THE ACTION MECHANISM OF RESERPINE COMPARED WITH THAT OF CERTAIN OTHER TRANQUILIZING SUBSTANCES

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Pharmacologists and clinicians have recently given much attention to the study and use of tranquilizing substances. A thorough understanding of the action mechanisms of these substances is necessary for their rational utilization.

There are many indications in the literature that the action mechanism of reserpine consists in its ability to liberate adrenalin, noradrenalin and serotonin from different tissues, brain tissue included, and from the reticular formation of the brain stem and the hypothalamus in particular [7, 11, 13]. One proof of this is the fact that the pharmacological effect of reserpine is reversed after the blockade of monoamine oxidase [5, 6, 8, 9, 10].

Beside reserpine, there are other substances of different chemical structure which possess a tranquilizing effect. Aminazine (chlorpromazine], a phenothiazine derivative, is one of these substances. Diphacyl [diphenylacetic acid diethylaminoethyl ester], one of the substances S. V. Anichkov has termed central cholinolytics (substances electively blocking the central cholinergic synapses), has an inhibitory effect on the central nervous system [1, 4]. Then there is the new preparation Antiffeine, a broken analog of caffeine synthesized and investigated by the Division of Pharmacology of the AMN SSSR Institute of Experimental Medicine, which has an effect antagonistic to that of caffeine [3]. Strophanthidin, which is steroid in structure, has a sedative effect according to the data of S. N. Asratyan [2]. Sygethin [dipotassium salt of 3,4-di-(paradisulfophenyl)-hexane], a diphenylhexane derivative, is similar in chemical structure to the synthetic substitutes for the steroid hormones. We found that Sygethin has, besides its known mild sedative effect on the gonadotropic and thyrotropic function of the hypophysis, an intensifying effect on the inhibitory process in castrated animals.

This work compares the effects of reserpine (obtained in the Soviet Union), Aminazine, Diphacyl, Antiffeine, strophanthidin and Sygethin after the blockade of monoamine oxidase. Our purpose in this work was to ascertain whether the action mechanisms of these substances all involved liberation of adrenalin, noradrenalin and serotonin.

METHODS

We used iproniazide and the new preparation phenylisopropyl hydrazine, the antiaminoxidase property of which was established by Horita [12], as monoamine oxidase inhibitors. All the experimental substances were used in the form of aqueous solutions. The reserpine solution was prepared as follows: a 1% solution was prepared in a 20% solution of ascorbic acid, then diluted with distilled water to the concentration required.

RESULTS

In the first series of experiments, we studied the effect of the experimental substances on the behavior and orientation reflexes of mice. We determined the degree to which the orientation reflexes were manifested 40 min

