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THE EFFECT OF PSYCHOPHARMACOLOGICAL AGENTS ON THE HYPERTENSIVE RESPONSE TO ESERINE IN THE RAT

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Summary—The phenothiazine derivatives prometazine, acetylpromazine, thioridazine and chlorpromazine depressed or blocked the hypertensive response to eserine. Only prometazine specifically blocked the action of eserine and the sino-carotid reflex, leaving at the same time intact the effect of noradrenaline. The other phenothiazines, as well as chlordiazepoxide, block in parallel the effects of eserine and noradrenaline, and also the sino-carotid reflex.

The "minor tranquillizers" meclizine, trioxazine and hydroxizine do not affect or slightly potentiate the hypertensive effect of eserine.

LSD by itself potentiates the effect of eserine. High doses of LSD, probably by a central antagonistic action, reverse the block in response to eserine caused by prometazine and acetylpromazine.

It is concluded that antagonism or synergism with the hypertensive response to eserine could be used for assessment of pro- or anti-adrenergic central activity of psychopharmacological agents, provided they do not exhibit a strong peripheral adrenergic blocking action.

INTRODUCTION

IT HAS been already found that eserine produces regularly a hypertensive response in the rat anaesthetized by urethane (VARAGIĆ, 1955; DIRNHUBER and CULLUMBINE, 1955; HORNYKIEWICZ and KOBINGER, 1956). The most probable explanation which was suggested for this effect is a central activation of the adrenergic neurons (MEDAKOVIĆ and VARAGIĆ, 1957; LEŠIĆ and VARAGIĆ, 1961; VARAGIĆ, *et al.*, 1962). These findings have been confirmed and even used for the assessment of general sympathetic function (CASS and SPRIGGS, 1961).

TOMAN (1963) has roughly classified the psychopharmacological agents as anti-adrenergic for the major anti-schizophrenics and pro-adrenergic for the major anti-depressives. The same author has pointed out that this classification is a very poor first approximation to the actual pharmacological spectra of psychopharmacological agents, because the action of these substances usually includes blocking or facilitating actions on various test systems with presumed receptors for acetylcholine, adrenergic transmitters, 5-hydroxytryptamine and histamine. It was therefore of interest to investigate the effect of various psychopharmacological agents on the hypertensive response to eserine. It was expected that these experiments might provide some additional data on the site and mechanism of action of psychopharmacological substances.

METHODS

The method used in the present experiments has been already described in detail in previous papers (VARAGIĆ, 1955; LEŠIĆ and VARAGIĆ, 1961; VARAGIĆ and VOJVODIĆ, 1962).

The following substances were used: reserpine (Serpasil), prometazine (Phenergan), chlorpromazine (Largactil), acetylpromazine (Plivaphen), thioridazine (Melleril), hydroxizine, meclizine (Postaphen), trioxazine (Sedoxazin), meprobamate, chlordiazepoxide (Librium), noradrenaline bitartrate, acetylcholine hydrochloride, histamine dihydrochloride and lysergic acid diethylamide (LSD).

RESULTS

Phenothiazines. Prometazine, chlorpromazine, acetylpromazine and thioridazine were found to depress or completely block the hypertensive response to eserine. In all these experiments the responses to carotid artery occlusion and to noradrenaline were tested in parallel with eserine. Prometazine was found to block both the hypertensive responses to eserine and to carotid artery occlusion, at the same time leaving intact the effect of noradrenaline. The doses of prometazine ranged from 0·5 to 4·2 mg/kg. A typical experiment is shown in Fig. 1. The control responses to carotid artery occlusion, to noradrenaline and to eserine are shown in A. Between A and B 1 mg/kg prometazine was injected intravenously and 20 min later the same procedure was repeated in B. This type of response was obtained in eight out of eleven experiments.

Chlorpromazine was found to block equally the responses to acetylcholine, eserine, noradrenaline and histamine (Fig. 2). The doses of chlorpromazine ranged from 0·5 to 3·3 mg/kg. These doses of chlorpromazine blocked also the hypertensive response to carotid artery occlusion. This type of response was obtained in six out of eight experiments.

