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AN INVESTIGATION OF THE ADRENERGIC BLOCKING ACTION OF CHLORPROMAZINE

BY

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Antagonism by chlorpromazine of the responses of the rabbit aortic strip and the rat seminal vesicle to adrenaline and noradrenaline fulfils the conditions of competitive antagonism. Chlorpromazine was a remarkably potent antagonist (pA_2 approximately 14) of adrenaline and noradrenaline. In the cat anaesthetized with chloralose small doses (1.8 to 4.5 mg/kg) of chlorpromazine greatly reduced or reversed the pressor effect of adrenaline but the pressor effect of noradrenaline was unaffected. A larger dose (9 mg/kg) of chlorpromazine slightly reduced the pressor effect of noradrenaline but caused a spectacular reversal of the pressor effect of adrenaline. This difference was not observed in rabbits and in cats treated with dichloroisoprenaline. Chlorpromazine potentiated the depressor effect of isoprenaline. On the basis of these findings it is concluded that in the cat chlorpromazine in small doses (1.8 to 4.5 mg/kg) has no real adrenergic blocking action and that the selective block of adrenaline pressor effects by these doses is due to a potentiation of adrenergic vasodilatation. Large doses (7.2 to 28.8 mg/kg) of chlorpromazine reduced the pressor effect of noradrenaline; reciprocal analysis showed that this inhibition is competitive.

Courvoisier, Fournel, Ducrot, Kolsky & Koetschet (1953) were the first to describe the inhibitory effect of chlorpromazine on pressor responses to adrenaline and noradrenaline. Since then chlorpromazine has been repeatedly claimed to exert an adrenergic blocking effect in animals of a number of species (Kopera & Armitage, 1954; Martin & Riehl, 1956; Martin, Riehl & Unna, 1960). However, a careful review of the literature reveals that, while chlorpromazine markedly and consistently reduces the pressor effect of adrenaline, the pressor response to noradrenaline is either unaffected or actually potentiated (Martin & Riehl, 1956; Martin *et al.*, 1960; Gokhale, Gulati & Kelkar, 1963). Thus the characterization of chlorpromazine as an adrenergic blocking agent rests primarily on its ability to diminish or reverse the pressor effect of adrenaline. No adequate explanation of this paradoxical property of chlorpromazine in selectively blocking the pressor effect of adrenaline is available at present.

Recently Martin *et al.* (1960) reported a large and prolonged inhibition of the responses of the rabbit aortic strip to adrenaline and noradrenaline following chlorpromazine and characterized the drug as a long-acting adrenergic blocking agent. However, information regarding the antagonistic potency of chlorpromazine and the precise nature of its antagonism of adrenergic effects is still lacking. The present work was undertaken to characterize further, and to measure, the adrenergic blocking

action of chlorpromazine and also to elucidate the selective block of the pressor effect of adrenaline by chlorpromazine.

METHODS

Rabbit aortic strip preparation

Strips were obtained from the thoracic aorta of young rabbits and prepared in the manner described by Furchgott & Bhadrakom (1953). Spirally cut aortic strips approximately 3.5 cm in length were placed in a 30 ml. organ-bath and tied to an isotonic frontal writing lever that placed the muscle under 4 g of tension in the horizontal equilibrium position. The bathing solution was Krebs-bicarbonate solution of the following composition (g/l. of distilled water): NaCl 6.88, KCl 0.42, anhydrous $CaCl_2$ 0.28, anhydrous $MgCl_2$ 0.112, $NaHPO_4$ 0.18, $NaHCO_3$ 2.1 and dextrose 1.8. The solution was maintained at 37 to 38° C, and 5% carbon dioxide in oxygen was bubbled through the solution in both bath and reservoir. The *p*H of the solution now was 7.4. All strips were stretched *in vitro* for 2 hr before study. The lever system employed gave a tenfold magnification.

Dose/response curves (five doses) for adrenaline (0.5×10^{-8} to 7.5×10^{-7}) and noradrenaline (0.41×10^{-8} to 4.1×10^{-7}) were obtained by cumulative administration of increasing concentrations of the amines allowing the contraction to develop fully after each administration. Dose/response relationships for adrenaline and noradrenaline were determined in replicate on each strip before the administration of chlorpromazine. In antagonism studies chlorpromazine was placed in the bath 15 min before administration of a catechol amine and remained in the bath thereafter.

In some experiments the receptor protection technique of Furchgott (1954) was used. For every experiment two strips from the same aorta were suspended each in an individual organ-bath. At the beginning of the experiment, control responses to adrenaline or noradrenaline were obtained from each of the preparations. Both strips were then exposed to the same concentration of chlorpromazine but one was protected throughout the entire period of exposure (6 min) by a high concentration of adrenaline or noradrenaline which was added to the bath 6 min before addition of chlorpromazine. Both the protected and unprotected strips were then repeatedly washed at 15 min intervals for a period of 90 min. Both the preparations were now tested for their sensitivity to adrenaline or noradrenaline by the addition of control doses of the amines at 15 min intervals.

