Br. J. Pharmac. (1974), **50**, 355-363

A COMPARISON OF THE ACTIONS OF SOME DRUGS ON DECEREBRATE RIGIDITY, MUSCLE SPINDLE ACTIVITY AND α-ADRENOCEPTORS

D.R. MAXWELL & EILEEN A. SUMPTER
Pharmacological Research Laboratories, May & Baker Ltd, Dagenham, Essex

1 The relative potencies of methotrimeprazine, (+)-methotrimeprazine, (±)-10-(3-dimethylamino-2-methylpropyl)-2-valeroyl phenothiazine hydrochloride (M & B 18,706) and (+)-M & B 18,706 in reducing the pressor action of noradrenaline in the spinal cat, reducing intercollicular decerebrate rigidity, and muscle spindle afferent activity have been studied.

2 Methotrimeprazine was eight times as potent as (+)-methotrimeprazine in reducing the pressor action of noradrenaline and six times as potent in reducing decerebrate rigidity. M & B 18,706 was also eight times as potent as (+)-M & B 18,706 in reducing the pressor action of noradrenaline and six times as potent in reducing decerebrate rigidity.

3 For the above compounds and chlorpromazine there was a significant correlation between the effective doses for the inhibition of the pressor action of noradrenaline and for the reduction of decerebrate rigidity.

4 The doses which reduced decerebrate rigidity were similar to those that reduced muscle spindle afferent discharge. It is likely that these drugs reduce decerebrate rigidity by inhibiting fusimotor activity.

5 Desipramine increased decerebrate rigidity and increased spindle afferent discharge.

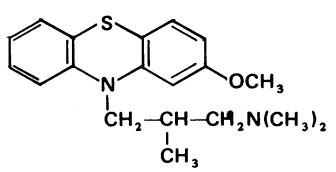
6 It is thought that the phenothiazine derivatives studied reduce decerebrate rigidity and spindle afferent discharge by inhibiting receptors for noradrenaline in the central nervous system.

Introduction

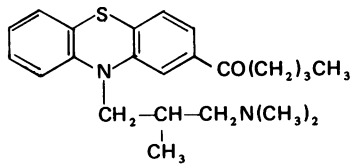
During the study of various phenothiazine derivatives for their ability to reduce decerebrate rigidity by an action on the central nervous system in reducing fusimotor activity, we observed that those compounds which were most potent in reducing decerebrate rigidity were also the most potent α-adrenoceptor blocking agents. In view of the suggestions (Dahlström & Fuxe, 1965; Ellaway & Pascoe, 1968) that a descending noradrenergic pathway might be involved in the control of fusimotor activity, we have investigated this possible relationship further.

Some of the drugs studied contained an asymmetric carbon atom and may be resolved into two optically active isomers. These optical isomers differ in their pharmacological activity and the experiments described here were designed to determine whether the difference in the α-adrenoceptor blocking activity of the isomers was accompanied by a corresponding difference in potency in reducing decerebrate rigidity and muscle spindle activity.

Two pairs of compounds were studied: (a) methotrimeprazine, which is a (−)-isomer and its corresponding (+)-isomer, subsequently referred to as (+)-methotrimeprazine; (b) (±)-10-(3-dimethylamino-2-methylpropyl)-2-valeroyl phenothiazine hydrochloride (M & B 18,706) and its corresponding (+)-isomer, subsequently referred to as (+)-M & B 18,706.



Methotrimeprazine



M & B 18,706

These compounds were compared for potency in reducing the pressor response to noradrenaline in the spinal cat and for potency in reducing rigidity and muscle spindle afferent discharge in the intercollicular decerebrate cat.

Some experiments were carried out with chlorpromazine and thymoxamine as reference standards and with desipramine. The potencies of M & B 18,706 and (+)-M & B 18,706 in antagonizing an action of 5-hydroxytryptamine (5-HT) were also compared.

A preliminary account of some of this work has been given (Maxwell & Sumpter, 1972).

Methods

Antagonism of noradrenaline-induced pressor responses in the spinal cat

Cats were anaesthetized with halothane and the spinal cord was sectioned at the level of the first cervical vertebra. The brain was destroyed, artificial respiration was maintained and the anaesthesia was discontinued.