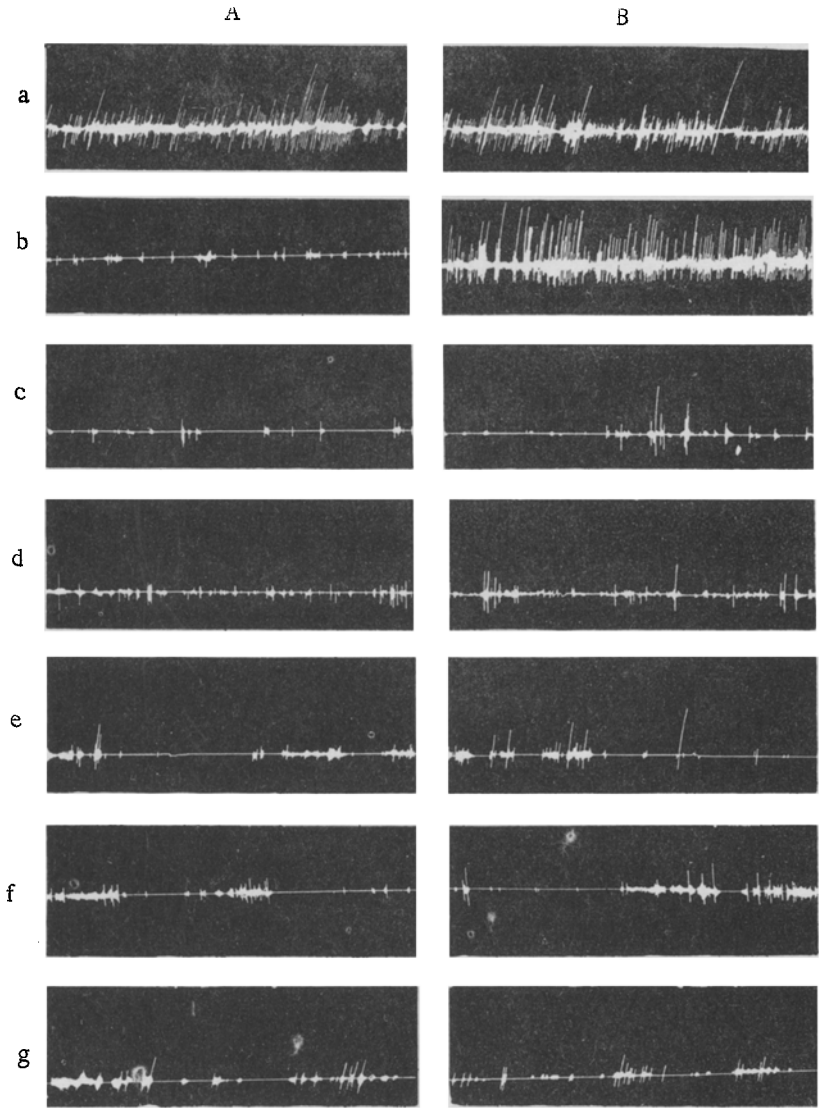

Fig. 1. Effect of reserpine, Aminazine, Diphacyl, Antiffeine, strophanthidin and Sygethin on the orientation reflexes of white mice normally (A) and after monoamine oxidase blockade (B). a) After intravenous injection of physiological solution; b) after intravenous injection of reserpine in a dose of 1 mg/kg; c) after intraperitoneal injection of Aminazine in a dose of 5 mg/kg; d) after intraperitoneal injection of Diphacyl in a dose of 40 mg/kg; e) after intravenous injection of Antiffeine in a dose of 50 mg/kg; f) after intraperitoneal injection of strophanthidin in a dose of 20 mg/kg; g) after intravenous injection of Sygethin-Na in a dose of 200 mg/kg; h*) time in 5-sec marks.

after the experimental substances were administered. The experiments were performed on 420 white mice. The experimental results (actograms) are shown in Fig. 1.

The intravenous injection of reserpine in a dose of 1 mg/kg caused the gradual development of a marked sedative effect. The orientation reflexes were acutely inhibited. We observed pronounced ptosis, endophthalmos and miosis in the animals. The same dose of reserpine administered two hours after the subcutaneous injection of phenylisopropyl hydrazine (5 mg/kg) or four hours after the intraperitoneal injection of iproniazide (100 mg/kg) caused a condition of motor excitation in the animals. The oriented reflexes were sharply enhanced. We observed exophthalmos, mydriasis and the pilomotor reflex. However, phenylisopropyl hydrazine and iproniazide did not cause in these doses any pronounced change in the behavior of the animals or in the manifestation of the orientation reflexes. The sedative effect of reserpine is evidently inverted after monoamine oxidase blockade.

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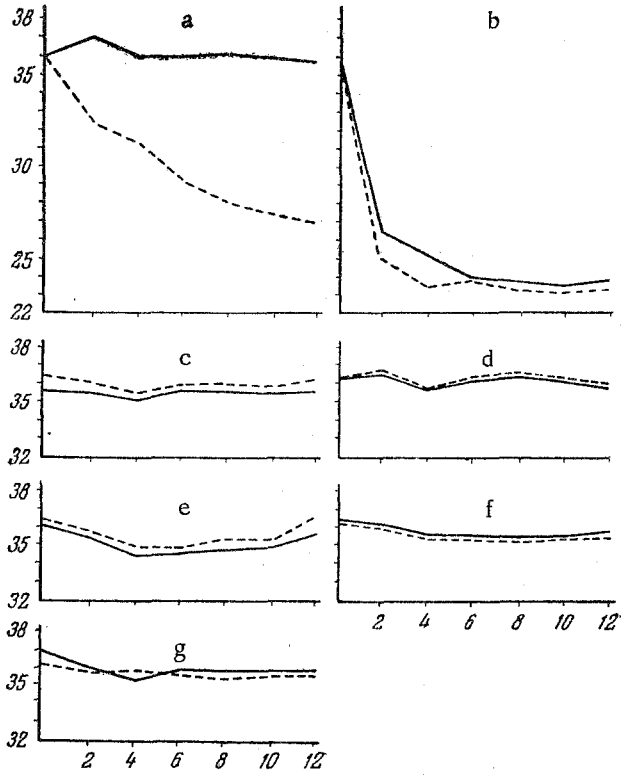

