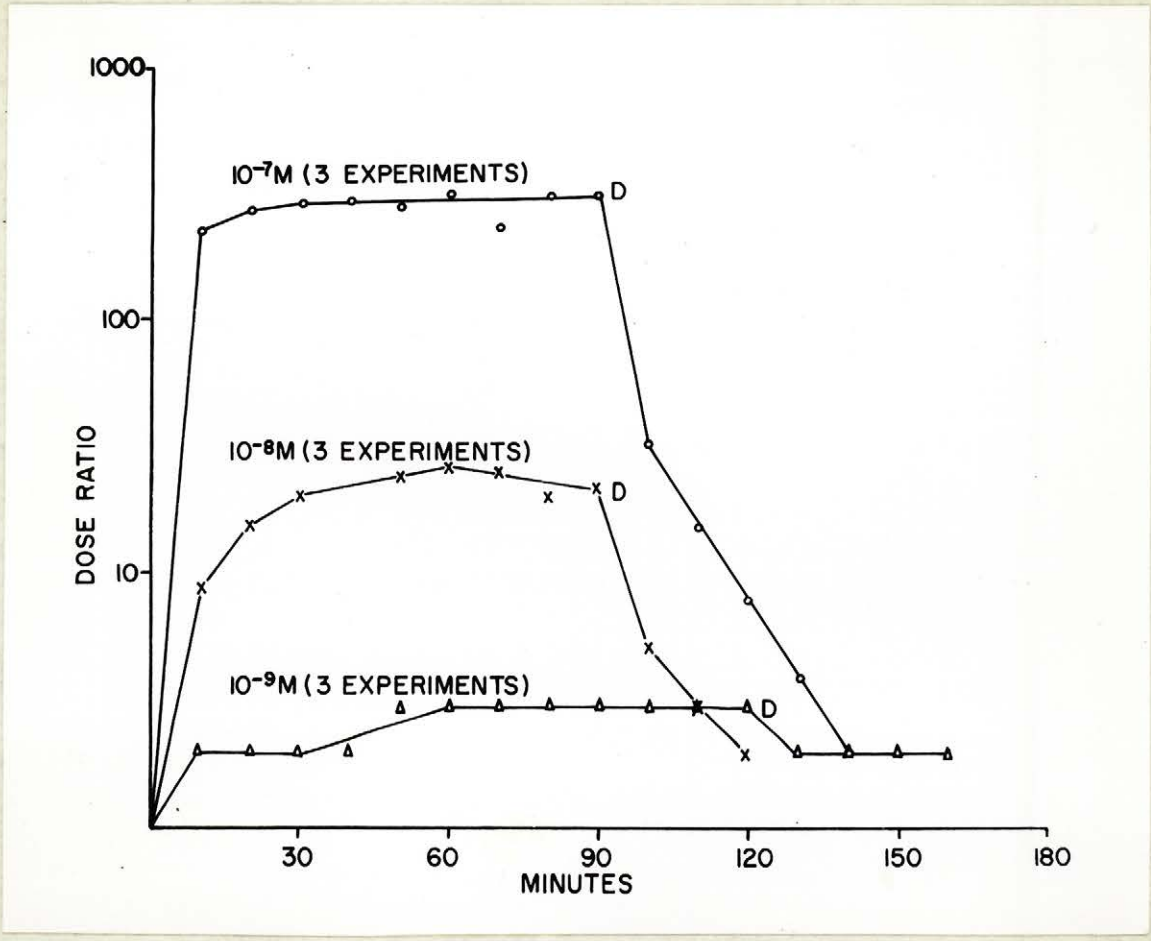


Fig. 6. Relation between dose-ratio of acetylcholine (log scale) and time of exposure to atropine in the isolated guinea pig atrium. Atropine was withdrawn at D.

TABLE 1

Ratio of doses of acetylcholine (± standard error) causing equal negative inoptropic effects on the guinea pig atrium in the presence and absence of atropine. (The number of experiments is given in parentheses).

