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THE ANTIADRENALINE ACTIVITY OF SOME PHENOTHIAZINE DERIVATIVES

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Phenothiazine derivatives are central nervous system depressants which apart from their wide use in psychiatry are of value in the relief of spasticity in conditions such as tetanus. In experimental tetanus in the rabbit it has been found that some phenothiazine derivatives diminish electromyographic activity in low doses but increase, or stimulate it, in high doses (Laurence & Webster, 1961). Although the mechanism of such stimulation has not been established it could be comparable to the Parkonisonian-like symptoms which often occur in man after relatively high doses of some phenothiazines.

In view of the recent observation that there may be a depletion of dopamine in the central nervous system of Parkinsonian patients (Ehringer & Hornykiewicz, 1960) and since a possible correlation between experimental antitetanus and antiadrenaline activities has been indicated previously (Webster, 1961) it was decided to investigate more fully the relative antiadrenaline activity of a number of phenothiazine derivatives and to consider this property in relation to the central actions of these compounds. The results of such studies on rabbit and cat blood pressure are reported below. Quantitative studies were performed on rabbits since data on antitetanus activity had previously been obtained for this species.

METHODS

Animal preparations

Anaesthetized or spinal rabbits and cats were used. Before spinal section rabbits were anaesthetized with intravenous thiopentone sodium (Intraval) and cats with intraperitoneal pentobarbitone sodium (Nembutal). In both cases the following procedure was then adopted. The trachea was cannulated, both carotid arteries were tied and artificial ventilation was started. The dorsal surface of the spinal cord was exposed between the base of the skull and the atlas vertebra without laminectomy by bending the head forward and resecting the appropriate muscle layers. The exposed cord was then sectioned and cotton wool was pushed into the brain with a blunt instrument.

Drug injections or adrenaline infusions were made through cannulae inserted into the femoral veins and blood pressure was recorded from a carotid artery with a mercury manometer.

Assay procedure

In early experiments some indication of antiadrenaline activity was obtained by comparing the pressor response to adrenaline before and after giving a phenothiazine derivative.

To obtain more quantitative comparisons of antiadrenaline activity the following course was followed. Adrenaline solution (50 μg/ml.) was infused at constant pressure at a rate of 3 to 10

μg/min from a small Mariott bottle into a femoral vein. The rate of flow was adjusted by altering the pressure head until a relatively constant blood pressure of about 120 mg Hg was obtained.

The phenothiazine to be tested was injected into the other femoral vein and the percentage reduction in blood pressure was recorded. When the drug effect began to wear off the drum was stopped and the infusion pressure was reduced so that the blood pressure levelled off at about 50 mm Hg. After 10 min the infusion pressure was again raised, the drum started, and the procedure repeated.

Heart rate and nictitating membrane contractions

A record of heart rate was obtained by using an electrocardiogram, recorded with electrodes placed in the skin above the thorax, to drive a Thorp impulse counter after amplification and pulse shaping. Contractions of the nictitating membrane were recorded in the usual manner by a thread running over a pulley and attached to a frontal-writing lever.

RESULTS

Antagonism of injected adrenaline

Pressor responses to graded doses of adrenaline were recorded. A phenothiazine derivative was then given and after 1 min the reduction in response to one of the doses of adrenaline was recorded. This procedure provided an estimate of antiadrenaline activity but the transient action of the phenothiazines made accurate matching and comparison difficult. The following procedures were therefore adopted.