Rat seminal vesicle preparation

Seminal vesicles were obtained from male albino rats weighing between 125 to 150 g and were prepared in the manner described by Leitch, Leibig & Haley (1954). Preparations were suspended in a continuous flow of the bathing medium (Leitch *et al.*, 1954) run at a rate of 15 ml./min and were attached to a balsa-wood frontal writing lever which placed them under a tension of 300 mg. Flow was interrupted when stimulant drugs were added to the bath (10 ml. capacity). The bathing solution was continuously bubbled with 5% carbon dioxide in oxygen.

Adrenaline (1×10^{-8} to 1.6×10^{-5}) or noradrenaline (0.82×10^{-8} to 0.82×10^{-5}) was added at 6 min intervals and the response was recorded for 30 sec. Four to five doses were used to construct a dose/response curve. In antagonism studies the preparations were perfused with solutions containing different concentrations of chlorpromazine and dose/response curves for the amines were redetermined 15 min after change of perfusion fluid.

Cat blood pressure

The cats used were of either sex and weighed between 2.5 and 3.6 kg. Anaesthesia was induced by ethyl chloride and maintained with an intravenous injection of chloralose (80 mg/kg). Arterial blood pressure was recorded with a mercury manometer connected to a common carotid artery. Drugs were injected through a polyethylene cannula inserted into a femoral vein.

Rabbit blood pressure

Rabbits were anaesthetized with urethane (1.5 g/kg, subcutaneously) and blood pressure was recorded with a mercury manometer connected to a common carotid artery; drugs were injected through a polyethylene cannula inserted into a jugular vein.

Statistical methods used for regression analysis and for analysis of variance were those described by Burn, Finney & Goodwin (1952).

The drugs used were: chlorpromazine hydrochloride, hexamethonium chloride, cocaine hydrochloride, isoprenaline sulphate, dichloroisoprenaline hydrochloride, (±)-noradrenaline hydrochloride and (−)-adrenaline. All doses are expressed in terms of the base.

RESULTS

Rabbit aortic strip preparation

Antagonism of adrenaline and noradrenaline responses. Cumulative administration of increasing concentrations of adrenaline or noradrenaline elicited increasing contractile responses from rabbit aortic strips, and, although sensitivity of individual strips to the amines varied somewhat, a statistically linear dose/response relationship was obtained when effect (percentage of maximal contraction) was plotted against log dose of the stimulant drugs. In individual experiments the height of maximal contraction was first determined by the cumulative addition of increasing concentrations of the amines and then the preparation was repeatedly washed for 90 min. Cumulative dose/response curves for adrenaline or noradrenaline (usually three to four and with responses between 20 and 80% of the maximal) were now determined at 60 min intervals until the last two curves were closely similar both with respect to heights of responses to successive additions of the amines and the height of the total response. There was no evidence of desensitization. In fact sensitivity of the strip to the amines increased during the first two determinations. When two successive dose/response curves were alike, the preparation was rested for 45 min and then exposed to chlorpromazine for a further 15 min before addition of amines, so that the interval between two successive determinations was always kept constant. Chlorpromazine caused a parallel shift to the right of the dose/response lines for adrenaline or noradrenaline. The degree of antagonism was expressed in terms of the " dose-ratio " which is the ratio of equiactive doses of the stimulant drug before and after the addition of the antagonist (Gaddum, Hameed, Hathway & Stephens, 1955). The log of the dose-ratio is given by the horizontal distance between the parallel lines. Fig. 1 illustrates the findings of a typical experiment. During an individual experiment the strip was exposed to chlorpromazine only once, and separate experiments were carried out for subsequent determination of the antagonistic potency of the same or a different concentration of chlorpromazine. This procedure, though tedious, yields more reliable results (Schild, 1947). In thirty experiments dose-ratios for five different concentrations of chlorpromazine were determined in triplicate separately with adrenaline and noradrenaline and the mean dose-ratio for each concentration of chlorpromazine was used in further analysis of the results (Table 1). Though the sensitivity of individual strips to the amines varied in different experiments the dose-ratios for a given concentration of chlorpromazine were remarkably alike (Table 1). This