Acetylpromazine and thioridazine were also found to depress or block equally well the responses to eserine, noradrenaline and to carotid artery occlusion (Fig. 3 and 4). The doses of acetylpromazine ranged from 0·56 to 2·6 mg/kg, and those of thioridazine from 0·6 to 3·8 mg/kg. This type of response with acetylpromazine was obtained in three out of four experiments. Thioridazine was found to depress the response to eserine in four out of seven experiments, and to block it in three out of seven experiments.

Chlordiazepoxide. This substance was found to inhibit more specifically the responses to eserine and to carotid artery occlusion than the effect of noradrenaline, as shown in Fig. 5. The control responses to carotid artery occlusion, to noradrenaline and to eserine are shown in A. Between A and B 77 mg/kg chlordiazepoxide was injected intravenously and B was taken 15 min thereafter.

Higher doses of chlordiazepoxide (100–125 mg/kg) inhibited more strongly the effect of noradrenaline together with the complete block of the responses to eserine and to carotid artery occlusion. This type of response was obtained in seven out of nine experiments.

Meclizine, hydroxizine and trioxazine. These substances were found not to alter or to potentiate the hypertensive responses to eserine and to carotid artery occlusion, at the same time leaving intact the effect of noradrenaline. Fig. 6 shows an experiment in which meclizine potentiated the response to eserine. The control responses to carotid artery occlusion, noradrenaline, acetylcholine and eserine are shown in A. Between A and B 8·4 mg/kg meclizine was injected intravenously, and B was taken 20 min thereafter. This type of response was obtained in three out of four experiments.

Trioxazine potentiated the response to eserine in all five experiments, whereas hydroxizine did so in two out of three experiments. Trioxazine was used in doses from 50 to 150 mg/kg, and hydroxizine in doses from 5·9 to 55 mg/kg.

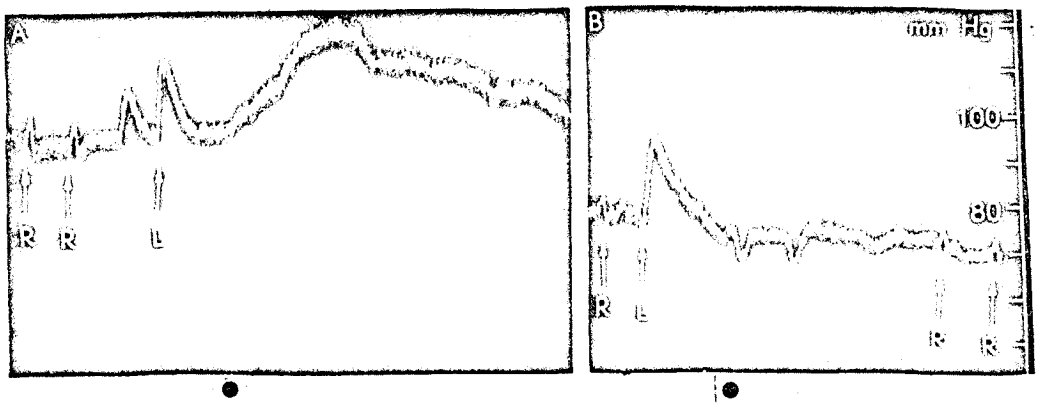

FIG. 1. The effect of promethazine on the blood pressure response to eserine, noradrenaline and sino-carotid reflex of the rat (185 g). At R: occlusion of right carotid artery for 15 sec. At L: 1 μg noradrenaline i.v. At ●: 20 μg eserine i.v. Between A and B: 250 μg promethazine i.v. Time: 2-min intervals