Fig. 2. Effect of reserpine, Aminazine, Diphacyl, Antiffeine, strophanthidin and Sygethin on the body temperature of mice normally (----) and after monoamine oxidase blockade (——). Abscissa axis: time (each division = 2 hr) after injection of experimental substances; ordinate axis: body temperature: a) after intravenous injection of reserpine in a dose of 2 mg/kg; b) after intraperitoneal injection of 10 mg/kg Aminazine; c) after intraperitoneal injection of 40 mg/kg Diphacyl; d) after intraperitoneal injection of 50 mg per kg Antiffeine; e) after intraperitoneal injection of 20 mg/kg strophanthidin; f) after intravenous injection of 200 mg/kg Sygethin-Na; g) after intravenous injection of physiological solution.

Larger doses of reserpine were administered in a few experiments (2-5 mg/kg). It was found that the larger the reserpine dose administered, the more rapid and pronounced its inhibitory effect. If, however, the monoamine oxidase inhibitors were administered first, the increased dose of reserpine caused a more rapidly developing and pronounced condition of excitation in the mice. If reserpine was administered to the animals first, on the other hand, the subsequent administration of the monoamine oxidase inhibitors did not invert the sedative effect of reserpine.

The results obtained concur with the literature data of other researchers [7].

Similar experiments were carried out in order to determine how blockade of monoamine oxidase influenced the sedative effect of the other tranquilizing substances. A sedative effect was also observed after the administration of 5 mg/kg Aminazine, 40 mg/kg Diphacyl, 20 mg/kg strophanthidin (intraperitoneally injected), 50 mg/kg Antiffeine or 200 mg/kg Sygethin (intravenously injected), but this effect was not materially altered by blockade of monoamine oxidase. The data obtained from our study of the degree to which the orientation reflexes were manifested were subjected to statistical processing, and the significance of the results was confirmed.

In a second series of experiments, we studied the effect of the monoamine oxidase inhibitors on the hypothermic effect of reserpine and the other tranquilizing substances. Experiments were performed on 300 mice. The temperature was determined in the rectum with the aid of a microelectrothermometer. It was found that both reserpine and Aminazine caused a sharp drop in the body temperature of the experimental animals. The antiaminooxidase preparations could remove reserpine's hypothermic effect, but did not materially alter that of Aminazine. Diphacyl, Antiffeine, strophanthidin and Sygethin-Na caused no significant change in the animals' body temperature, either when used alone or when used in connection with the antiaminoxidase preparations. Fig. 2 gives the results of this experimental series.

According to the literature data, reserpine can liberate adrenalin, noradrenalin, and serotonin from the endings of the sympathetic nerves and from other tissues as well as from the tissues of the central nervous system. We performed a third series of experiments in order to compare this peripheral effect of reserpine with the effects of the other tranquilizing substances. We used 75 rats weighing over 230 g each in these experiments. The blood pressure was determined while the animals were under amytal anesthesia. The experimental results are shown in Fig. 3.

Reserpine intravenously injected in a dose of 1.5 mg/kg caused a gradual fall of blood pressure. However, when Hexonium [hexamethonium] was preliminarily administered (10 mg/kg intraperitoneally injected) in order to exclude the central effect of the blood pressure, the same dose of reserpine did not produce a hypotensive effect; the blood pressure even rose slightly in some experiments. After the blockade of monoamine oxidase (either by 5 mg/kg phenylisopropyl hydrazine subcutaceously injected two hours before the experiment or by 100 mg/kg iproniazide intraperitoneally injected six hours before the experiment) and on a background of Hexonium action, reserpine caused a prolonged and pronounced pressor reaction. Analogous experiments were carried out with