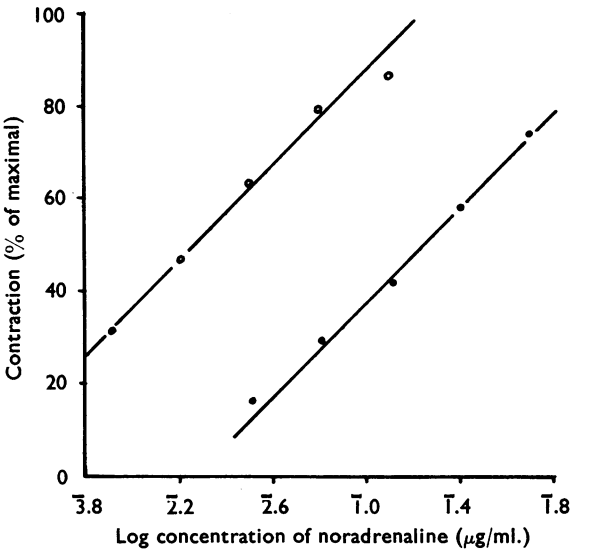

Fig. 1. Rabbit aortic strip preparation: log dose/response curves for noradrenaline alone (○— ○) and in the presence of 3.6×10^{-14} of chlorpromazine (●— ●). Chlorpromazine causes a parallel shift of the dose/response curve to the right and the horizontal distance between the two curves gives the ratio of the doses of noradrenaline causing equal contractions in the presence and in the absence of the inhibitor (chlorpromazine). The dose-ratio was 9.55.

indicates that variation in sensitivity of a tissue to the action of the antagonist is small and is independent of variation in sensitivity to the agonist.

Arunlakshana & Schild (1959) have shown that if an antagonist shifts the dose/response curve of an agonist without altering the slope of the curve (as in the present experiments) then this effect is consistent with competitive antagonism. This, however, does not provide complete proof of competitive antagonism. The present results were, therefore, examined more closely to see whether they fitted the hypothesis of competitive antagonism.

TABLE 1

ANTAGONISM BY CHLORPROMAZINE OF THE RESPONSES OF THE RABBIT AORTIC STRIP AND THE RAT SEMINAL VESICLE TO ADRENALINE AND NORADRENALINE

The degree of antagonism is expressed in terms of the dose-ratio, and means and standard errors are given

Dose of chlorpromazine (g/ml. × 10^{-15})	Dose-ratio			
	Rabbit aortic strip		Rat seminal vesicle	
	Adrenaline	Noradrenaline	Adrenaline	Noradrenaline
0·9	—	1·58±0·13	1·37±0·14	—
1·8	1·54±0·15	—	1·85±0·02	2·00±0·16
3·6	—	—	2·51±0·10	2·77±0·10
4·5	2·18±0·03	2·45±0·09	—	—
7·2	—	—	—	3·73±0·11
9·0	3·75±0·06	3·38±0·05	4·64±0·13	—
18·0	5·92±0·35	5·25±0·14	—	6·26±0·37
36·0	12·77±1·21	9·30±0·42	14·45±0·78	10·36±1·06

The logarithm of (x – 1) was plotted against the negative logarithm of B, where x is the dose-ratio and B the corresponding molar concentration of the antagonist, namely chlorpromazine. The results from six sets of determinations are plotted in Fig. 2 in which the lines are the calculated regression lines. The lines are significantly different from zero ($P<0.001$). The intercepts of these lines with the abscissa (at zero level) gave the pA_2 values for the antagonist. pA_{10} values were determined from the regression lines. The pA_2 value for chlorpromazine in antagonizing responses to adrenaline was 14.0; in antagonizing responses to nor-