Molar concentration	Dose ratio	
	1 hr. contact	2 hr. contact
10^{-9}	3 ± .1 (3)	3 ± 1 (3)
10^{-8}	26 ± 8 (3)	22 ± 5 (3)
10^{-7}	323 ± 47 (3)	318 ± 51 (3)

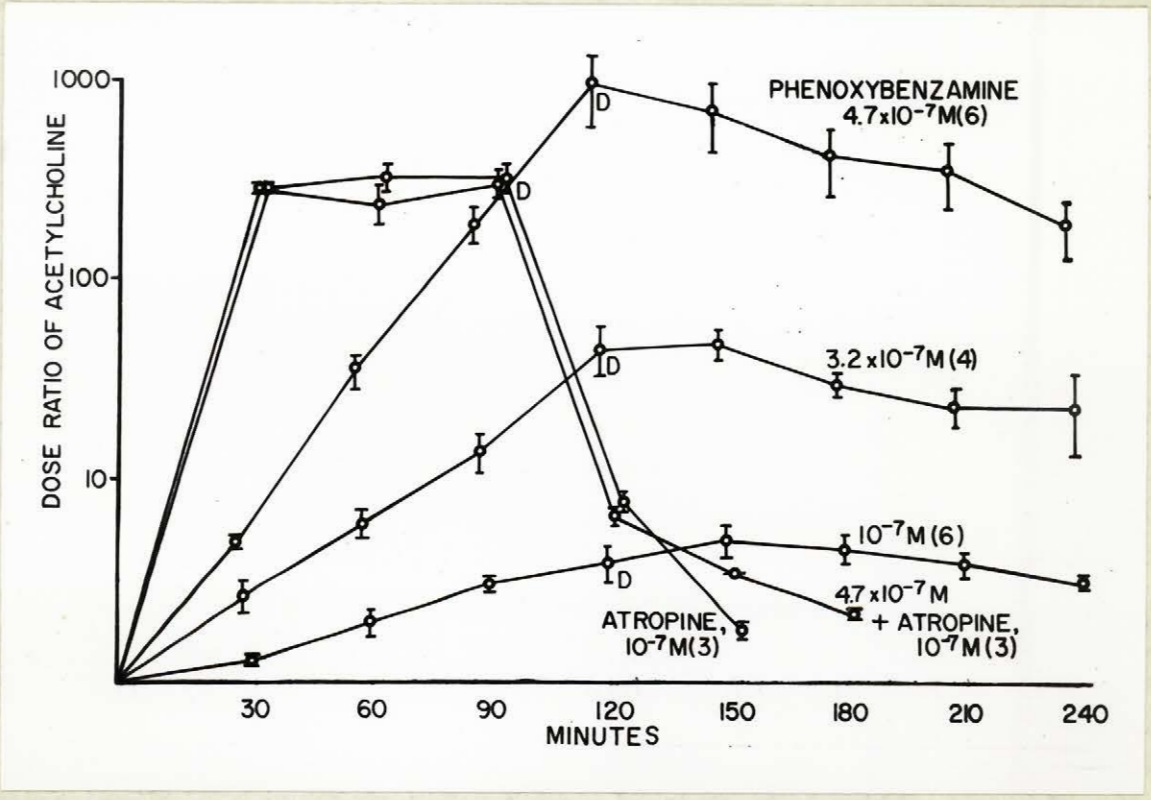


Fig. 7. Relation between dose-ratio of acetylcholine (log scale) and time of exposure to antagonist in the isolated guinea pig atrium. Antagonists were withdrawn at D. The number of experiments is in parentheses and the standard errors are represented by the vertical bars.

TABLE 2

Ratio of doses of acetylcholine (± standard error) causing equal negative inotropic effects on the guinea pig atrium and equal stimulant effects on the guinea pig ileum in the presence and absence of antagonists. (The number of experiments is given in parentheses).

Antagonist	Molar concentration	Dose ratio		
		Atrium		Ileum
		1 hr. contact	2 hr. contact	1 hr. contact
Phenoxybenzamine	10^{-7}	2 ± 0 (6)	4 ± 1 (6)	
"	3.2×10^{-7}	6 ± 1 (4)	46 ± 13 (4)	14 ± 4 (4)
Phenoxybenzamine after reserpine	"	10 ± 2 (5)	59 ± 17 (5)	14 ± 2 (5)
Phenoxybenzamine	4.7×10^{-7}	36 ± 7 (6)	944 ± 363 (6)	37 ± 15 (3)
"	7.6×10^{-7}			388 ± 115 (3)

of the combination of phenoxybenzamine and atropine the dose ratio was significantly lower ($P < 0.05$) than 30 minutes after phenoxybenzamine alone.