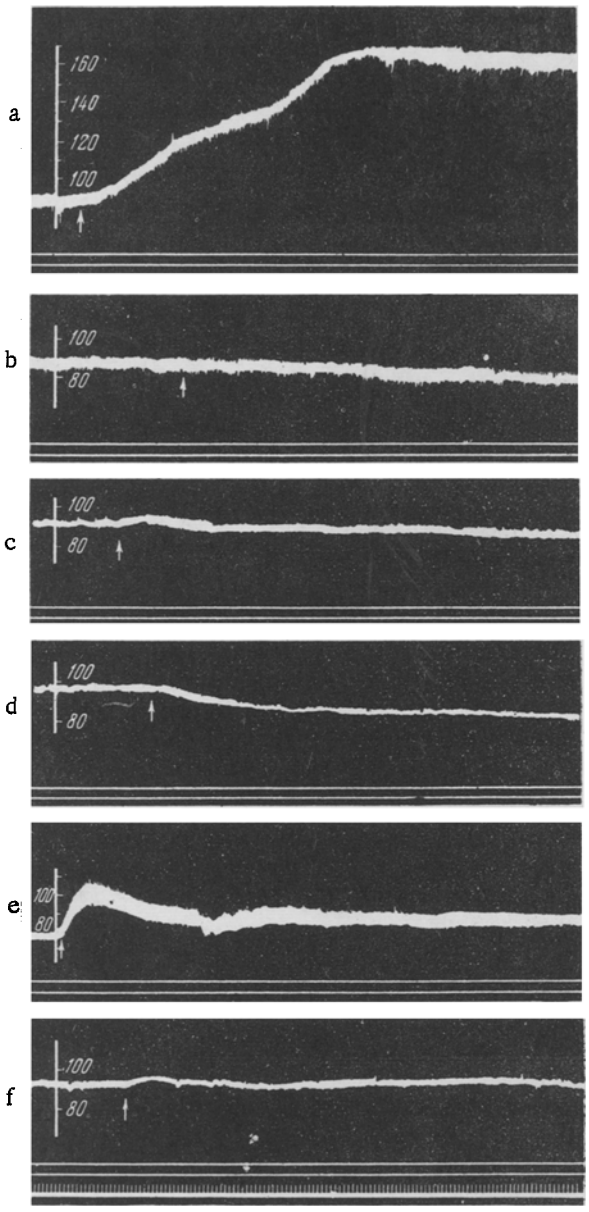

Fig. 3. Effect of reserpine, Aminazine, Diphacyl, Antiffeine, strophanthidin and Sygethin on the blood pressure under conditions of phenylisopropyl hydrazine blockade of monoamine oxidase. a) After injection of 1.5 mg/kg reserpine; b) after injection of 5 mg/kg Aminazine; c) after injection of 20 mg/kg Diphacyl; d) after injection of 25 mg/kg Antiffeine; e) after injection of 5 mg/kg strophanthidin; f) after injection of 100 mg/kg Sygethin-Na; arrow represents the intravenous injection of the preparation; time shown below in 5-sec marks.

Aminazine, Diphacyl, Antiffeine, strophanthidin and Sygethin. Except for strophanthidin, none of these preparations caused a clear pressor effect after the blockage of monoamine oxidase. Strophanthidin caused a slight rise of blood pressure, but this was not connected with the monoamine oxidase blockage, because the same rise of blood pressure was observed when strophanthidin was injected without preliminary use of the monoamine oxidase inhibitors.

The data obtained allow one to conclude that the sedative, hypotensive and hypothermic effects of reserpine become inverted under conditions of preliminary phenylisopropyl hydrazine or iproniazide blockade of monoamine oxidase, while the latter does not materially alter the pharmacological effects of Aminazine, Diphacyl, Antiffeine, strophanthidin and Sygethin. This indicates that the action mechanism of these substances is very different from that of reserpine. The action mechanism of reserpine consists in the ability of the drug to liberate adrenalin, noradrenalin and serotonin from different tissues, while the action of the other preparations studied in this work is caused by other mechanisms.

According to the literature data, the adrenolytic effect of Aminazine acts selectively to block the transmission of impulses in the ascending activating reticular system. Diphacyl's effect is due to its cholinolytic action. Antiffeine evidently enters into competition with purine derivative metabolites. The effect of strophanthindin and other central-inhibiting steroids may be connected with their capacity for metabolic absorption. Sygethin probably primarily affects the central formations sensitive to the ovarian steroid hormones.

SUMMARY

A study of the effect of reserpine in comparison with the action of Aminazine, Diphacyl, Antiffeine, strophanthidin and Sygethin has demonstrated differences in the mechanism of their action.

After blocking monoaminoxidase with phenylisopropyl hydrazine or iproniazide, the sedative, hypotensive and hypothermic effects of reserpine are inverted, whereas the pharmacological action of Aminazine, Diphaycl, Antiffeine, strophanthidin and Sygethin does not change materially.

The mechanism of reserpine action consists of its ability to liberate adrenalin, noradrenalin and serotinin from different tissues; the action of other preparations studied in this work (according to literature data) is caused by other mechanisms.

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