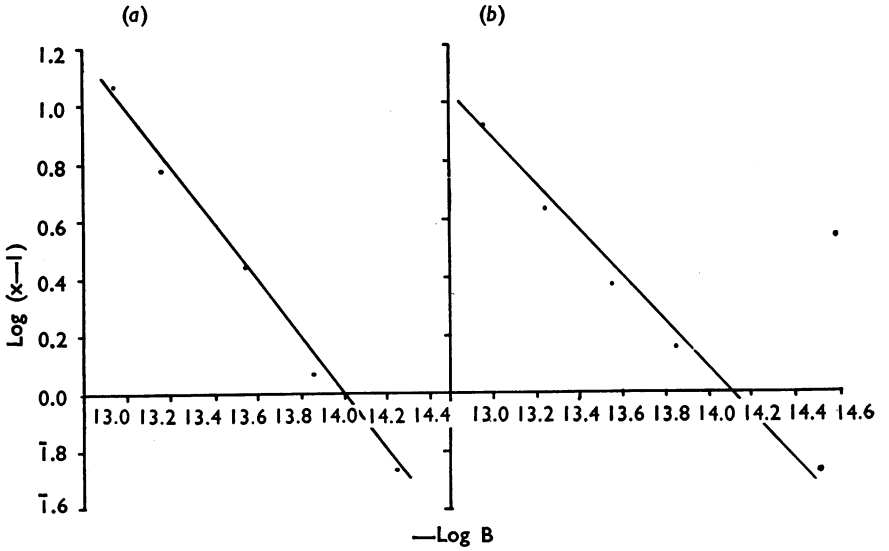

Fig. 2. Results with a rabbit aortic strip preparation plotted by the method of Arunlakshana & Schild (1959) to determine the values of pA_2 and pA_2–pA_{10}. Ordinate: log (x–1), where x is the ratio of equiactive doses of adrenaline (in *a*) or noradrenaline (in *b*) in the presence and in the absence of chlorpromazine. Abscissa: negative log B where B is the molar concentration of chlorpromazine. The best-fitting straight lines through the plotted points were determined by regression analysis. They are very highly significant ($P<0.001$). The lines intersect the abscissa at 14.0 (in *a*) and at 14.12 (in *b*) which are the pA_2 values for antagonism of adrenaline and noradrenaline respectively. The values of pA_2–pA_{10} are 0.95 in (*a*) and 1.21 in (*b*); these values are in good agreement with the theoretical value of 0.95 for competitive antagonism.

adrenaline the pA_2 value was 14.12. pA_2—pA_{10} values for antagonism of adrenaline and noradrenaline responses were 0.95 and 1.21 respectively. Under conditions of competitive antagonism, pA_2—$pA_{10}=0.95$ (Arunlakshana & Schild, 1959). The values for pA_2—pA_{10} obtained in the present experiments are in good agreement with the theoretical value of 0.95 for competitive antagonism.

Log K_2 values for each response in the presence of chlorpromazine were calculated according to the formula $\log (x-1)/B = \log K_2$. The mean log K_2 values for antagonism of adrenaline and noradrenaline were 13.99 and 14.01 respectively. These are closely similar to the corresponding pA_2 values indicating the competitive nature of the antagonism.

Receptor protection. If competitive blockade involves the occupation of the specific agonist receptors by the antagonist, the presence of the agonist in high concentrations should protect the specific receptors from blockade by the antagonist. In six paired preparations, each obtained from the same aorta, either adrenaline (1×10^{-5}) or noradrenaline (0.82×10^{-5}) was employed to protect the receptors from blockade by chlorpromazine (4.5×10^{-7}). In these experiments it was observed that the unprotected strips were totally insensitive to adrenaline or noradrenaline whereas the protected strips were still sensitive to the stimulant drugs although the responses were reduced. These results accord well with the thesis of competitive antagonism. The findings of a typical experiment are illustrated in Fig. 3.

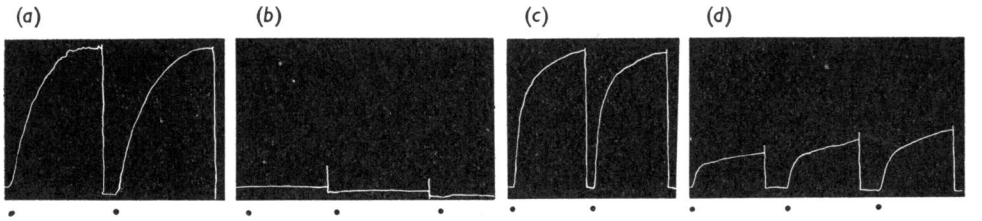

Fig. 3. A paired rabbit aortic strip preparation from the same aorta. Both the strips were exposed to tne same concentration (4.5×10^{-7}) of chlorpromazine, but one was protected throughout the entire period of exposure by a high concentration (1×10^{-5}) of adrenaline which was added to the bath 6 min before the addition of chlorpromazine. The records show responses of the unprotected (*a* and *b*) and the protected (*c* and *d*) strips to adrenaline (1×10^{-5}; at dots) before (*a* and *c*) and 60 min after a 6 min exposure to chlorpromazine (*b* and *d*).

Rat seminal vesicle preparation

In order to confirm and extend our observations on the rabbit aortic strip, antagonism of responses to amines by chlorpromazine was studied using the rat seminal vesicle. The plan of study was similar to that described for the rabbit aortic strip and the results were analysed in the same way. As with the rabbit aortic strip chlorpromazine caused a parallel shift of the dose/response lines to the right (Fig. 4). Dose-ratios for five different concentrations of chlorpromazine were determined in triplicate separately with adrenaline and noradrenaline (Table 1). pA_2 values for antagonism of adrenaline and noradrenaline responses were 14.08 and 14.20 respectively. The pA_2—pA_{10} values for antagonism of adrenaline and noradrenaline were 0.99 and 1.19 respectively. The mean log K_2 value for adrenaline antagonism was 14.08; for noradrenaline antagonism the mean log K_2 value was 14.08. These results are closely similar to those obtained with the aortic strip and support the hypothesis of competitive antagonism (Fig. 5).