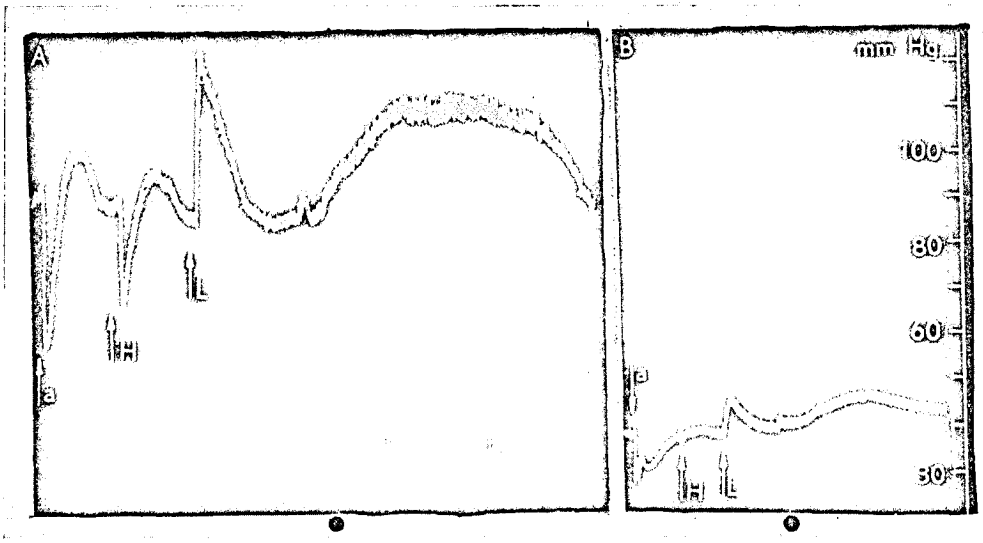

FIG. 2. The effect of chlorpromazine on the blood pressure response to acetylcholine, histamine, noradrenaline and eserine in the rat (200 g). At a: 2 μg acetylcholine i.v. At H: 3 μg histamine i.v. At L: 0·5 μg noradrenaline i.v. At ● : 20 μg eserine i.v. Between A and B: 300 μg chlorpromazine i.v. Time: 2-min intervals.

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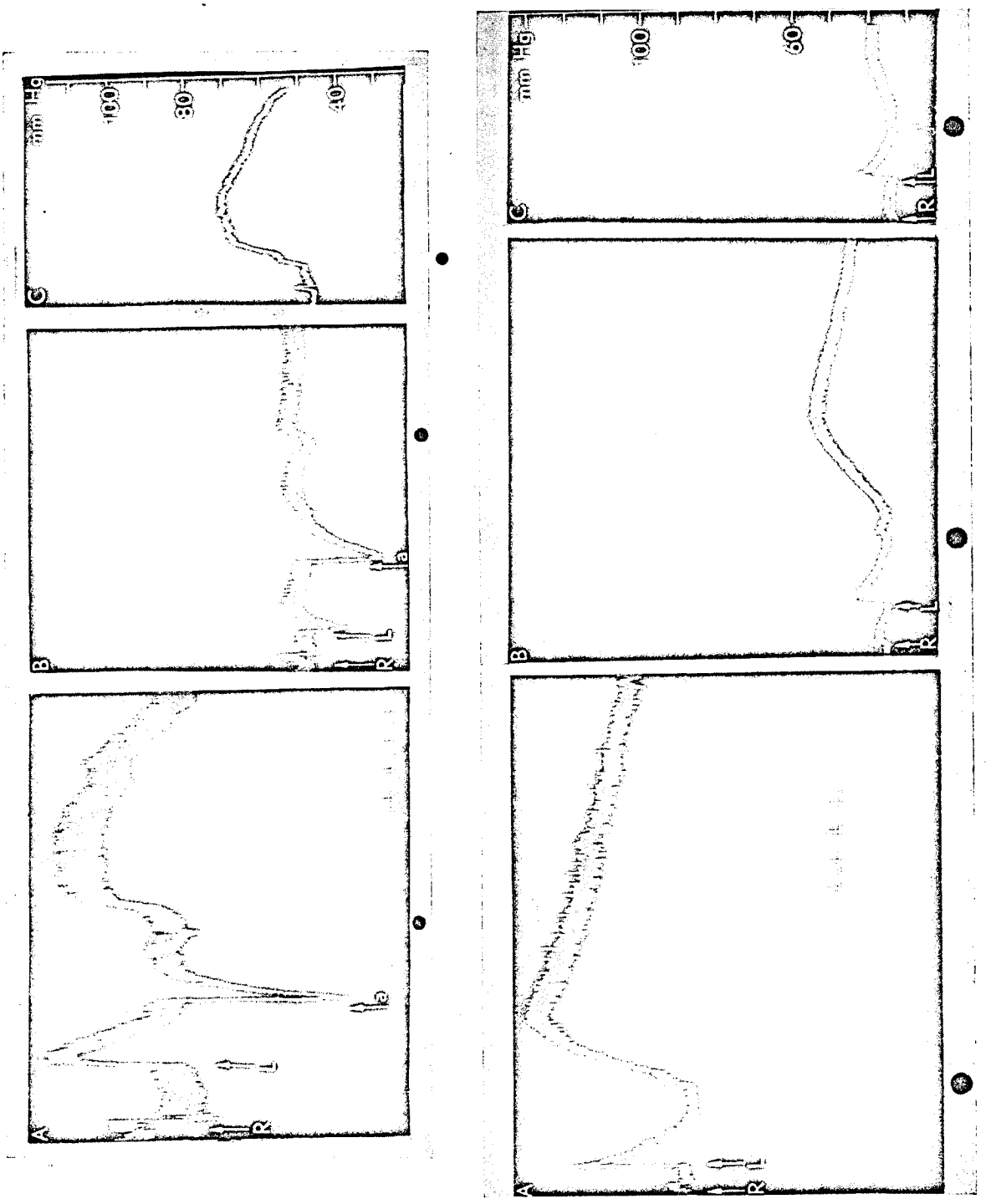