Phenoxybenzamine also antagonized acetylcholine on the isolated ileum (Fig. 8). Small concentrations (3.2×10^{-7} M) flattened the slope of the dose-response curve and larger concentrations (7.6×10^{-7} M) depressed its maximum.

Pretreatment of guinea pigs with reserpine did not significantly change the response of the atrium and ileum to acetylcholine or the effect of phenoxybenzamine thereupon. This is evident from Table 2. Fig. 9 shows the dose-response curves for acetylcholine in the atrium and ileum of animals treated with reserpine which were not significantly different from those of normal guinea pigs (Fig. 5).

3. Chlorpromazine.

The effect of chlorpromazine in the atrium developed faster than that of phenoxybenzamine, and a maximum was reached in approximately 90 minutes (Fig. 10). After withdrawal of chlorpromazine the dose ratio declined slowly. When chlorpromazine was combined with atropine the dose ratio was higher than with atropine alone and, when the two antagonists were discontinued, it declined slowly.

The highest concentration of chlorpromazine used (8.4×10^{-6} M, present for two hours) did not prevent complete inhibition of the atrium by acetylcholine, indicating

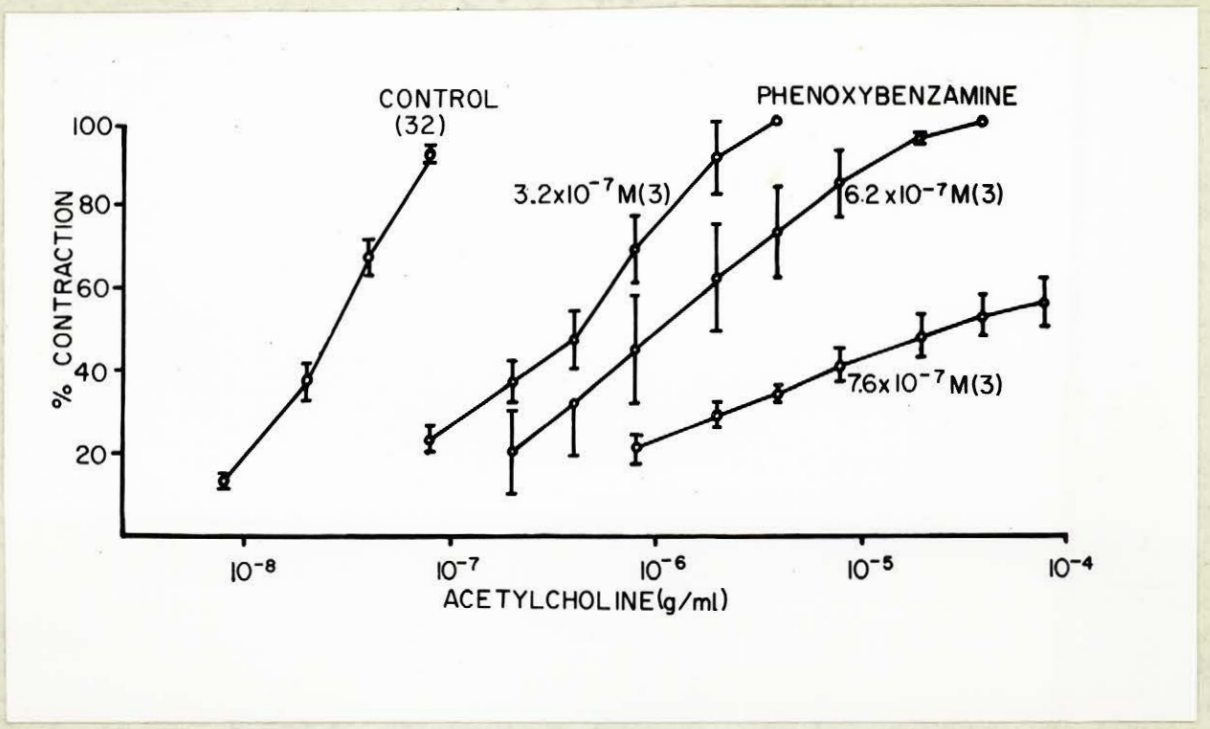


Fig. 8. Dose-response curves for acetylcholine in the isolated guinea pig ileum before and after one hour contact with phenoxybenzamine. The number of experiments is in parentheses and the vertical bars represent standard errors.