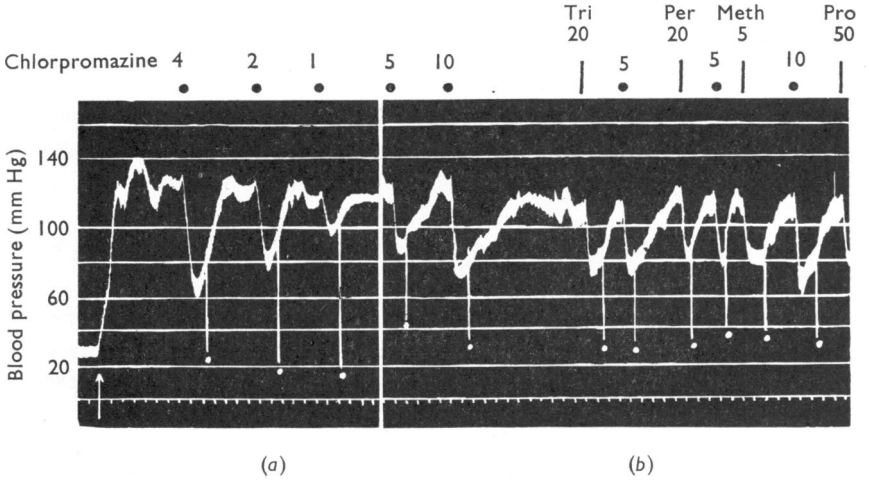

Fig. 1. Adrenaline-maintained blood pressure in the spinal rabbit. (*a*) Graded depressor responses to chlorpromazine. (*b*) Comparative depressor activities of some phenothiazine derivatives. The start of the adrenaline infusion is indicated by the arrow. At the vertical line (shown by a dot) in each depressor response the drum was stopped and the adrenaline infusion rate was decreased. After about 10 min the infusion rate was again increased. The drum was restarted when the blood pressure reached its previous level. Chlorpromazine injections are shown by black dots. All doses are in μg. Tri=trimeprazine, Per=perphenazine, Meth=methotrimeprazine, Pro=promazine. Time marks, 30 sec.

Antagonism of infused adrenaline

Adrenaline was infused into a femoral vein until a constant blood pressure was obtained which was then antagonized by the phenothiazines (see Methods). At the beginning of the experiment three or four graded doses of chlorpromazine were injected to obtain a standard regression line (Fig. 1,*a*). In some experiments it was possible to obtain a regression line for the test phenothiazine as well as for chlorpromazine, so that activity ratios could be obtained graphically from the two regression lines (Fig. 2). In other instances the activity of the test phenothiazine was determined from the standard regres-

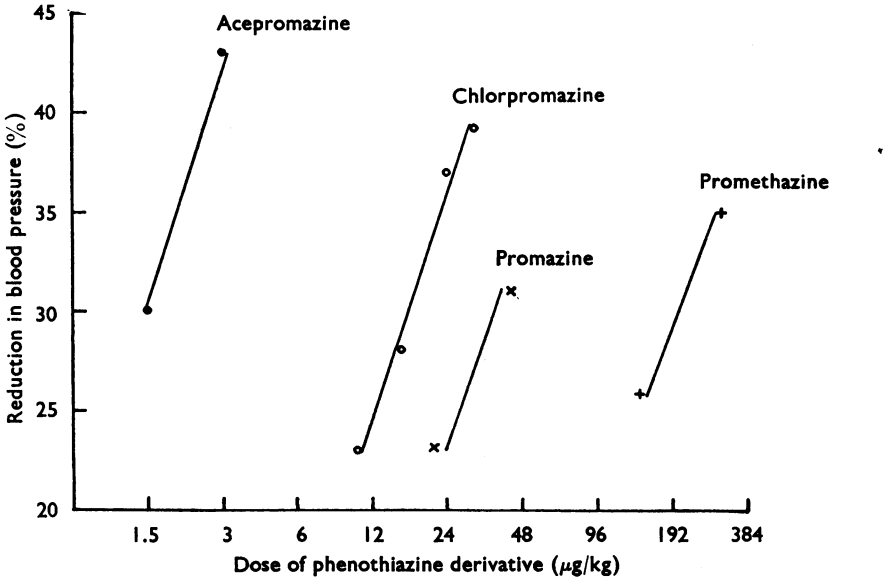

Fig. 2. Log dose/response curves for the adrenolytic activity of some phenothiazine derivatives. Ordinate: percentage reduction of adrenaline-maintained blood pressure in the spinal rabbit.

sion line for chlorpromazine established at the beginning and reconfirmed in the course of the experiment (Fig. 1,*b*).