FIG. 3. The effect of acetylpromazine and LSD on the sino-carotid reflex and on the blood pressure response to noradrenaline, acetylcholine and eserine in the rat (220 g). At R: occlusion of right carotid artery for 30 sec. At L: 2μg noradrenaline i.v. At a: 0·5 μg acetylcholine i.v. At ●: 30 μg eserine i.v. Between A and B: 250 μg acetylpromazine i.v. Between B and C: 400 μg LSD slowly i.v. (The animal was kept on artificial respiration). Time: 2-min intervals.

FIG. 4. The effect of thioridazine on sinocarotid reflex and on the blood pressure response to noradrenaline and eserine in the rat (300 g). At R: occlusion of right carotid artery for 15 sec. At L: 1 μg noradrenaline i.v. Between A and B: 220 μg thioridazine i.v. Between B and C: another dose of 100 μg thioridazine i.v. Time: 2-min intervals.

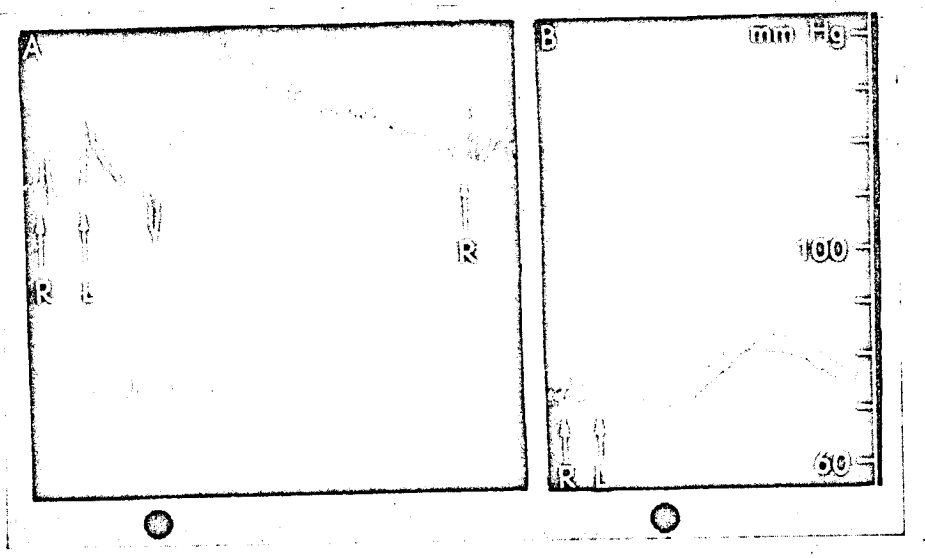

FIG. 5. The effect of chlordiazepoxide on sino-carotid reflex and on the blood pressure response to noradrenaline and eserine in the rat (260 g). At R: occlusion of right carotid artery for 15 sec. At L: 1 μg noradrenaline i.v. At ●: 20 μg eserine i.v. Between A and B: 20 mg chlordiazepoxide slowly i.v. Time: 2-min intervals.