Blood pressure was recorded from a carotid artery, with a pressure transducer and pen recorder. Noradrenaline was injected automatically at 3.5-7 min intervals into a cannulated external jugular vein. Two doses of noradrenaline were chosen, one being twice or four times the other, such that both gave pressor responses on the linear part of the dose-response curve. Doses between 2 and 20 μg were normally used. When responses were constant, the drug under investigation was injected intravenously. Antagonism of noradrenaline was expressed in terms of a reduction in its apparent pressor potency. The effective dose of the drug was defined as that required to reduce the apparent pressor potency of noradrenaline by 50%, and was determined from the dose-response curve for the drug.

Antagonism of 5-hydroxytryptamine-induced contractions of the nictitating membrane in the spinal cat

Cats were spinalized as indicated above, and the cervical sympathetic nerve sectioned pre-ganglionically. A cannula was inserted into the lingual artery for the retrograde intra-arterial injections of 5-HT. Test drugs were injected into a cannulated jugular vein. A thread was tied to the nictitating membrane and contractions of the membrane produced by the intra-arterial injection of 5-HT (10-20 μg) recorded isotonically. The dose of test drug required to reduce the height of the contraction produced by the 20 μg dose to that of the 10 μg dose was determined.

Effect on intercollicular decerebrate rigidity in the cat

Cats were decerebrated at the intercollicular level whilst under halothane anaesthesia; the anaesthesia was then discontinued. The method used to measure the degree of decerebrate rigidity and its reduction by drugs was that described by Maxwell & Read (1972) and Maxwell, Read & Sumpter (1974). The electromyogram (EMG) of the quadriceps muscle was recorded and integrated whilst that muscle was slowly stretched by the weight of the lower leg. The change in EMG as this stretch was applied was used as a measure of decerebrate rigidity.

Drugs were administered by slow intravenous infusion at a rate of 0.05-0.5 mg kg^{-1} min^{-1}. In order to compare the potency of the drugs in reducing decerebrate rigidity, regression lines of percentage inhibition of the EMG response to stretch against dose were obtained, and the dose producing a 50% reduction in the EMG response determined for each drug.

Effect on muscle spindle afferent discharge in the decerebrate cat

The method described by Maxwell & Rhodes (1970) was used. Briefly, the rate of discharge of primary or secondary afferent fibres for a muscle spindle in the soleus muscle of an intercollicular decerebrate cat was recorded whilst that muscle underwent a rapid controlled stretch. After control responses had been obtained the test drug was infused intravenously at the same rate as in the experiments on decerebrate rigidity. Recordings of the spindle afferent discharge following two stretch responses of soleus were made 2 min after the end of infusion. The infusion of the test drug was then recommenced until the next higher dose had been administered, and recording of spindle afferent activity during two successive stretch responses again determined. At the end of the experiment the conduction velocity of the afferent fibre was determined.