Cat blood pressure

Effect of chlorpromazine on responses to adrenaline, noradrenaline and isoprenaline. In twelve experiments chlorpromazine (1.8 to 4.5 mg/kg, intravenously) severely depressed and often reversed the pressor effect of adrenaline (2 to 10 μg/kg). Pressor responses to noradrenaline (4.1 to 8.2 μg/kg) were either unaltered or slightly potentiated, while the depresor effect of isoprenaline (1.3 μg/kg) was potentiated.

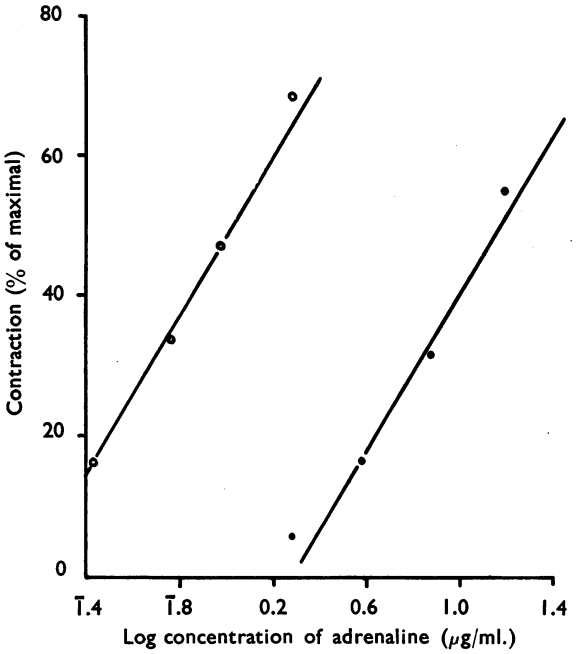

Fig. 4. Rat seminal vesicle preparation. Log dose/response curves for adrenaline alone (o— o) and in the presence of 3.6×10^{-14} of chlorpromazine (●—●). Chlorpromazine causes a parallel shift of the dose/response curve to the right and the horizontal distance between the two curves gives the ratio of the doses of adrenaline causing equal contractions in the presence and in the absence of the inhibitor (chlorpromazine). The dose-ratio was 14.45.

Cats treated with hexamethonium or cocaine. Circulating adrenaline and noradrenaline are taken up, bound and retained at or near sympathetic nerve endings (Axelrod, Weil-Malherbe & Tomchick, 1959 ; Whitby, Axelrod & Weil-Malherbe, 1961). Chlorpromazine inhibits the uptake of the free hormones at these sites (Hertting, Axelrod & Whitby, 1961). Of the two amines, tissue-binding plays a more significant part in the inactivation of noradrenaline. It was, therefore, likely that with noradrenaline potentiation caused by inhibition of uptake masked the adrenergic blocking action of chlorpromazine. With this in mind, the effect of chlorpromazine was studied in animals in which the tissue uptake of amines was already blocked by treatment with hexamethonium or cocaine (Muscholl, 1961 ; Vane, 1962). Hexamethonium (7.4 mg/kg, in three experiments) or cocaine (4.5 mg/kg, in three experiments) was administered slowly intravenously over a period of 10 min. Neither treatment modified the effect of chlorpromazine (1.8 to 4.5 mg/kg) on the pressor effect of adrenaline or noradrenaline.

Cats treated with dichloroisoprenaline. In contrast to noradrenaline which exerts an almost purely vasoconstrictor effect, adrenaline has both vasoconstrictor and vasodilator components of action and the manifest change in blood pressure after adrenaline is the resultant of the algebraic sum of these components. Chlorpromazine considerably potentiated the vasodepressor effect of isoprenaline (see