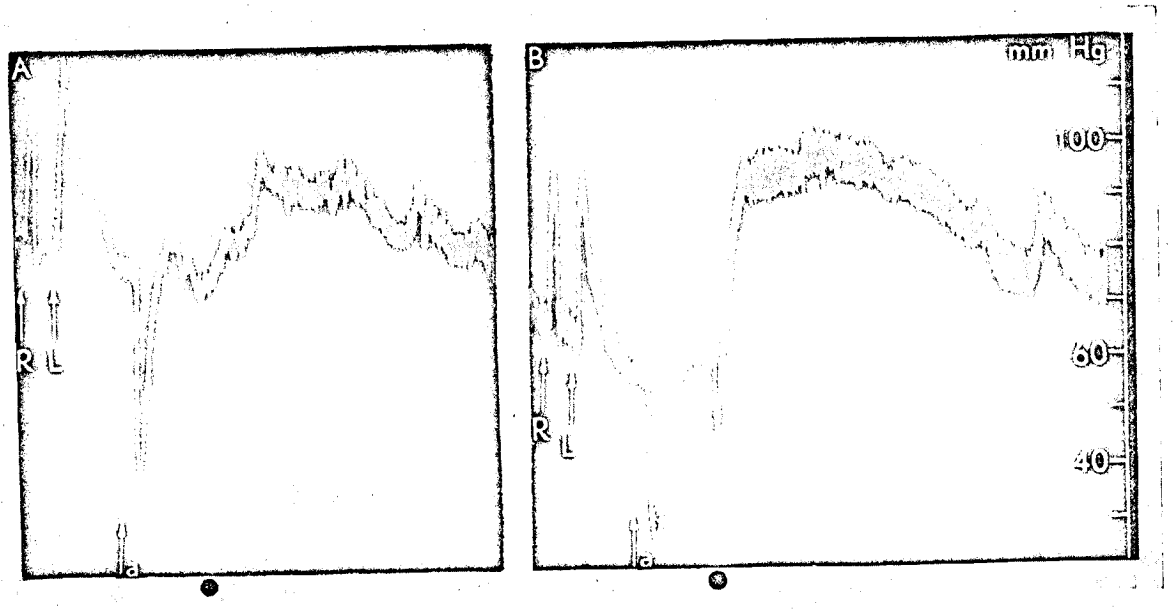

FIG. 6. The effect of meclizine on sino-carotid reflex and on the blood pressure response to noradrenaline, acetylcholine and eserine in the rat (235 g). At R: occlusion of right carotid artery for 15 sec. At L: 2 μg noradrenaline i.v. At a: 0·5 μg acetylcholine i.v. Between A and B: 2 mg meclizine i.v. Time: 2-min intervals.