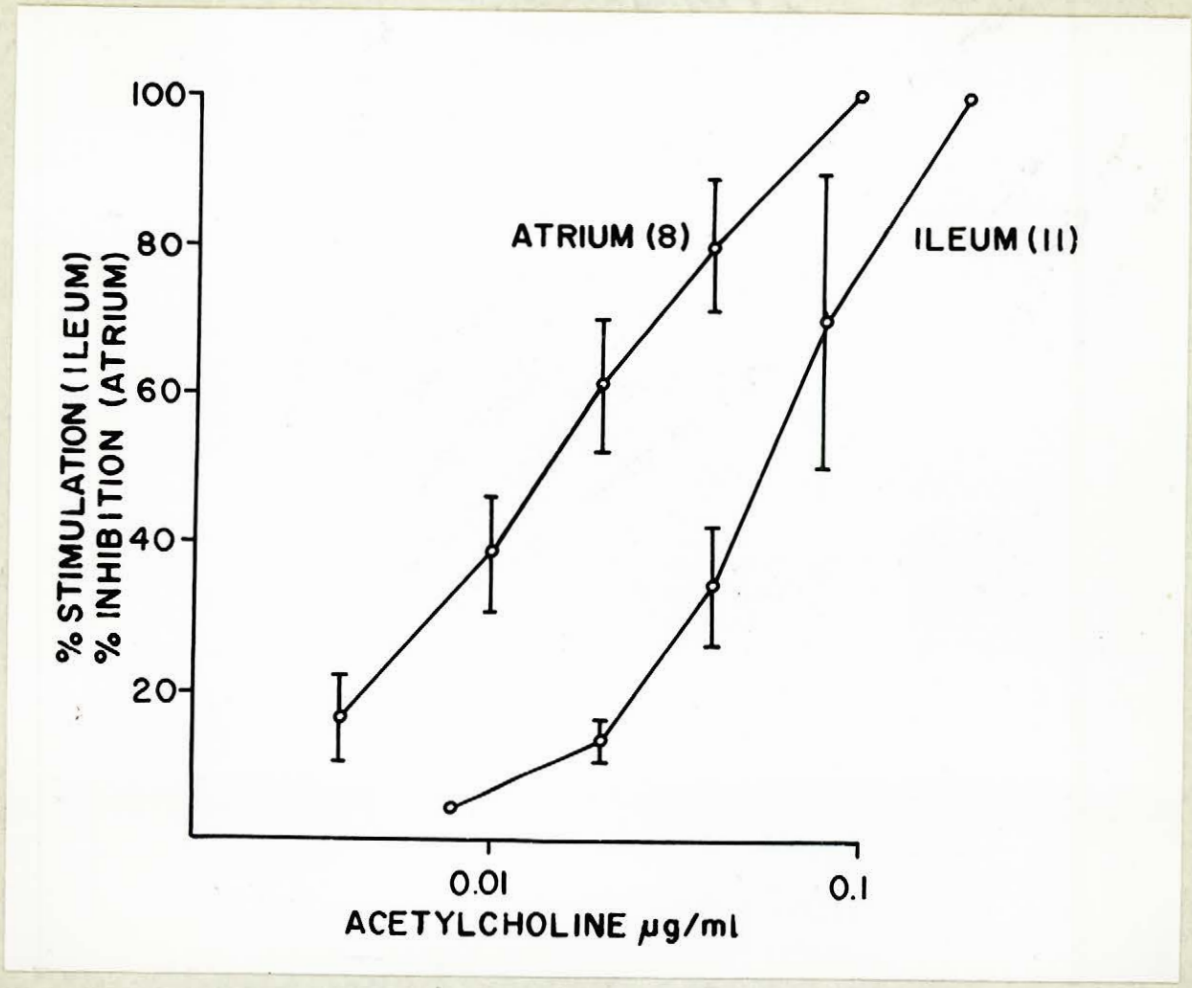


Fig. 9. Dose-response curves for acetylcholine in the isolated guinea pig atrium and ileum pretreated with reserpine. The numerals in parantheses refer to the number of preparations. The vertical bars represent standard errors.