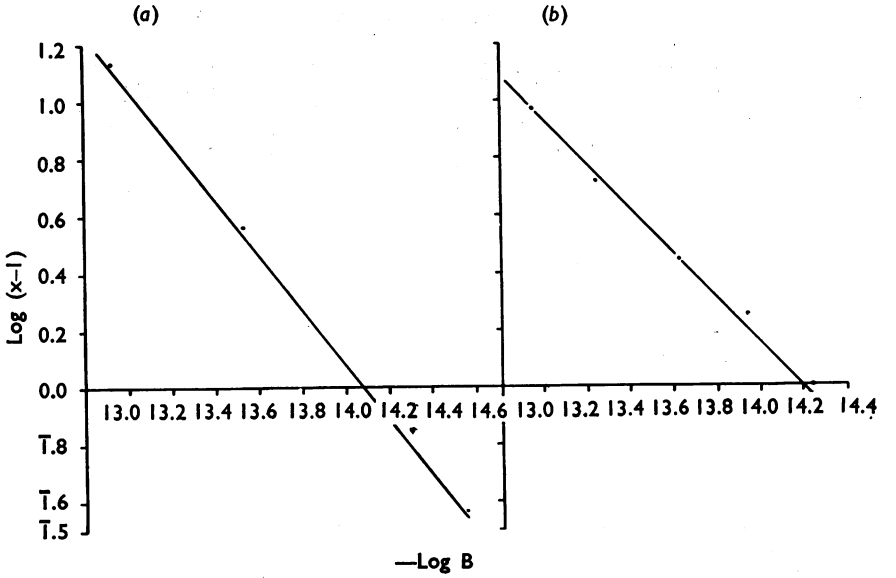

Fig. 5. Results with the rat seminal vesicle preparation plotted by the method of Arunlakshana & Schild (1959) to determine the values of pA_2 and pA_2-pA_{10}. Ordinate and abscissa as in Fig. 2. The lines are calculated regression lines and are very highly significant ($P<0.001$). They intersect the abscissa at 14.08 (in *a*) and 14.2 (in *b*) which are the pA_2 values respectively for antagonism of adrenaline and noradrenaline responses. The pA_2-pA_{10} values are 0.99 in (*a*) and 1.19 in (*b*). These values are closely similar to those obtained with the rabbit aortic strip and support the hypothesis of competitive antagonism.

above). The reduction of the pressor effect of adrenaline observed after small doses (1.8 to 4.5 mg/kg) of chlorpromazine could thus be due to a potentiation of the vasodilator component of adrenaline action. To test this possibility the effect of chlorpromazine on responses to amine was examined after complete blockade of the vasodilator action of adrenaline by large doses of dichloroisoprenaline.

Dichloroisoprenaline (8.7 mg/kg) was administered intravenously in three divided doses given at 5 min intervals. Blockade of adrenergic vasodilatation was demonstrated by injecting isoprenaline (2.1 μg/kg), which now had no depressor effect; 15 min later, chlorpromazine (4.5 mg/kg) did not block the pressor effect of adrenaline; in fact a slight potentiation of responses both to adrenaline and to noradrenaline was observed. Now a large dose (14.4 mg/kg) of chlorpromazine reduced the pressor effects both of adrenaline and of noradrenaline to the same extent (Fig. 6).

In another set of six experiments, 9.0 mg/kg of chlorpromazine reduced the pressor response to noradrenaline, caused a spectacular reversal of the pressor effect of adrenaline, and potentiated the depressor response to isoprenaline. Dichloroisoprenaline (8.7 mg/kg) given at this stage did not alter the reduction of the response to noradrenaline but considerably restored the pressor effect of adrenaline so that now the adrenaline and noradrenaline responses were reduced to the same extent; isoprenaline now had a slight pressor effect (Fig. 7).

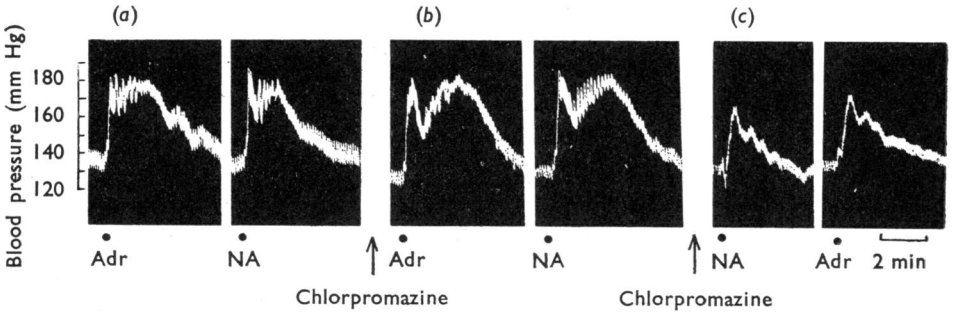

Fig. 6. Cat (2.5 kg) treated with dichloroisoprenaline (8.7 mg/kg, 15 min previously). Chloralose anaesthesia. Record of carotid arterial blood pressure. Responses (at dots) to adrenaline (10 μg at Adr) and noradrenaline (8.2 μg at NA) alone in (*a*); 10 min after chlorpromazine (4.5 mg/kg) in (*b*); and 10 min after chlorpromazine (14.4 mg/kg) in (*c*). Time mark, 2 min. Injections were intravenous.