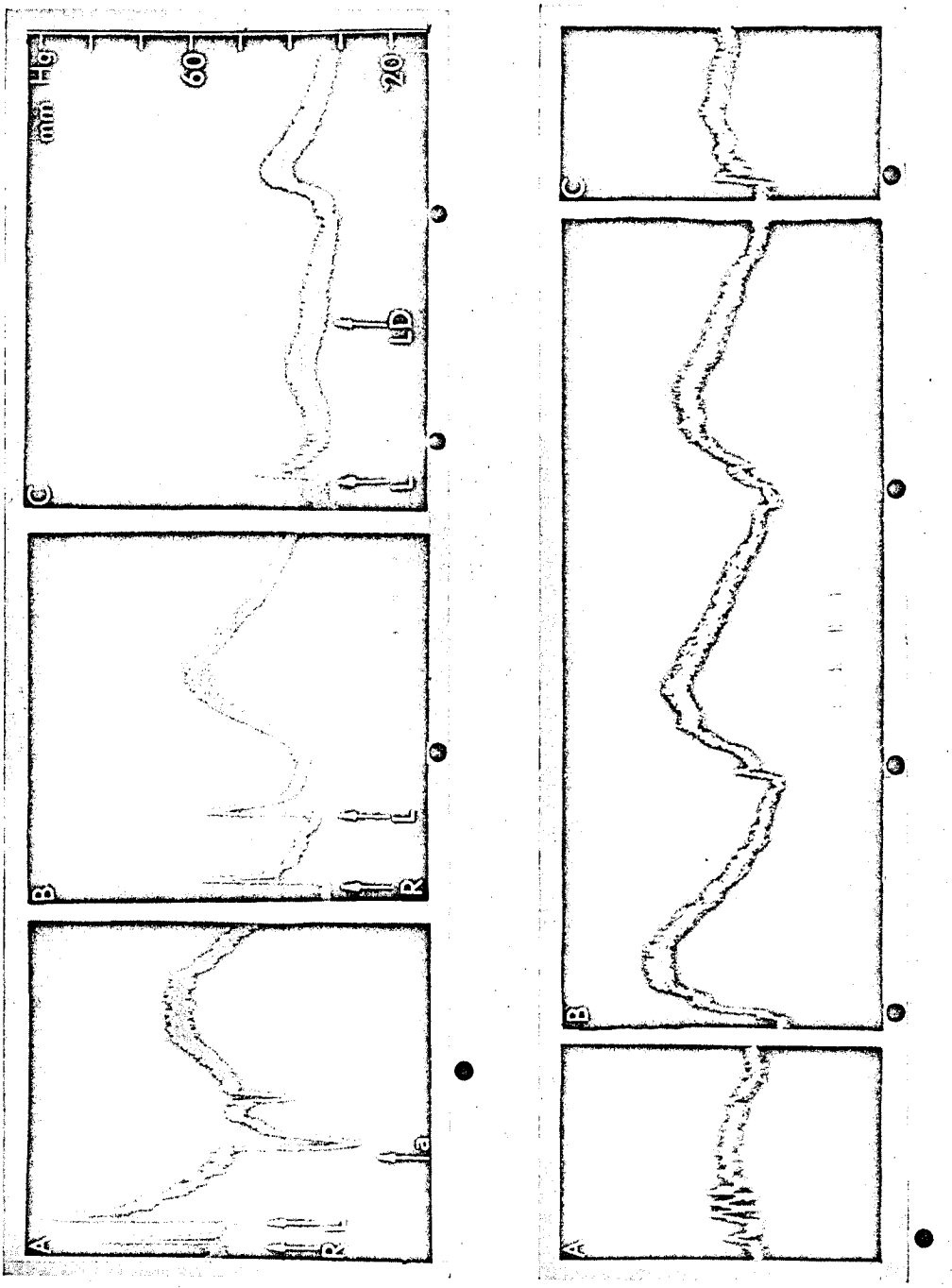

FIG. 7. The effect of LSD and acetylpromazine on sino-carotid reflex and on the blood pressure response to noradrenaline and eserine in the rat (190 g). At R: occlusion of right carotid artery for 15 sec. At L: 2 μg noradrenaline i.v. At ●: 30 μg eserine i.v. Between A and B: 500 μg LSD i.v. (the animal was on artificial respiration). Between B and C: 175 μg acetylpromazine i.v. At LD in C: another dose of 300 μg LSD i.v. Time: 2-min intervals.

FIG. 8. The effect of acetylpromazine and LSD on the blood pressure response to eserine in the rat (220 g). The effect of eserine (as shown in A) was blocked by previous injection of acetylpromazine (250 μg i.v.). At ●: 20 μg eserine i.v. Between A and B: 400 μg LSD slowly i.v. (the animal was on artificial respiration). (C) was taken 15 min after (B). Time: 2-min intervals.

Meprobamate. It was shown previously that mebutamate, a derivative of meprobamate, blocked the hypertensive response to eserine (VARAGIĆ and VOJVODIĆ, 1962). Contrary to mebutamate, meprobamate was found in the present experiments to depress slightly the effect of eserine or to leave it unchanged (in three experiments). The doses of meprobamate ranged from 34 to 136 mg/kg.