The antiadrenaline activities of various phenothiazine derivatives were determined relative to chlorpromazine. Relative potencies from several experiments are given in Table 1 together with mean values. In all cases relative activity is expressed in terms of base. There is a correlation between antiadrenaline and antitetanus activities ($r=0.93$, $P=0.01$). Three derivatives, methotrimeprazine, trimephazine and promethazine, were, however, less effective in antagonizing adrenaline than might have been expected from their antitetanus activity.

Relative antagonism of adrenaline and noradrenaline by chlorpromazine

In the cat chlorpromazine is known to antagonize the effects of adrenaline more than those of noradrenaline (Huidobro, 1954; Martin, Riehl & Unna, 1960; Gokhale, Gulati & Kelkar, 1963). The effectiveness of chlorpromazine against the two amines was therefore tested in the rabbit. Matched pressor responses to adrenaline and noradrenaline

TABLE 1

ANTIADRENALINE ACTIVITY OF SOME PHENOTHIAZINE DERIVATIVES RELATIVE TO THAT OF CHLORPROMAZINE, FROM EXPERIMENTS ON NINE RABBITS

Values for antitetanus activity are taken from Webster (1961)

Compound	Antiadrenaline activity for expt. no. 1	2	3	4	5	6	7	8	9	Mean	Anti-tetanus activity
Acepromazine	10·6	10·7	5·0			7·0				8·3	9·4
Methotrimeprazine					0·85	1·36	1·6		1·4	1·3	2·4
Chlorpromazine	1	1	1	1	1	1	1	1	1	1	1
Promazine		0·5	0·45			0·6	0·34		0·47	0·47	0·47
Trimeprazine					0·28	0·32	0·22		0·32	0·29	0·5
Promethazine		0·08	0·06			0·14				0·09	0·34
Perphenazine				0·3	0·31		0·28			0·30	0·25
Prochlorperazine						0·25	0·14	0·28	0·23	0·22	0·2

were obtained and the injections were repeated after chlorpromazine. The results (Fig. 3) indicate that, in the rabbit, adrenaline is consistently more effective as a pressor agent than is noradrenaline and that chlorpromazine antagonizes both amines to the same extent.

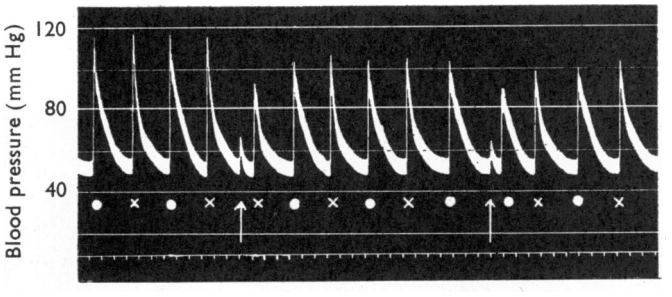

Fig. 3. Antagonism by chlorpromazine (10 μg/kg at each arrow) of pressor responses to adrenaline (6 μg at crosses) and noradrenaline (8 μg at circles) in a spinal rabbit. Time marks, 30 sec.

Classification of adrenaline antagonism by chlorpromazine

Characteristics of antagonism. The mechanism underlying drug antagonism is difficult to demonstrate *in vivo* as the concentration of the antagonist cannot be maintained constant. When dose/response curves for adrenaline were obtained before and after increasing doses of chlorpromazine, a shift of the regression line was invariably obtained after the first dose of chlorpromazine, but further graded doses did not produce corresponding shifts. In some experiments the responses to adrenaline returned to, or exceeded, the control level. The results of one such experiment on a spinal cat are shown in Fig. 4. Similar results were obtained in rabbits but the loss in adrenolytic activity after high doses of chlorpromazine was not as great.