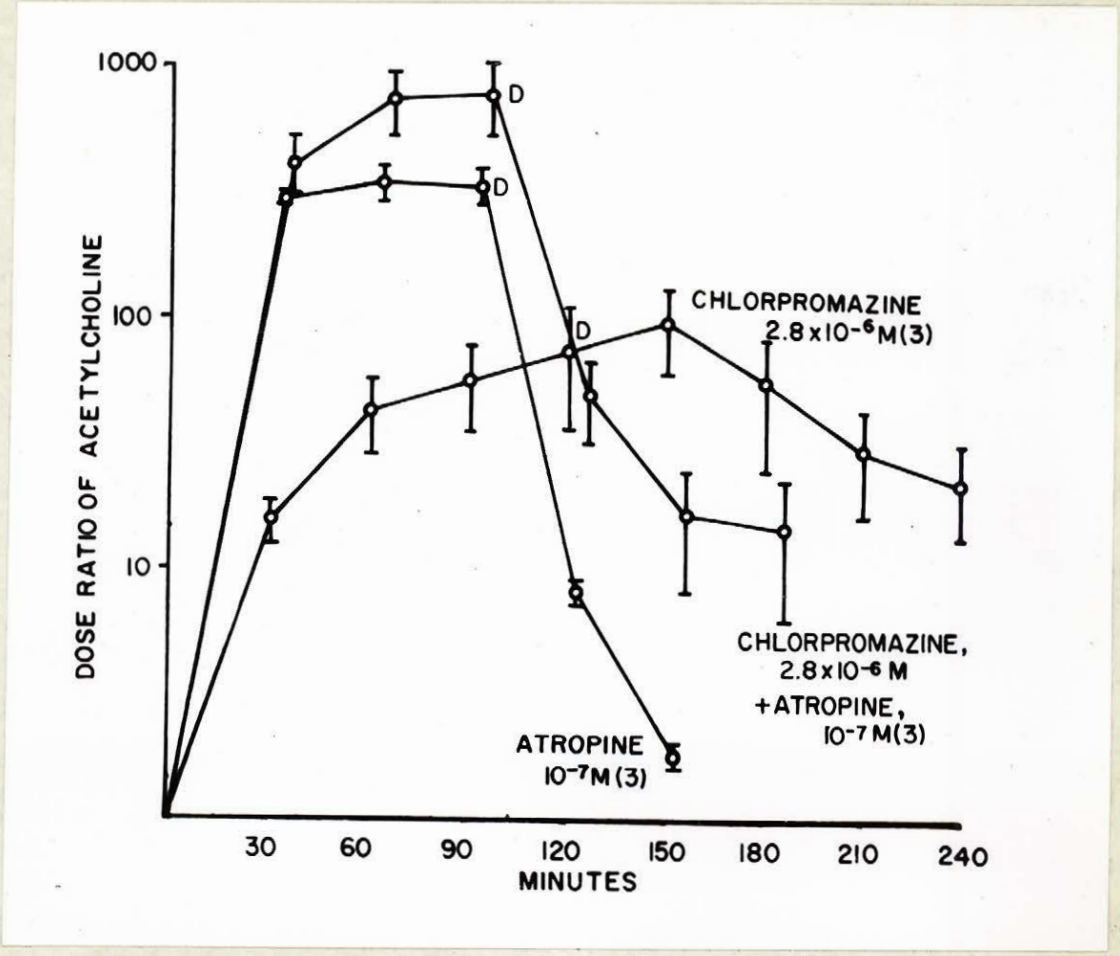


Fig. 10. Relation between dose ratio of acetylcholine (log scale) and time of exposure to antagonist in the isolated guinea pig atrium. Antagonists were withdrawn at D. The number of experiments is in parantheses and the standard errors are represented by the vertical bars.

surmountable blockade.

In the ileum a small concentration of chlorpromazine (5.6×10^{-7} M) did not change the slope of the dose-response curve, while a larger concentration (2.3×10^{-6} M) flattened it and a very large concentration (4.5×10^{-6} M) depressed its maximum below 50% (Fig. 11).

The dose ratios of acetylcholine in the presence of chlorpromazine are given in Table 3.

Fig. 12 correlates the molar concentrations of atropine, phenoxybenzamine and chlorpromazine with the dose ratio of acetylcholine. The values for atropine in the ileum were taken from Schild (1947) and Arunlakshana and Schild (1959). This plot was used to obtain the pA_{10} values given in Table 4. This table shows that phenoxybenzamine was approximately 40 times less potent than atropine, and chlorpromazine approximately ten times less potent than phenoxybenzamine.