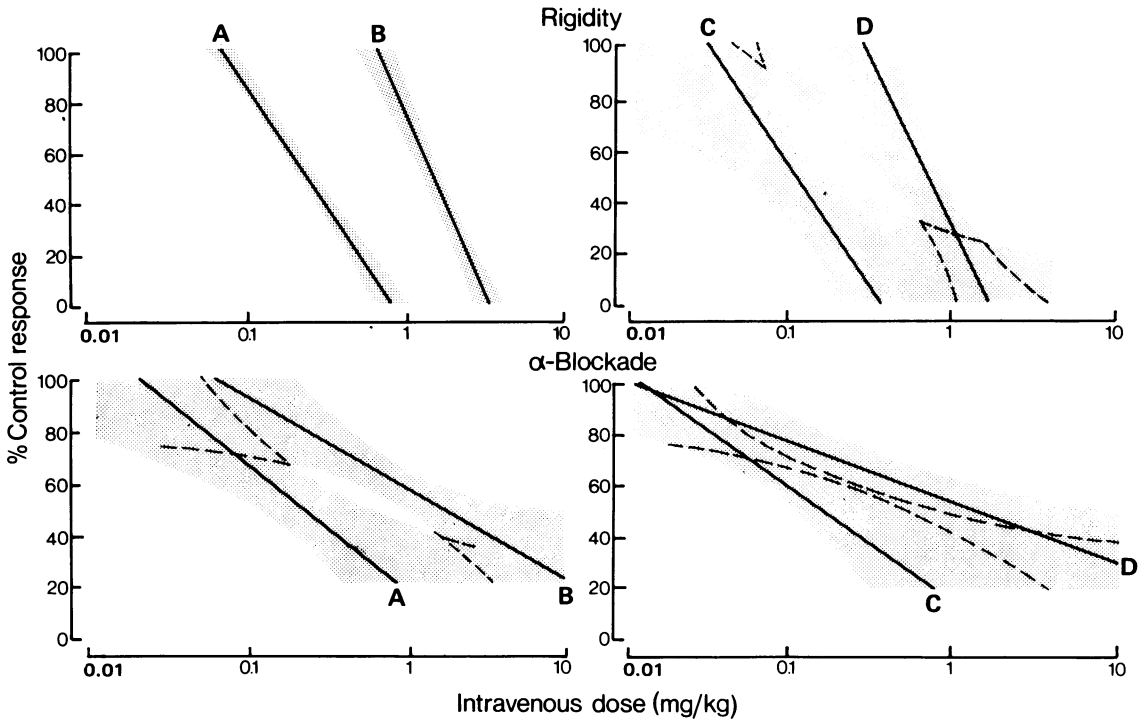


Fig. 1 Regression lines computed for M & B 18,706, (A); (+)-M & B 18,706, (B); methotrimeprazine (C); and (+)-methotrimeprazine (D) in reducing the rigidity of the intercollicular decerebrate cat (upper pair) and inhibiting the pressor response to noradrenaline in the spinal cat (lower pair). The ordinates refer to the percentage reduction of decerebrate rigidity and pressor potency of noradrenaline respectively. The abscissae give the intravenous doses on a logarithmic scale. The envelopes (stippled) enclose the 95% confidence limits of the regression lines.

Drugs

M & B 18,706, (+)-M & B 18,706 (supplied as M & B 21,897), methotrimeprazine, chlorpromazine, thymoxamine (W.R. Warner) and desipramine (Geigy) were used as the hydrochlorides. (+)-Methotrimeprazine (supplied as 7185 R.P.) was used as the tartrate, noradrenaline as the bitartrate and 5-hydroxytryptamine as the creatinine sulphate. All doses are expressed in terms of the active base. Drugs were dissolved in saline immediately before use, care being taken to keep phenothiazine derivatives out of sunlight.

Results

Antagonism of noradrenaline-induced pressor responses in the spinal cat

Increasing intravenous doses of methotrimeprazine, (+)-methotrimeprazine, M & B 18,706 or (+)-M & B 18,706, produced a graded reduction in the apparent pressor potency of noradrenaline in the spinal cat until about 70% reduction in potency was achieved.

It was found difficult to reduce the pressor effects of noradrenaline by more than about 70% with these phenothiazine derivatives. Higher doses of, for example, methotrimeprazine produce little further inhibition of the pressor responses to noradrenaline. In calculating the regression lines the flattening of the dose-response curve at high doses has been neglected.

The doses required to halve the pressor potency of noradrenaline were determined from the computed regression lines (Figure 1). M & B 18,706 was eight times as potent as (+)-M & B 18,706 in this respect, and methotrimeprazine was eight times as potent as (+)-methotrimeprazine. The potencies of M & B 18,706 and methotrimeprazine were similar to that of chlorpromazine (Table 1), and greater than that of thymoxamine.

Table 1 Effective doses of various compounds for reducing pressor response to noradrenaline (NA) in spinal cat and for reducing decerebrate rigidity and muscle spindle afferent discharge in the decerebrate cat.

	Effective intravenous dose (mg/kg)							
	M & B 18,706 (A)	*(+)-M & B 18,706 (B)*	*Ratio (B/A)*	*Methotrimeprazine (C)*	*(+)-Methotrimeprazine (D)*	*Ratio (C/D)*	*Chlorpromazine*	*Thymoxamine*
50% reduction in apparent pressor potency of NA in spinal cat	0.2 (0.12-0.56)	1.6 (0.9-5.9)	8	0.17 (0.1-0.82)	1.4 (0.59-24)	8	approx. 0.24	0.6 (0.5-0.9)
50% reduction in decerebrate rigidity	0.25 (0.22-0.27)	1.5 (1.3-1.7)	6	0.11 (0.04-0.2)	0.7 (0.38-0.93)	6	0.09 (0.05-0.13)	approx. 0.3
Reduction in spindle afferent discharge	0.1-0.2 (17)	Not tested	–	0.05-0.1 (4)	0.5-1 (3)	–	Not tested	0.5 (2)

Figures in parentheses refer to the 95% fiducial limits of the effective dose except for data on spindle discharge where they refer to number of experiments.