α- and β-receptor antagonism. Although chlorpromazine is a relatively potent antiadrenaline agent very little is known of its relative antagonism at α- and β-receptor sites as defined by Ahlquist (1948). Its relative effectiveness at different dose levels against adrenaline, noradrenaline and isoprenaline on typical α- and β-receptor effects was there-

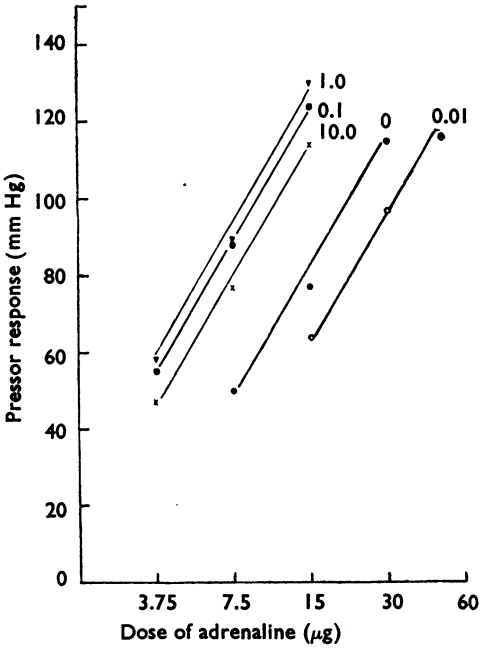

Fig. 4. Log dose/response curves in the spinal cat of the pressor responses to adrenaline before (●——●), and after 0.01 (○——○), 0.1 (⊗——⊗), 1.0 (▼——▼) and 10 (×——×) mg/kg of chlorpromazine.

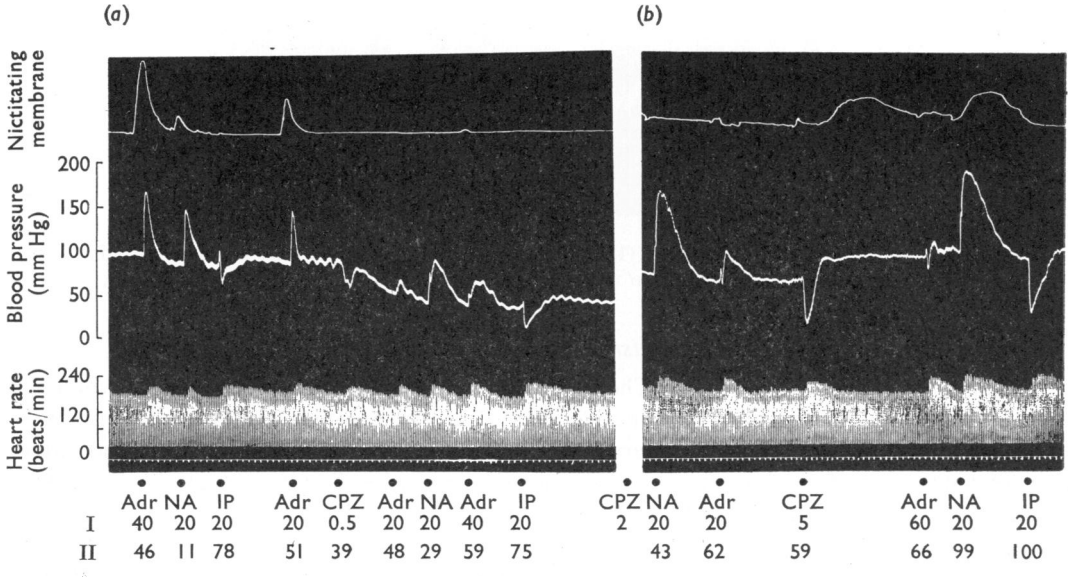

Fig. 5. Effect of increasing doses of chlorpromazine on some α- and β-receptor effects of adrenaline, noradrenaline and isoprenaline in the cat during pentobarbitone anaesthesia. Top tracing; nictitating membrane contractions. Middle tracing; blood pressure. Lowest tracing; heart rate. Time marks, 30 sec. The upper row of numbers (I) gives the doses of adrenaline (Adr), noradrenaline (NA) and isoprenaline (IP) in μg and those of chlorpromazine (CPZ) in mg/kg. The lower row of numbers (II) gives the numbers of additional heart beats in the 2 min immediately after each drug injection. Between records (*a*) and (*b*) there was an interval of approximately 2 hr during which two further 1 mg/kg doses of chlorpromazine (CPZ) were given.

fore tested in two anaesthetized cats and one spinal cat after vagotomy. Increased heart rate was taken as a measure of β-receptor effect and contraction of the nictitating membrane as a measure of α-receptor effect. Blood pressure changes were also recorded.