4. Phentolamine, yohimbine and prosympal.

These inhibited acetylcholine in the atrium and ileum but required higher concentrations than chlorpromazine. The dose ratios are given in Table 5.

In the atrium the drugs had a slow onset of action and their effect was slowly reversible. A higher concentration of yohimbine (1.5×10^{-4} M) inhibited the contractions of the atrium. In the ileum there was no change in the slope of the dose-response curve following one hour exposure to phentolamine, yohimbine, or prosympal.

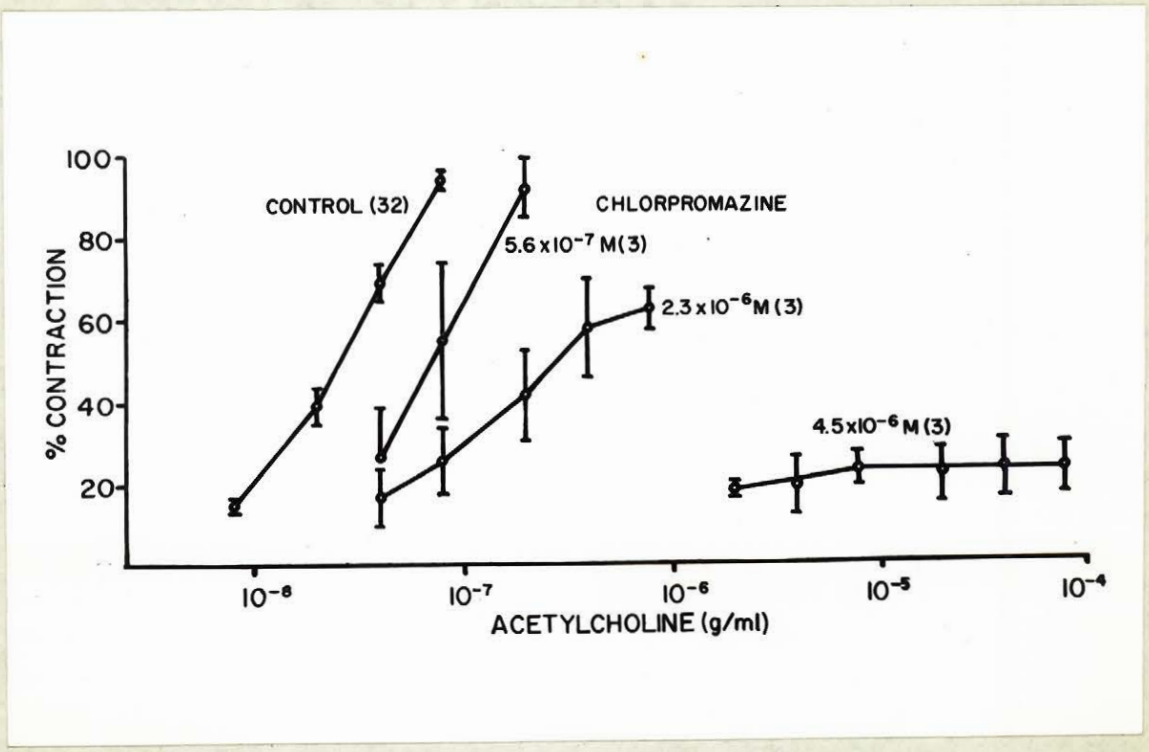


Fig. 11. Dose-response curves for acetylcholine in the isolated guinea pig ileum before and after one hour contact with chlorpromazine. The number of experiments is in parantheses and the vertical bars represent standard errors.

TABLE 3

Ratio of doses of acetylcholine (± standard error) causing equal negative inotropic effects on the guinea pig atrium and equal stimulant effects on the guinea pig ileum in the presence and absence of chlorpromazine. (The number of experiments is in parentheses).