Antagonism of 5-hydroxytryptamine-induced contractions of the nictitating membrane

M & B 18,706 was only a weak antagonist of 5-HT-induced contractions of the cat nictitating membrane. From a series of five experiments in which doses of 0.2-20 mg/kg were administered, the dose of M & B 18,706 required to halve the potency of 5-HT on the nictitating membrane was computed to be 22 mg/kg. (+)-M & B 18,706 was studied in two experiments, and from these the effective antagonistic dose to 5-HT was found to be 5.2 mg/kg. Although the fiducial limits for the effective dose of M & B 18,706 were wide, it appears that M & B 18,706 was less potent than (+)-M & B 18,706 as an antagonist of 5-HT in the cat.

Since M & B 18,706 is more potent in reducing decerebrate rigidity than (+)-M & B 18,706 (see below) the relationship between the effects of these drugs in reducing decerebrate rigidity and antagonism of 5-HT was not investigated further.

Effects on decerebrate rigidity

α-Adrenoceptor antagonists. M & B 18,706 was six times more active than (+)-M & B 18,706 in reducing decerebrate rigidity (Figure 1). Similarly, methotrimeprazine was six times as potent as (+)-methotrimeprazine in this respect. Chlorpromazine and thymoxamine were also effective in reducing decerebrate rigidity, in doses comparable with those required to halve the pressor potency of noradrenaline (Table 1).

Desipramine. In order to investigate the possibility that desipramine might increase decerebrate rigidity the effect of the compound was studied both in preparations which had a low degree of rigidity after decerebration and in some experiments in which rigidity had been reduced or abolished by the prior administration of a phenothiazine derivative.

Three experiments were carried out in cats which showed a low degree of rigidity after decerebration. In all three preparations an intravenous administration of desipramine (2 mg/kg) produced a considerable increase both in the EMG response to stretch of quadriceps (Fig. 2) and in rigidity. The increase in rigidity was sustained over 30-60 minutes.

The compound was also studied in two preparations in which rigidity has been reduced by the prior administration of a phenothiazine derivative. In one experiment in which decerebrate rigidity had been abolished by the administration of (+)-methotrimeprazine (0.6 mg/kg), desipramine (2 mg/kg) restored the integrated EMG response