As can be seen from the results of one experiment on an anaesthetized, vagotomized cat (Fig. 5) typical effects were obtained with the control injections of the three amines. As the dose of chlorpromazine was increased the responses to the three amines were further modified. After 5 mg/kg chlorpromazine, 2.5 hr after the first injection noradrenaline produced a large pressor response and a contraction of the nictitating membrane. Isoprenaline effects, both vascular and cardiac, were potentiated but the pressor effect of adrenaline was further reduced although the tachycardia remained unaltered. A striking feature was the prolonged duration of action of the three amines after large doses of chlorpromazine.

Basically similar results were obtained in a second anaesthetized cat and in a spinal animal, and although in the latter eventual potentiation of noradrenaline was obtained the adrenaline antagonism was not as marked.

Time course of the antiadrenaline activity of some phenothiazine derivatives

Since the above experiments showed tachyphylaxis to the antiadrenaline activity of chlorpromazine the effect of repeated doses of some phenothiazine derivatives on the pressor effects of adrenaline and noradrenaline was studied in spinal cats.

The result of a typical experiment is shown in Fig. 6. The initial dose of chlorpromazine (0.25 mg/kg) reduced the pressor effect of adrenaline more than that of noradrenaline. Despite further doses of 0.25, 0.25 and 0.5 mg/kg at 1, 2 and 3 hr respectively the pressor responses to both amines gradually returned to, and, in the case of nor-

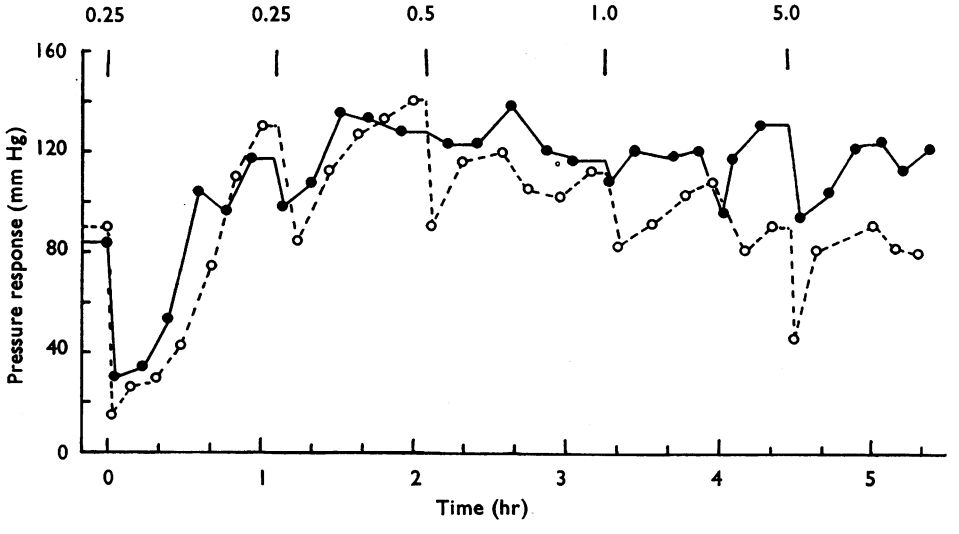

Fig. 6. Time course of the effect of repeated doses of chlorpromazine (at vertical lines, doses in mg/kg) on the pressor response to adrenaline (30 μg, ○) and noradrenaline (20 μg, ●) in a spinal cat.

adrenaline, exceeded the control. Larger doses of chlorpromazine (5 mg/kg) produced some secondary depression of the adrenaline effect. The antiadrenaline activity of chlorpromazine is evidently not maintained as well in the spinal as in the anaesthetized animal (Fig. 5).