Lysergic acid diethylamide (LSD). LSD by itself did not alter or exceptionally potentiate the hypertensive response to eserine, at the same time leaving intact or even inhibiting the effect of noradrenaline. This type of response was obtained in four out of five experiments. The doses of LSD ranged from 1–4 mg/kg. It was also found that LSD produced reversal of the block in response to eserine caused by prometazine (in three out of six experiments) and by acetylpromazine (in three out of four experiments). A typical experiment is shown in Fig. 3 and 7. The control responses to carotid artery occlusion, noradrenaline, acetylcholine and eserine in Fig. 7 are shown in A. Between A and B 2 mg/kg LSD was injected slowly intravenously, divided in two doses. The animal was kept on artificial respiration. B was taken 10 min after second dose of LSD and it shows a slight potentiation of the response to eserine and carotid artery occlusion, while the effect of noradrenaline is slightly depressed. Between B and C 1 mg/kg acetylpromazine was injected and 15 min later the response to eserine was blocked, as shown in C. At LD in C, a third dose of 1·5 mg/kg LSD was injected and it produced reversal of the previous block in response to eserine, as shown at the second dot in C. Such reversal lasted up to 160 min. The gradual decline of the reversed response to eserine is shown in Fig. 8. The response to eserine after previous injection of 1·3 mg/kg acetylpromazine is shown in A. Between A and B 1·8 mg/kg LSD was slowly injected and it produced reversal of the previous block in response to eserine, as shown in B. This reversal then gradually disappeared, as shown in C.

It was found previously that pretreatment with reserpine in doses from 1 to 2 mg/kg intraperitoneally significantly depressed or abolished the hypertensive response to eserine in the rat (HORNIKIEWICZ and KOBINGER, 1956; LEŠIĆ and VARAGIĆ, 1961). It was now found that LSD in doses from 1 to 2 mg/kg into previously reserpine treated rats slightly potentiated the hypertensive effect of eserine in three experiments and restored it in one experiment, whereas in one experiment there was no change after injection of LSD.

Imipramine. This substance was found to depress the hypertensive response to eserine in four out of five experiments. The doses of imipramine ranged from 1·3 to 4·2 mg/kg.

DISCUSSION

The present experiments show that phenothiazine derivatives prometazine, chlorpromazine, acetylpromazine and thioridazine invariably depressed or even blocked the hypertensive response to eserine. At the same time, these drugs blocked or depressed the hypertensive effect due to carotid artery occlusion. With the exception of prometazine, all the other phenothiazines significantly depressed or blocked the hypertensive effect of noradrenaline as well. Prometazine has been found to have a very slight anti-adrenaline action (SEIFTER *et al.*, 1957; GLASSMAN *et al.*, 1958; GLASSMAN *et al.*, 1960), in contrast to chlorpromazine and other phenothiazine derivatives. It would therefore mean that block of the hypertensive response to eserine by prometazine could not be due to its peripheral antiadrenaline action but to its central activity. This is supported by the simultaneous depression of the hypertensive reflex due to carotid artery occlusion. On the contrary, this

differentiation is impossible with other phenothiazines because they equally blocked both the hypertensive response to eserine and the effect of noradrenaline, as well as the sinocarotid reflex. Similar differentiation between prometazine and other phenothiazines was found when evaluating their ability to affect H^3-noradrenaline storage (ROSELL and AXELROD, 1963). All the phenothiazines, which have anti-adrenaline property, produce a pronounced effect on storage of H^3-noradrenaline. Prometazine, on the other hand, has only a slight anti-adrenaline action and has no significant effect on H^3-noradrenaline storage.

Chlordiazepoxide as a member of a new class of compounds with central nervous system depressant effect, inhibited or even blocked the hypertensive response to eserine. Provided sufficiently high doses of chlordiazepoxide were used, the effect of noradrenaline was depressed parallelly with depression of eserine response.

On the other hand, a group of "minor tranquillizers" (meclizine, trioxazine, hydroxizine) did not affect or even potentiate the hypertensive response to eserine. This might indicate that these substances do not affect the central adrenergic tonus or to affect it in a different way from phenothiazines.