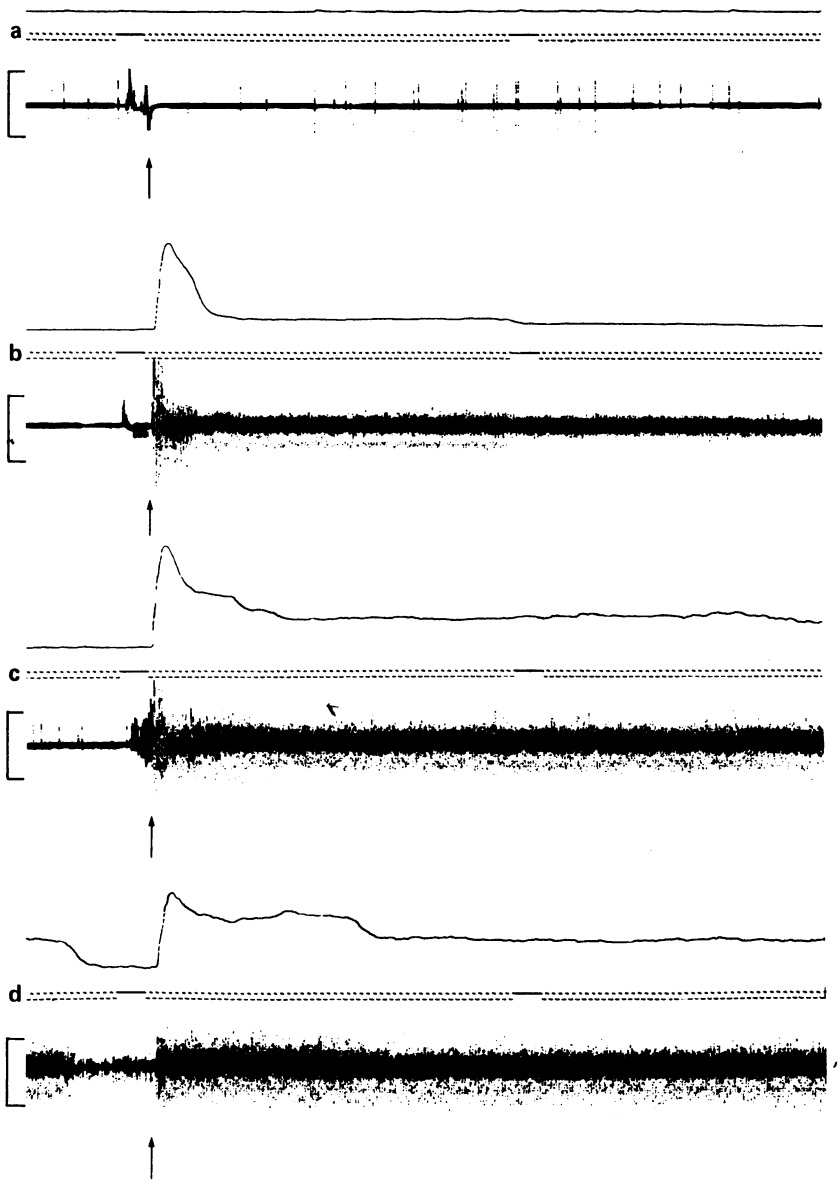


Fig. 2 Effect of desipramine on the EMG from the quadriceps muscle of a decerebrate cat with no spontaneous rigidity. In all panels the upper trace is the integrated EMG and the lower the recorded EMG. (a) Control recordings; (b), (c) and (d) recordings taken 15, 30 and 60 min after desipramine (2 mg/kg) intravenously. At the arrow, quadriceps were stretched by raising the lower leg. Time marks: seconds; vertical scale: 100 μV.

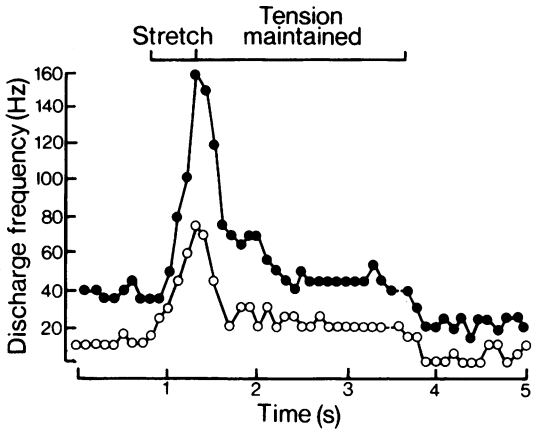


Fig. 3 Decerebrate cat (2.3 kg), with dorsal roots (L_6, L_7, S_1, S_2) cut. Effect of intravenous M & B 18,706 on discharge of primary spindle ending (conduction velocity 86 m/s) from soleus undergoing 2 cm stretch at 20 mm/second. Control, (•); M & B 18,706 (0.4 mg/kg) intravenously, (○).

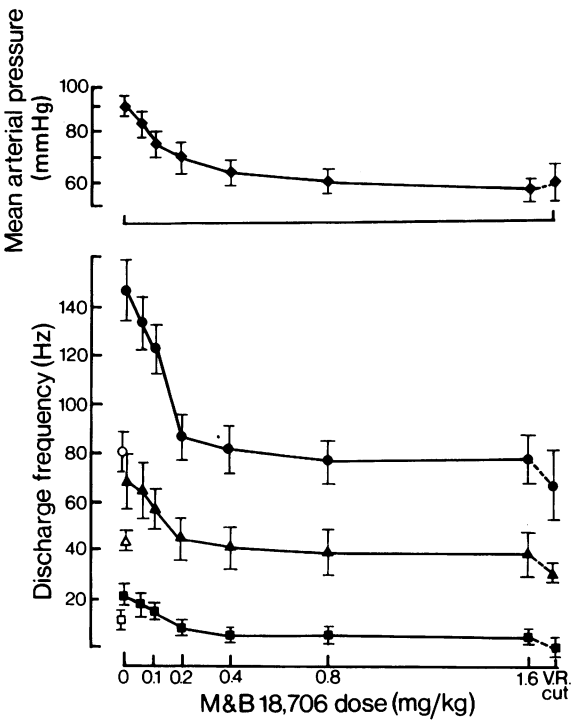


Fig. 4 Effect of intravenous M & B 18,706 on the discharge frequency of afferent fibres from spindle primary endings in response to stretch. Mean values for 11 experiments. Intercollicular decerebrate cats with sectioned dorsal roots (L_6-S_2) and intact ventral roots. Upper curve shows mean arterial pressure change during 14 experiments. Vertical lines indicate standard errors. V.R., ventral roots sectioned at the end of drug infusion. (•), dynamic discharge frequency; (▲), static discharge frequency; (■), resting discharge frequency. Open symbols show mean control value for four experiments with sectioned dorsal and ventral roots with no drug present.

from 0-92% of the control pre-drug level. This increase in the EMG response was accompanied by an increase in decerebrate rigidity.