Similar experiments were performed with other phenothiazine derivatives such as acepromazine, methotrimeprazine, prochlorperazine and ethopropazine. Methotrimeprazine proved similar to chlorpromazine except that its adrenolytic effect wore off more rapidly and did not return with large doses. Ethopropazine only produced transitory adrenolytic effects. Both acepromazine and prochlorperazine showed progressive antiadrenaline activity although the doses of prochlorperazine required to antagonize the effects of adrenaline were considerably greater than those of acepromazine. In all cases adrenaline was antagonized more than noradrenaline.

Attempts to perform similar experiments in rabbits were not generally successful since the spinal rabbit has a very low blood pressure and soon succumbs to high doses of chlorpromazine, and in the anaesthetized preparation potentiation of the anaesthetic also proves fatal after a short while. The result of one experiment on a large spinal rabbit was sufficiently similar to that obtained in the cat, however, to conclude that the time course of the adrenolytic activity of the phenothiazine derivatives is similar in the two species, but that the strong secondary potentiation probably does not occur in rabbits.

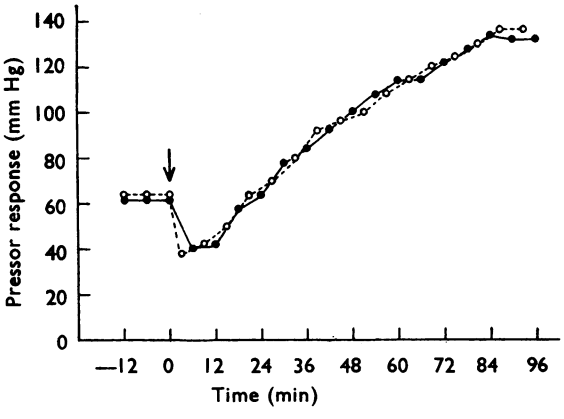

Fig. 7. Time courses of the effect of hexamethonium on the pressor response to adrenaline and noradrenaline in a spinal cat. Pressor responses to a constant dose of adrenaline (10 μg, ○) and noradrenaline (7.5 μg, ●) are shown both before and after 2 mg/kg of hexamethonium (at the arrow).

Effect of hexamethonium on pressor activity due to adrenaline

Since hexamethonium is known to potentiate the catechol amines (Bartorelli, Carpi & Cavalca, 1954; Vane, 1962) it was decided to see whether it would produce any differential effect on adrenaline and noradrenaline in the spinal cat. The result of one such experiment (Fig. 7) shows that hexamethonium potentiates equally the degree of response to both amines. The duration of each amine response was not affected.

DISCUSSION

The present experiments have shown some correlation between the antitetanus and antiadrenaline activities of some phenothiazine derivatives, but closer analysis reveals a more complicated situation since the phenothiazines may produce both antagonism and potentiation of adrenaline and noradrenaline.

Chlorpromazine antagonized the pressor activity of adrenaline more than that of noradrenaline in the spinal cat but the difference was not as great as that previously recorded in anaesthetized cats (Huidobro, 1954; Martin *et al.*, 1960; Gokhale *et al.*, 1963a), dogs (Courvoisier, Fournel, Ducrot, Kolsky & Koetschet, 1953; Delga & Hazard, 1957), or rats (Gokhale, Gulati & Joshi, 1963). By starting with a small dose (0.25 mg/kg) of a phenothiazine followed by increasing doses it was found that the antagonism of both amines is basically similar and that the differential effect can be quite small. In every experiment the first dose of chlorpromazine, and of the other derivatives tested, reduced the pressor response of both amines though adrenaline was invariably more affected. After more chlorpromazine the amine responses generally returned towards the control level with eventual potentiation of noradrenaline and in some instances adrenaline (Fig. 6). This tachyphylaxis to antiadrenaline activity did not occur with acepromazine and prochlorperazine. It was not as great in anaesthetized (pentobaritone) cats, in which pressor responses to adrenaline were in fact always more noticeably reduced, so exaggerating the differential antagonism to the two amines. Thus the degree to which this differential antagonism of noradrenaline and adrenaline can be achieved with the phenothiazines probably depends on two opposing factors, antagonism and potentiation, and it varies with the phenothiazine tested, the dose used, the interval between injection of the phenothiazine and of the sympathomimetic amine, and the degree of anaesthesia.