Molar Concentration	Dose ratio		
	Atrium		Ileum
	1 hr. contact	2 hr. contact	1 hr. contact
5.6×10^{-7}			4 ± 1 (3)
8.4×10^{-7}	4 ± 1 (3)	5 ± 2 (3)	
2.3×10^{-6}			27 ± 12 (3)
2.8×10^{-6}	41 ± 14 (3)	71 ± 37 (3)	
8.4×10^{-6}	244 ± 91 (3)	756 ± 219 (3)	

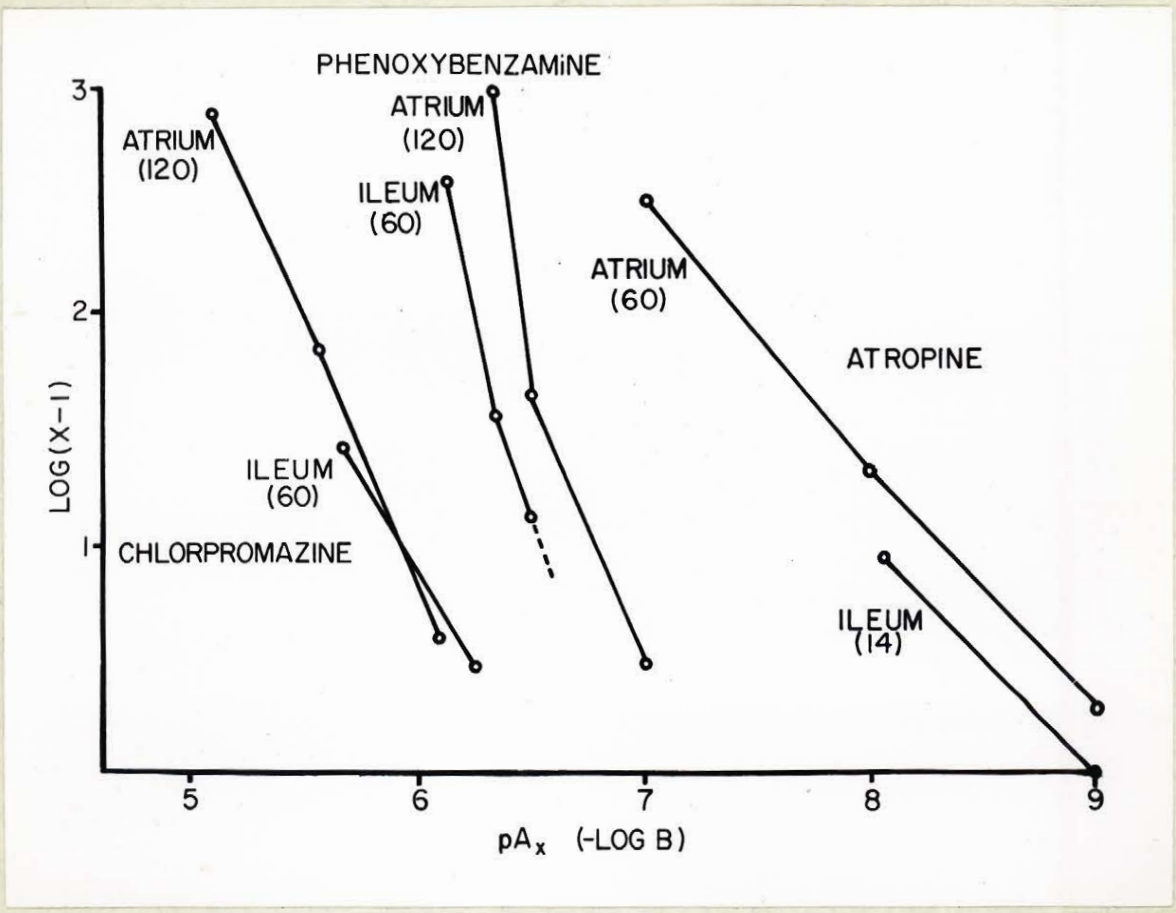


Fig. 12. Relation between the negative logarithm of the molar concentration of antagonist (pA_x) and the logarithm of the dose-ratio of acetylcholine minus 1 (log X-1). The numbers in parentheses are minutes of exposure to antagonist. The pA_x values for atropine in the experiments on the ileum were taken from Schild (1947) and Arunlakshana and Schild (1959).

TABLE 4

pA_{10} values with acetylcholine in the isolated guinea pig atrium and ileum.

Antagonist	Preparation	Time of contact (min.)	pA_{10}
Atropine	atrium	60	8.4
Atropine (Schild, 1947)	ileum	14	8;1
Phenoxybenzamine	atrium	60	6.4
Phenoxybenzamine	atrium	120	6.8
Phenoxybenzamine	ileum	60	6.6
Chlorpromazine	atrium	60	5.8
Chlorpromazine	atrium	120	5.9
Chlorpromazine	ileum	60	5.9

TABLE 5

Ratio of doses of acetylcholine (± standard error) causing equal negative inotropic effects on the guinea pig atrium and equal stimulant effects on the guinea pig ileum in the presence and absence of antagonists. (The number of experiments is given in parentheses).