In the second experiment decerebrate rigidity had been abolished by the administration of M & B 18,706 (0.3 mg/kg) and rigidity had subsequently returned almost to the control level. The administration of desipramine (2 mg/kg) increased the EMG response from 97 to 123% of the control pre-drug level. This was accompanied by an increase in rigidity.

Effect on muscle spindle afferent activity

α-Adrenoceptor antagonists. These experiments were additional to those used to measure decerebrate rigidity. Four parameters have been described (Maxwell & Rhodes, 1970) which can be used to measure a drug effect on spindle afferent discharge. These are (see Fig. 3): (a) the resting discharge frequency before stretch of soleus; (b) the maximum frequency during the dynamic phase of stretch; (c) the discharge frequency during maintained stretch; and (d) the discharge frequency on relaxation of the muscle tension.

In the present experiments drug effects were studied on the first three of these parameters, termed respectively, resting, dynamic and static discharge frequencies.

Intravenous doses of M & B 18,706 (between 0.05 and 0.4 mg/kg; Fig. 3) produced a reduction in resting, dynamic and static discharge frequencies of primary afferent fibres in the 11 preparations used (Figure 4). A similar effect was seen in the six experiments carried out in which afferent fibres from secondary endings were studied. Larger doses of between 0.4 and 1.6 mg/kg had little further effect on the frequency of response of a primary or secondary ending to stretch.

Similarly, intravenous doses of methotrimeprazine (four experiments) between 0.05 and 0.3 mg/kg caused reductions in resting, dynamic and static discharges of primary and secondary endings while (+)-methotrimeprazine (three experiments) had a similar effect in higher doses of between 0.5 and 4 mg/kg.

These effects are qualitatively similar to results

previously obtained with dimethothiazine in which doses of 0.5-4.0 mg/kg of dimethothiazine were required to produce a gradual reduction in spindle afferent discharge (Maxwell & Rhodes, 1970).

In four preparations in which the ventral roots L_6 to S_2 were sectioned, M & B 18,706 had no effect on primary afferent spindle discharge. This had also been shown for dimethothiazine (Maxwell & Rhodes, 1970) and indicates that these phenothiazines probably do not reduce spindle afferent discharge by a direct effect on the muscle spindle, but rather by an effect on fusimotor discharge. In two experiments, thymoxamine (0.5 mg/kg i.v.) reduced spindle afferent discharge in a manner qualitatively similar to the phenothiazines.

Desipramine. The effects of desipramine on spindle afferent discharge were studied in eight preparations. In five preparations desipramine (2 mg/kg) produced an increase in the pattern of spindle afferent discharge produced by stretch of soleus. In one of these preparations, spindle discharge had previously been depressed by the administration of (+)-methotrimeprazine (4 mg/kg). In three other preparations desipramine (2 mg/kg) had no significant effect on the spindle discharge frequencies. Other doses of the drug were not studied.

Effects on arterial pressure

In the majority of the experiments on spindle discharge, arterial pressure was recorded from a brachial artery. The intravenous administration of the phenothiazine derivatives used caused a gradual reduction of arterial pressure and spindle discharge (Figure 4).

In one experiment in which the rate of discharge of an afferent fibre from a primary ending was studied, the ganglion blocking agent pempidine was administered in order to reduce arterial pressure. Doses of pempidine (1-3 mg/kg i.v.) produced a fall in arterial pressure but little significant decrease in the discharge frequency. The subsequent administration of M & B 18,706 (0.1-0.2 mg/kg) produced little further change in arterial pressure, but the discharge frequency was markedly reduced. It thus seems that the effects observed on spindle discharge were not secondary to effects on arterial pressure.

Comparison of α-adrenoceptor blocking potency with effects on decerebrate rigidity

M & B 18,706 was eight times as potent as (+)-M & B 18,706 in the test of α-adrenoceptor blocking potency and six times as potent in reducing decerebrate rigidity (Table 1). Methotrimeprazine was also eight times as potent as (+)-methotrimeprazine as an α-blocker and six times as potent in reducing decerebrate rigidity. With these four compounds, and chlorpromazine there was a significant positive correlation ($r = 0.922$, $P = 0.024$) between the effective dose required to cause 50% reduction in the pressor action of noradrenaline in the spinal cat and the dose required to produce 50% reduction in the rigidity of the decerebrate cat.

With all these compounds the doses required to reduce decerebrate rigidity were similar to those that reduced the frequency of spindle afferent discharge from soleus.