The antagonism and potentiation of adrenaline and noradrenaline may be explained in terms of the effect of chlorpromazine on α- and β-receptors. Contractions of the nictitating membrane by adrenaline and noradrenaline were antagonized by chlorpromazine which is consistent with the α-receptor antagonism demonstrated by Martin *et al.* (1960) and confirmed by Gokhale, Gulati & Parikh (1964) on the rabbit isolated aortic strip preparation. More striking than this antagonism however, was the potentiation of the β-receptor effects (hypertension and tachycardia) of isoprenaline. If the vasodilatation (β-receptor effect) produced by adrenaline is also potentiated then it is likely that this would considerably reduce the pressor response to adrenaline. This effect when added to any α-receptor blocking activity of chlorpromazine would produce a greater reduction in the pressor response to adrenaline than to noradrenaline. This would explain why in the rabbit, in which adrenaline does not produce vasodilatation, chlorpromazine antagonizes adrenaline and noradrenaline pressor activities to the same extent. Also on this basis, if the β-receptor effects of adrenaline were blocked by an appropriate antagonist such as dichloroisoprenaline, then the differential antagonism would be lost also in the cat, and Gokhale *et al.* (1964) have now shown this to be so.

Large doses of chlorpromazine may prolong and potentiate the pressor effects of the catechol amines, probably by reducing tissue uptake (Rosell & Axelrod, 1963) which is a major route of their metabolism (Gillespie & Kirpekar, 1965). If tissue uptake is more important in the metabolism of noradrenaline than adrenaline, then chlorpromazine may help to overcome its own antagonism to the pressor activity of noradrenaline and

consequently this would provide an alternative explanation of its greater depressant effect on adrenaline. On this basis if there is no eventual potentiation of noradrenaline after large doses of chlorpromazine then there should be no differential antagonism. This was thought to be so in the rabbit but, due to the difficulty of keeping a spinal rabbit alive for long periods to show potentiation, the result may not be valid. Hexamethonium, which is also believed to potentiate catechol amines by inhibiting tissue uptake (Bartorelli *et al.*, 1954 ; Vane, 1962), potentiated equally the degree, but not the duration, of the response to both amines. Thus on this basis it appears that in respect of pressor responses to the two amines the slight antagonism at α-receptors by chlorpromazine is eventually overcome through potentiation of the catechol amines by blocking their tissue uptake, though in the case of adrenaline this is masked by a concurrent potentiation of its β-receptor effects. An apparent differential antagonism of the two amines is thus obtained. Studies on blood pressure obviously require to be supplemented by experiments on simpler systems so that cardiac responses can be distinguished from peripheral ones. Chlorpromazine sulphoxide, the major metabolite of chlorpromazine, must also be considered since this apparently has little antiadrenaline activity (Martin *et al.*, 1960) but potentiates the effects of noradrenaline and to a lesser extent those of adrenaline. The cumulative effect of the metabolite could modify the response to chlorpromazine itself and might contribute to the potentiation of noradrenaline.

Although a statistically significant correlation was found between the antiadrenaline and antitetanus activities of a series of phenothiazine derivatives when tested by single dose administrations at low dose levels the pattern of antiadrenaline activity changes so much after repeated doses that the correlation no longer holds. There is even an indication that when antiadrenaline activity is maintained it might be correlated with the ability of these compounds to stimulate the central nervous system as in the induction of extrapyramidal systems.

In studies of the time course of action of the antiadrenaline and antinoradrenaline activity of the phenothiazines in spinal cats only two derivatives, acepromazine and prochlorpromazine, maintained their adrenolytic activity. The antiadrenaline effects of methotrimeprazine did not persist, whilst that of chlorpromazine was variable. Ethopropazine, the only phenothiazine commonly used in the treatment of Parkinsonism, showed practically no antiadrenaline activity at reasonable dose levels.