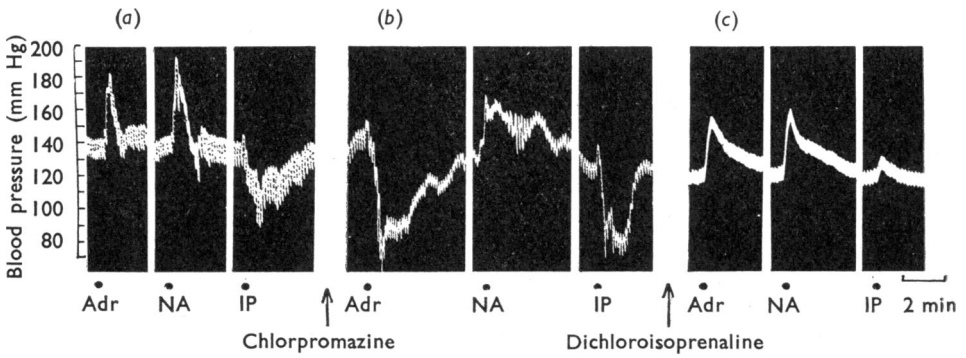

Fig. 7. Cat, 3 kg. Chloralose anaesthesia. Record of carotid arterial blood pressure. Responses (at dots) to adrenaline (10 μg at Adr), noradrenaline (8.2 μg at NA) and isoprenaline (2.6 μg at IP) alone in (*a*); 10 min after chlorpromazine (9.0 mg/kg) in (*b*); and 10 min after subsequent dichloroisoprenaline (8.7 mg/kg) in (*c*). Time mark, 2 min. Injections were intravenous.

Antagonism of pressor responses to noradrenaline by large doses of chlorpromazine. In six experiments dose/response curves for noradrenaline were established, alone and following three different doses (7.2, 14.4 and 28.8 mg/kg) of chlorpromazine. In competitive antagonism the lines relating 1/V to 1/S after various doses of the antagonist will have different slopes but a common intercept which lies on the line corresponding to infinite dose, where S is the dose and V the response (Chen & Russel, 1950). In Fig. 8 are shown plots of 1/V versus 1/S for noradrenaline, alone and after different doses of chlorpromazine ; V is the pressor response in mm Hg and S the dose of noradrenaline in μg/kg. It can be seen that the resultant lines all have different slopes but a common intercept which lies on the line corresponding to infinite dose.

Rabbit blood pressure

In the rabbit adrenaline has no vasodilator action and the drug acts as a pressor agent in all circumstances (H. H. Dale ; cited by Burn & Rand, 1958). If selective

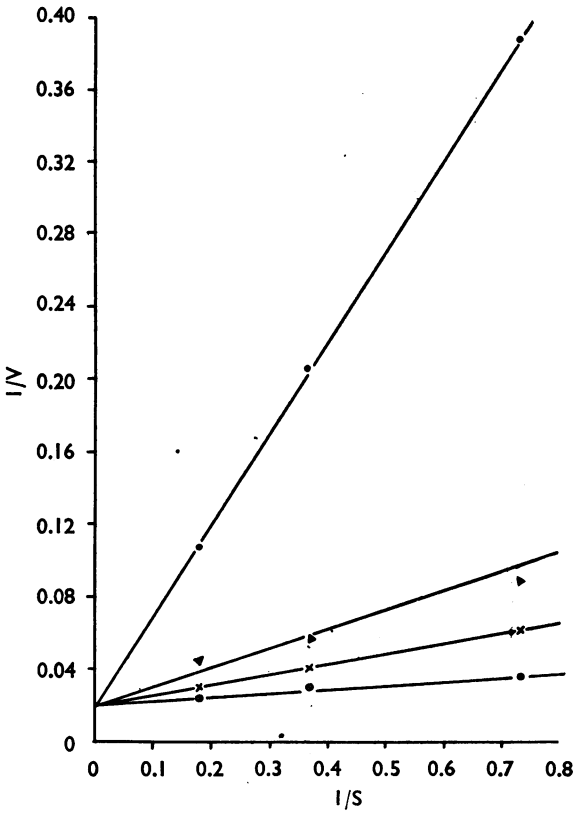

Fig. 8. Reciprocal analysis of the pressor effect of noradrenaline in the cat. Ordinate: 1/V, where V is the pressor effect (in mm Hg). Abscissa: 1/S, where S is the dose of noradrenaline (in μg/kg). ⊙—⊙ control; ×—× after chlorpromazine (7.2 mg/kg); ▲—▲ after chlorpromazine (14.4 mg/kg); ●—● after chlorpromazine (28.8 mg/kg). Regression lines for the four sets of conditions have different slopes but a common intercept which lies on the line corresponding to infinite dose. This indicates that the inhibition caused by each of these doses of chlorpromazine is competitive.

block by chlorpromazine of the pressor effect of adrenaline is due to a potentiation of the vasodilator effect of adrenaline then this differentiation should not occur in the rabbit. This was indeed found to be so. In six experiments chlorpromazine (0.9 mg/kg) caused a parallel shift of the dose/response lines for adrenaline and noradrenaline to the right. The dose-ratio (mean and standard error) for adrenaline antagonism was 22.14 ± 0.25; for noradrenaline antagonism it was 23.3 ± 0.96. These values are not significantly different from each other ($P > 0.4$).