Discussion

The experiments described in this paper arose from the observation that, with compounds related chemically to dimethothiazine or to M & B 18,706, potency in reducing decerebrate rigidity was paralleled by potency in inhibiting peripheral α-adrenoceptors. In view of the suggestion (Dahlström & Fuxe, 1965; Ellaway & Pascoe, 1968) that a descending noradrenergic pathway might be involved in the control of fusimotor activity, it seems possible that the phenothiazine derivative we were studying affected decerebrate rigidity by an action on receptors for noradrenaline within the CNS.

It is difficult to draw conclusions concerning the mechanism of action of drugs in the CNS from their actions on the peripheral autonomic nervous system since the ability of chemically distinct compounds to penetrate the CNS and their distribution within it may vary considerably. It was thought however, that these differences might be minimized by a comparison of the pharmacological actions of two optical isomers (methotrimeprazine, a (−)-isomer and (+)-methotrimeprazine), or of an optical isomer with the racemic mixture (M & B 18,706 and (+)-M & B 18,706). If the distribution of two optical isomers within the CNS is similar, and if noradrenergic receptors are involved in the control of fusimotor activity in the CNS and furthermore if these receptors are similar to peripheral α-adrenoceptors, then one might expect to find some correlation between the potency of the optical isomers to inhibit peripheral α-adrenoceptors and their potency in reducing decerebrate rigidity and fusimotor activity.

In general terms the data we have obtained would appear to be in agreement with this. Firstly, M & B 18,706 is eight times as potent as (+)-M & B 18,706 in inhibiting peripheral α-adrenoceptors and is six times as potent in reducing decerebrate

rigidity. For methotrimeprazine, the ratios obtained were surprisingly similar. The closeness of the agreement between the two pairs of compounds is fortuitous since in one case the comparison is between a racemic mixture and the (+)-isomer, and in the other case between (+)- and (−)-isomers. Furthermore, the fiducial limits of the effective doses are wide.

For chlorpromazine and thymoxamine such comparisons cannot be made, nevertheless the effective doses of these compounds required to inhibit peripheral α-adrenoceptors were of the same order as those required to reduce decerebrate rigidity.

Difficulty in obtaining clear-cut dose-response lines for the α-adrenoceptor blocking action of phenothiazines such as chlorpromazine or methotrimeprazine has been reported by Webster (1965). The difficulty of obtaining a complete inhibition of the pressor action of noradrenaline in the spinal cat is probably related to the complex action of phenothiazines on α-adrenoceptors. Thus, Thoenen, Hurlimann & Haefely (1965) have shown that chlorpromazine has three distinct actions at the sympathetic nerve ending. It inhibits the uptake of noradrenaline into sympathetic neurones, it blocks α-adrenoceptors and it inhibits the release of noradrenaline.

The experiments on muscle spindle afferent discharge in the decerebrate cat were carried out to confirm that the drugs were reducing decerebrate rigidity by reducing fusimotor activity. The evidence that dimethothiazine reduces decerebrate rigidity by an action on the fusimotor system has been analysed by Maxwell & Rhodes (1970), and is as follows. Firstly, the drug reduces spindle afferent discharge at doses comparable to those required to reduce decerebrate rigidity, and increasing the dose further has little further action on spindle afferent discharge. Secondly, the drug has no action on spindle afferent discharge in preparations in which the ventral roots were cut prior to drug administrations. Thirdly, the spindle afferent discharge in a preparation after a high dose of dimethothiazine is not significantly altered by subsequently cutting the ventral roots, and is similar to that recorded in preparations with cut ventral roots.

Furthermore, dimethothiazine, chlorpromazine (Maxwell & Read, 1972) and M & B 18,706 (Maxwell *et al.*, 1974) have less than one-tenth the potency in reducing the rigidity of cats decerebrated by the ischaemic method than they do in reducing intercollicular decerebrate rigidity. The rigidity of cats decerebrated by the ischaemic method is not due to enhanced activity of fusimotor neurones (Granit, 1970). The importance of ensuring that the phenothiazine derivatives we have studied are acting by a central mechanism is emphasized by the recent report (Zaimis, 1973) that drugs with β-adrenoceptor stimulant actions are to some extent effective in lessening the muscular hypertonia of clinical spasticity.

It would appear unlikely that inhibition of 5-HT in the central nervous system is implicated in the reduction of decerebrate rigidity produced by the drugs we used; M & B 18,706 as distinct from methotrimeprazine is a weak antagonist of 5-HT on peripheral tissues and was not more potent than (+)-M & B 18,706 in this respect. Methotrimeprazine is a potent 5-HT antagonist (Parratt & West, 1957).