Meprobamate and its derivative mebutamate affect the hypertensive effect of eserine differently. Mebutamate depressed or blocked this effect of eserine (VARAGIĆ and VOJVODIĆ, 1962), whereas meprobamate, in doses used, only slightly inhibited the hypertensive action of eserine or left it unchanged. Mebutamate has been known to lower blood pressure by a central mechanism (BERGER *et al.*, 1961) and meprobamate has been found to produce this effect in some patients suffering from essential hypertension (DUNSMORE *et al.*, 1957; BOYD *et al.*, 1959).

Lysergic acid diethylamide (LSD) injected in doses from 1 to 4 mg/kg was found to potentiate slightly the hypertensive response to eserine. LSD also reversed the previous block in response to eserine caused by phenothiazines: prometazine and acetylpromazine. This effect of LSD was very weak if the block in eserine response was produced by pretreatment with reserpine. It is generally accepted that, in spite of similarity in clinical effects, mechanism and site of action of phenothiazines and reserpine are different (DOMINO, 1962; KILLAM, 1962). It is possible that LSD potentiates the effect of eserine and antagonizes the phenothiazine block in response to eserine by its central action, probably on the same sites where the action of eserine takes place. Still, these experiments do not exclude possible peri pheral mechanisms of LSD action in restoring the effect of eserine previously blocked by phenothiazine derivatives prometazine and acetylpromazine.

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Résumé—Les dérivés de la phénothiazine, la prométhazine, l'acétylpromazine, la thioridazine et la chlorpromazine, entravent ou inhibent l'effet hypertenseur de l'ésérine. Seule la prométhazine inhibe sélectivement l'action de l'ésérine et le réflexe sino-carotidien, tout en laissant intact l'effet de la noradrénaline. Les autre dérivés de la phénothiazine, ainsi que la chlordiazepoxide, bloquent respectivement les effets de l'esêrine et de la noradrénaline de même que le réflexe sino-carotidien.

Les "tranquillisants mineurs", tels que la méclizine, la trioxazine et l'hydroxyzine, ne modifient pas ou renforcent légèrement l'effet hypertenseur de l'ésérine.

Le LSD potentialise l'effet de l'ésérine. Des doses élevées de LSD contrecarrent probablement grâce à une action antagoniste centrale, l'inhibition de l'effet de l'ésérine due à la prométhazine et à l'acétylpromazine.

En conclusion, l'antagonisme ou la synergie envers l'effet hypertenseur de l'ésérine pourrait servir à la détermination de l'activité centrale pro- ou anti-adrénergique des agents psycho-pharmacologiques, à condition qu'ils n'exercent pas une forte action adrénolytique périphérique.

Zusammenfassung—Die durch Eserin ausgelöste Blutdrucksteigerung bei der Ratte konnte durch die Phenotiazinderivaten Promethazin, Acetylpromazin, Thioridazin und Chlorpromazin verminden oder aufgehoben werden. Nur Promethazin blockierte spezifisch die Wirkung von Eserin und sino-karotid Reflex, nicht dagegen die Wirkung von Noradrenalin. Die andere Phenothiazinen, als auch Chlordiazepoxid, blockierten in gleichen Ausmass sowohl die Wirkungen von Eserin und Noradrenalin, als auch die sino-karotid Reflex.

Die "minor tranquillizers" meclizin, trioxazin und hydroxyzin hatten keine Einfluss oder potenzierten schwach die blutdrucksteigernde Wirkung des Eserins.

Die vorhergehende Gaben von LSD potenzierte die Wirkung von Eserin. Die grossen LSD Dosen, wirkend wahrscheinlich zentral antagonistisch, revertierten den durch Promethazin und Acetylpromazin ausgelösten Block der Eserin Wirkung.

Auf Grund diesen Resultate es wurde festgestellt dass der Antagonismus oder Synergismus mit der Wirkung von Eserin könnte angewendet werden zur Einschätzung der pro- oder anti-adrenergischen zentralen Wirkungen von Psychopharmaka, unter Bedingung dass diese keine starke periphere anti-adrenergische Wirkung aufweisen.

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