The part played by the catechol amines, if any, in extrapyramidal disorders such as Parkinsonism is not clear but it is known that areas of the brain which have been implicated in Parkinsonism are rich in dopamine (Bertler & Rosengren, 1959 ; Carlsson, 1959 ; Bertler, 1961), that urinary dopamine levels are low in Parkinsonian patients (Barbeau, 1962 ; Barbeau & Sourkes, 1961) and that *post mortem* studies of Parkinsonian patients have revealed a low concentration of dopamine in the caudate nucleus (Ehringer & Hornykiewicz, 1960).

Drugs that increase the concentration of dopamine, such as dopa (McGeer, Boulding, Gibson & Foulkes, 1961 ; Barbeau, 1962) and the monoamine oxidase inhibitors (Barbeau, Sourkes & Murphy, 1961), have been shown to reduce the symptoms of Parkinsonism though methyldopa is also claimed to have this effect (Marsh, Schneiden & Marshall, 1963). Although the present studies give no evidence of the antidopamine effects of the

phenothiazines it could be assumed that their order of efficacy in this respect would be similar to their antiadrenaline activity.

Obviously other pharmocological aspects of the phenothiazines must be considered. Several of them are potent antihistamines, and some antihistamines are used in the treatment of Parkinsonism. Three compounds, methotrimeprazine, trimeprazine and promethazine, which were found to be more effective antitetanus than antiadrenaline agents in the correlative studies, are all potent antihistamines. In this respect it is of interest that tremorine, which can be used experimentally to produce symptoms which are thought to be similar to those of Parkinsonism, apart from decreasing brain stem noradrenaline (Friedman, 1963) also increases brain histamine (Ungar & Witten, 1963). Anticholinergic activity may also be important.

Considerable antiadrenaline activity may confer on a phenothiazine derivative a high order of central nervous system activity possibly due to some common structural feature. Certainly of the phenothiazines tested the three most potent antiadrenaline derivatives produce central effects (sedation or antitetanus activity) at low dose levels. Whether the central effect persists as depression may then be determined by some other property such as antihistamine activity. Those phenothiazines with antihistamine activity rarely cause extrapyramidal disorders, whereas prochlorpromazine and acepromazine which are not antihistamines frequently do. Chlorpromazine would fall between these two categories whilst ethopropazine having little antiadrenaline activity is relatively ineffective centrally apart from its use as an anticholinergic agent in Parkinsonism. Such a concept is basically similar to that proposed by McGeer *et al.* (1961), who envisage Parkinsonism to be brought about by a disturbance in a normal brain equilibrium between 5-hydroxytriptamine and the catechol amines on the one hand and histamine and acetylcholine on the other.

A detailed correlative study between antiadrenaline, antihistamine and antiacetylcholine activities of the phenothiazines and their central nervous system activities could be rewarding.

SUMMARY

1. A method of assaying antiadrenaline activity on the blood pressure of the spinal rabbit, maintained by adrenaline, is described.

2. The relative antiadrenaline activities of a number of phenothiazine derivatives were determined and found to correlate with their ability to reduce the spasm of experimental tetanus.

3. From studies of the antagonism of chlorpromazine to catechol amine α- and β-receptor effects it is concluded that chlorpromazine antagonizes the pressor response to noradrenaline more than that to adrenaline probably because it potentiates the β-receptor vasodilator activity of adrenaline. No differential antagonism was observed in the rabbit.

4. Time course studies of phenothiazine adrenolytic activity showed that some derivatives retained this effect on repeated administration whereas a marked tachyphylaxis developed with others.

5. The ability of some phenothiazines to induce extrapyramidal disorders is discussed in relation to their relative antiadrenaline and antihistamine activities.

Much of this work was done whilst the author was Stothert Research Fellow of the Royal Society. I am much indebted to Mr J. Hinshelwood for his invaluable technical assistance. Chlorpromazine, prochlorperazine, methotrimeprazine and promethazine were given by May & Baker, acepromazine by Bengers Laboratories, promazine by John Wyeth, and perphenazine by Allen and Hanbury's.

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