The possibility that the drugs we have studied are reducing decerebrate rigidity by inhibiting receptors for noradrenaline within the CNS is considerably strengthened by the results obtained with desipramine, a drug which is well known to inhibit the uptake of noradrenaline into noradrenergic neurones and to potentiate some adrenergically mediated effects. Desipramine increased decerebrate rigidity both when rigidity was spontaneously low and when it had been reduced by drugs. This increase in rigidity was sometimes quite dramatic. In separate experiments, it increased the spindle afferent discharge produced by controlled stretch of soleus. The site of action of desipramine in these experiments has not been studied but we would suggest that it is due to an action on the CNS rather than on the spindle itself.

Since experiments in the decerebrate cat may have some predictive value for the effects of drugs in spastic patients (Matthews, Rushworth & Wakefield, 1972), it would be of interest to know whether there are any reports of an increase in the muscle tonus of spastic patients to whom desipramine has been given as, say, an anti-depressant.

Our data confirm and extend the preliminary report of Ellaway & Pascoe (1968). These workers recorded the discharge of single gastrocnemius fusimotor neurones from decerebrate rabbits with the spinal cord transected at a low thoracic level. They found that desipramine prolonged the discharge evoked by electrical stimulation of the spinal cord immediately caudal to the transection and that chlorpromazine blocked these discharges. An adrenergic control has also been implicated in the control of tendon jerks in man (Phillips, Richens & Shand, 1973).

We feel that the present data support the view that a descending noradrenergic pathway in the central nervous system may be important in the control of fusimotor activity and that the phenothiazine derivatives we have studied reduce decerebrate rigidity and fusimotor afferent discharge by inhibiting these receptors for noradrenaline.

The authors thank Mr A.H. Loveless for help with the statistical analysis of the data and in preparation of the manuscript.

References

DAHLSTRÖM, A. & FUXE, K. (1965). Experimentally induced changes in the intraneuronal amine levels of bulbospinal neuron systems. *Acta. Physiol. Scand.*, **64**, (supplement 247), 7-36.

ELLAWAY, P.H. & PASCOE, J.E. (1968). Noradrenaline as a transmitter in the spinal cord. *J. Physiol., Lond.*, **197**, 8-10P.

GRANIT, R. (1970). *The basis of motor control.* Academic Press, London & New York.

MATTHEWS, W.B., RUSHWORTH, G. & WAKEFIELD, G.S. (1972). Dimethothiazine in spasticity; a further attempt at pharmacological control. *Acta Neur. Scand.*, **48**, 635-644.

MAXWELL, D.R. & READ, M.A. (1972). The effects of some drugs on the rigidity of the cat due to ischaemic or intercollicular decerebration. *Neuropharmacology*, **11**, 849-855.

MAXWELL, D.R., READ, M.A. & SUMPTER, E.A. (1974). Pharmacology of M & B 18,706, a drug which selectively reduces decerebrate rigidity. *Br. J. Pharmac.*, **50** (in press).

MAXWELL, D.R. & RHODES, K.F. (1970). The effects of dimethothiazine on muscle spindle activity in the decerebrate cat. *Br. J. Pharmac.*, **39**, 520-532.

MAXWELL, D.R. & SUMPTER, E.A. (1972). Noradrenergic receptors and the control of fusimotor activity. *J. Physiol., Lond.*, **222**, 173-175P.

PARRATT, J.R. & WEST, G.B. (1958). Inhibition by various substances of oedema formation in the hind-paw of the rat induced by 5-hydroxytryptamine, histamine, dextran, egg white and compound 48/80. *Br. J. Pharmac. Chemother*, **13**, 65-70.

PHILLIPS, S.J., RICHENS, A. & SHAND, D.G. (1973). Adrenergic control of tendon jerk reflexes in man. *Br. J. Pharmac.*, **47**, 595-605.

THOENEN, H., HURLIMANN, A. & HAEFELY, W. (1965). On the mode of action of chlorpromazine on peripheral adrenergic mechanisms. *Int. J. Neuropharmac.*, **4**, 79-89.

WEBSTER, R.A. (1965). The antiadrenaline activity of some phenothiazine derivatives. *Br. J. Pharmac. Chemother.*, **25**, 566-576.

ZAIMIS, E. (1973). Spasticity alleviation by drugs acting directly on skeletal muscle. *Lancet*, **i**, 403-405.

(Received September 14, 1973)