Antagonist	Molar concentration	Dose ratio		
		Atrium		Ileum
		1 hr. contact	2 hr. contact	1 hr. contact
Phentolamine	3.1×10^{-5}	19 ± 7 (4)	32 ± 16 (4)	5 ± 1 (3)
Yohimbine	5.1×10^{-5}	3 ± 1 (2)	3 ± 2 (2)	
"	1.5×10^{-4}			3 ± 1 (2)
Prosympal	7.8×10^{-5}			3 ± 1 (2)
"	1.6×10^{-4}	18 ± 4 (3)	19 ± 5 (3)	

DISCUSSION

The anti-acetylcholine potency of all adrenergic blocking drugs evaluated in this study was not related to their anti-adrenaline potency. This was also shown for certain 2-halogenoalkylamines by Graham (1960).

The pA_{10} of atropine in the guinea pig atrium (8.4) was similar to that in the frog atrium (8.3) which was determined by Clark and Raventos (1937). Arunlakshana and Schild (1959) observe "that the pA_{10} values of atropine in different preparations, such as guinea pig ileum, rat intestine, perfused guinea pig lung and frog atrium, are on the whole remarkably similar" (7.6 - 8.3). They conclude "The finding that different tissues have receptors with similar affinities for antagonists is interesting since it gives support to the notion that receptors are definite chemical entities."

Ahmed and Marshall (1962) found the pA_{10} of chlorpromazine in the guinea pig ileum to be 5.61 (our value was 5.9). They do not give the time of contact, but it appears to be 14 minutes, similar to that of Arunlakshana and Schild (1959), which would explain their lower pA value. As we have shown on the atrium, the onset of action of chlorpromazine is slow. Our time of contact with the ileum was 60 minutes.

It is interesting that the slow onset and long duration of the antagonism of acetylcholine by phenoxybenzamine are also characteristics of its antagonism to adrenaline. Furthermore, the related drug, Dibenamine, has a slow onset and long persistence of action against 5-hydroxytryptamine in the rat uterus (Gaddum, Hameed, Hathway and Stephens, 1955), against acetylcholine, histamine, and 5-hydroxytryptamine in isolated strips of rabbit aorta, and against acetylcholine in isolated strips of rabbit stomach and isolated rat atria (Furchgott, 1954). Another 2-halogenoalkylamine, GD-121, exerts a prolonged antihistamine effect in the guinea pig ileum (Nickerson, 1956).

It may be worth mentioning that the concentrations of phenoxybenzamine used in this study did not inhibit stimulation of the atrium by histamine or calcium and were approximately 100 times smaller than those needed to potentiate stimulation by noradrenaline (Benfey and Greeff, 1961).

Phenoxybenzamine probably acts at sites which are protected by atropine, as it did not exert a slowly reversible antagonism in the presence of atropine. Such a protective action of atropine has been previously shown by Furchgott (1954) who found that atropine protected the isolated rabbit aorta against the prolonged effects of Dibenamine. Thus phenoxybenzamine probably exerts a specific acetylcholine antagonism, a fact which should be considered when employing the drug for its usual adrenaline antagonism.

SUMMARY

Phenoxybenzamine exerted an antagonism of the inhibitory action of acetylcholine on the isolated guinea pig atrium, which was slow in onset, very slowly reversible, and could be overcome with increasing concentrations of acetylcholine. In contrast, atropine inhibited acetylcholine quickly, and the effect disappeared soon after withdrawal.

The pA_{10} of phenoxybenzamine (two-hour contact) was 6.8, that of atropine (30-minute contact) 8.4.

In the presence of atropine phenoxybenzamine did not exert a slowly reversible antagonism, and the dose ratio of acetylcholine returned to normal soon after withdrawal of both drugs.

Phenoxybenzamine also antagonized acetylcholine in the isolated guinea pig ileum, but with higher concentrations acetylcholine could not overcome the antagonism.

The pA_{10} (60-minute contact) was 6.6.

The pA_{10} of chlorpromazine in the atrium (2-hour contact) and ileum (60-minute contact) was 5.9.

Phentolamine, prosympal, and yohimbine antagonized acetylcholine in the atrium and ileum but required higher concentrations than chlorpromazine.

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