DISCUSSION

Experiments with isolated smooth muscle structures

The results of our experiments show that the antagonism by chlorpromazine of the responses of the rabbit aortic strip and the rat seminal vesicle to adrenaline

and noradrenaline fulfils the conditions of competitive antagonism as outlined by Arunlakshana & Schild (1959). Thus (1) chlorpromazine shifted the dose/response lines to the right without altering their slope ; (2) the values for $pA_2 - pA_{10}$ (0.95 and 1.21 respectively for antagonism of adrenaline and noradrenaline with the rabbit aortic strip and 0.99 and 1.19 respectively for antagonism of adrenaline and noradrenaline with the rat seminal vesicle) are closely similar to the theoretical value of 0.95 for competitive antagonist ; and (3) the mean log K_2 values (13.99 and 14.01 respectively for antagonism of adrenaline and noradrenaline with the rabbit aortic strip and 14.08 and 14.08 respectively with the rat seminal vesicle) are nearly the same as the corresponding pA_2 values (14.0 and 14.12 with the rabbit aortic strip and 14.08 and 14.2 with the rat seminal vesicle).

Results of " receptor protection " experiments with the rabbit aortic strip provide further evidence of competitive antagonism.

The pA_2 value described by Schild (1947) is a precise and generally accepted measure of the potency of an antagonist. The high pA_2 values for chlorpromazine indicate that the drug is a remarkably potent adrenergic blocking agent.

The results with the rabbit aortic strip and the rat seminal vesicle show a close similarity. This similarity would indicate that the sympathetic α-receptors present in these two preparations are identical.

Experiments with intact animals

A secure pharmacological characterization of chlorpromazine as an adrenergic blocking agent has been made difficult by the inability of the drug to block the pressor effect of noradrenaline in doses which greatly reduce the effect of adrenaline. This difference could not be attributed to inhibition of tissue amine uptake by chlorpromazine as a prior block of amine uptake by cocaine or hexamethonium did not interfere with the selective reduction of the pressor effect of adrenaline by chlorpromazine.

In the cat, small doses (1.8 to 4.5 mg/kg) of chlorpromazine greatly reduced the pressor effect of adrenaline but had no effect on the response to noradrenaline. A large dose (9.0 mg/kg) conspicuously reversed the pressor effect of adrenaline but caused only a small reduction of the response to noradrenaline. Dichloroisoprenaline both prevented and reversed this differential effect of chlorpromazine. Chlorpromazine considerably potentiated the depressor effect of isoprenaline.

These results may be interpreted in terms of the sympathetic α- and β-receptor theory as postulated by Ahlquist (1948). In relation to the blood vessels α-receptor excitation results in vasoconstriction, while activation of the β-receptors causes vasodilation. Noradrenaline, which excites only the α-receptors, is pressor under all circumstances whereas the direction and magnitude of the blood pressure change following adrenaline depends on the relative prominence of its vasoconstrictor and vasodilator effects.

Following a dose of chlorpromazine which is too small to exert a true adrenergic blocking action, a potentiation of the vasodilator component of action of adrenaline would result in a reduction of its pressor effect but the pressor effect of noradrenaline

would remain unaffected. If the dose of chlorpromazine is large enough the effect of noradrenaline would also be reduced but responses to adrenaline would be affected to a far greater extent. If the vasodilator action of adrenaline is abolished by blocking the β-receptors, as would occur following dichloroisoprenaline, then chlorpromazine should no longer discriminate between adrenaline and noradrenaline. This was indeed what happened.

It is concluded that in the cat small doses of chlorpromazine have no real adrenergic blocking effect and the discrimination between adrenaline and noradrenaline by chlorpromazine is due to a potentiation of adrenergic vasodilatation by chlorpromazine.

Results of experiments with the rabbit blood pressure provide further support for this contention. In the rabbit where adrenaline has no vasodilator effect chlorpromazine did not discriminate between adrenaline and noradrenaline and the pressor effects of both the amines were equally reduced.

In the cat large doses (7.2 to 28.8 mg/kg) of chlorpromazine blocked the pressor effect of noradrenaline. Reciprocal analysis of the results of these experiments showed that this antagonism is competitive.

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