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INHIBITION OF HYPOTHALAMIC, MEDULLARY AND REFLEX VASOMOTOR RESPONSES BY CHLORPROMAZINE

BY

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In the course of an extensive pharmacological investigation Courvoisier, Fournel, Ducrot, Kolsky and Koetschet (1953) noticed that chlorpromazine (3-chloro-10(3′-dimethylaminopropyl)phenothiazine; 4560 R.P.; "Largactil"; "Megaphen") abolished the pressor reflex elicited by electrical stimulation of the central end of the vagus nerve. In the dose used for the demonstration of this effect, chlorpromazine also antagonized the pressor effects of adrenaline and noradrenaline. Dasgupta, Mukherjee and Werner (1954) observed that chlorpromazine very effectively suppressed the sham rage of diencephalic animals in doses considerably lower than those used by Courvoisier *et al.*; it was therefore concluded that chlorpromazine could block certain hypothalamic responses and that severance of cortico-hypothalamic tracts made such an action apparent. Other observations on central effects of chlorpromazine—such as the potentiation of the activity of narcotics (Courvoisier *et al.*, 1953; Zipf and Alstaedter, 1954) and of analgesics, block of conditioned reflexes (Courvoisier *et al.*, 1953) and behaviour changes with simultaneous alterations of the electroencephalogram (Das, Dasgupta and Werner, 1954)—made us wonder whether a central depressant action participated in the inhibition of vasomotor reflexes. Experiments were therefore undertaken to find whether, and under what conditions, chlorpromazine could block vasomotor responses centrally.

METHODS

Chlorpromazine was injected intracisternally into rhesus monkeys, anaesthetized with allobarbitone (50 mg./kg.). The blood pressure was recorded from the femoral artery, and carotid sinus reflexes were elicited by clamping both carotid arteries.

In cats under chloralose anaesthesia (60–80 mg./kg., i.v.) or decorticated under ether, pressor responses were elicited by electrical stimulation of the sciatic nerve with an induction coil, and by stimulation of medullary and hypothalamic pressor areas with a Horsley-Clark stereotaxic instrument. In the latter, the electrodes, insulated except for the tip, conveyed rectangular pulses of 0.5 msec. duration, at 100/sec.

In all experiments on cats the brain specimens were fixed in formol saline and the electrode position was verified histologically (Weil-stain). In most experiments under chloralose, and in all experiments on decorticate cats, artificial respiration was used throughout after paralysis of the spontaneous respiration with decamethonium (50–100 μg./kg. i.v., repeated when necessary).

RESULTS

Intracisternal Application of Chlorpromazine.—In a dose of 0.25–0.5 mg. per animal chlorpromazine caused a fall of blood pressure on intracisternal injection. Depending on the initial pressure, a reduction of the mean arterial pressure by 30 to 50 mm. Hg was observed in 4 such experiments on rhesus monkeys (5–7 kg. body weight).

The pressor reflex elicited by clamping both common carotid arteries was always abolished for at least 40 min. and then gradually returned to its original height in the course of 2–3 hr. The pressor response to intravenously injected adrenaline was not altered during the hypotension and reflex inhibition.

Experiments in Cats under Chloralose Anaesthesia.—In 14 such experiments, attempts were made to determine the effect of chlorpromazine on the sciatic pressor reflex, and on the pressor response caused by direct electrical stimulation of medullary and hypothalamic pressor areas. It was not always possible to obtain good responses to all three stimuli in the same animal, but at least two of the three tests could usually be carried out with satisfactory responses as regards height of blood-pressure rise (30–50 mm. Hg) and constancy of the response on repeated stimulation before administration of the drug. The posterior hypothalamus was aimed at with the Horsley-Clark instrument, and the actual site of stimulation was later verified histologically. The medullary pressor points selected for our experiments were, for reasons of

easier accessibility, chosen around the lateral wings of the caudal reticular formation, dorso-lateral to the inferior olivary nucleus (Alexander, 1946).

The results with chlorpromazine were not very uniform. In 8 experiments, 0.5 mg. kg. i.v. abolished reflex as well as direct medullary and hypothalamic pressor responses. In other experiments, however, doses even higher than 1 mg./kg. did not significantly lower the pressor responses. To assure better uniformity of the experimental conditions and to avoid complications arising from respiratory inhibition due to the central or reflex stimulation, the animals were, in some experiments, paralysed with decamethonium and artificially ventilated; however, the results with chlorpromazine did not gain in uniformity. These experiments, therefore, provide no evidence for a specific central vasomotor reflex blocking action, because the reduction of the pressor effects could be accounted for by the peripheral adrenolytic action of chlorpromazine.

In a few experiments the electrode tips were found to be situated in the pedunculi cerebri, or in the rostral parts of the pons, instead of the hypothalamus; no correlation between sensitivity of the pressor response to chlorpromazine and the site of the stimulated area was observed.

In view of our previous observation (Dasgupta *et al.*, 1954) that the central depressant activity of chlorpromazine greatly increases after decortication, the following experiments were undertaken.

Experiments on Decorticate Cats.—Hypothalamic and medullary pressor areas were stimulated in decorticate cats. In addition, the sciatic pressor reflex was used as a test response in some experiments. In all eleven experiments of this group, a more specific effect was now obtained with chlorpromazine. In doses of 50–100 μg./kg. intravenously, the pressor responses of reflex and central origin were completely abolished usually for several hours (Fig. 1); indeed, complete recovery was seldom obtained. The suppression of the pressor response was always accompanied by a large fall of blood pressure (20–40 mm. Hg), which also persisted for several hours. This marked hypotensive action was in sharp contrast to the lack of any significant effect of chlorpromazine on the blood pressure in animals with an intact central nervous system, even if administered in doses more than 10 times higher. Cannon and Britton (1925) have given evidence for a hypersecretion from the adrenal medulla in decorticated animals, which could be abolished by an additional transection at the level of the mid-brain; obviously the central blocking effect of chlorpromazine will appear more effective against the background of such a high sympathetic activity. In this connexion, reference can also be made to several of our experiments in which, following decortication, regular blood pressure waves were observed for about 15–30 min.; these animals were paralysed with decamethonium and artificially ventilated. Chlorpromazine in doses of 50–100 μg./kg. abolished the rhythmic blood pressure waves completely and at the same time lowered the mean arterial pressure by 30–50 mm. Hg (Fig. 2).

Discussion

The observations reported here show that, in certain circumstances, a central depressant effect of chlorpromazine on vasomotor tone and reflex activity can be demonstrated. The conditions necessary for the demonstration of this effect are either intracisternal application of the drug in anaesthetized, or intravenous administration in decorticated, animals. Particularly in the latter, a very pronounced suppression of vasomotor reflexes and of pressor effects of central origin can be detected in doses which are so low as to be devoid of any peripheral actions (Courvoisier *et al.*, 1953). The

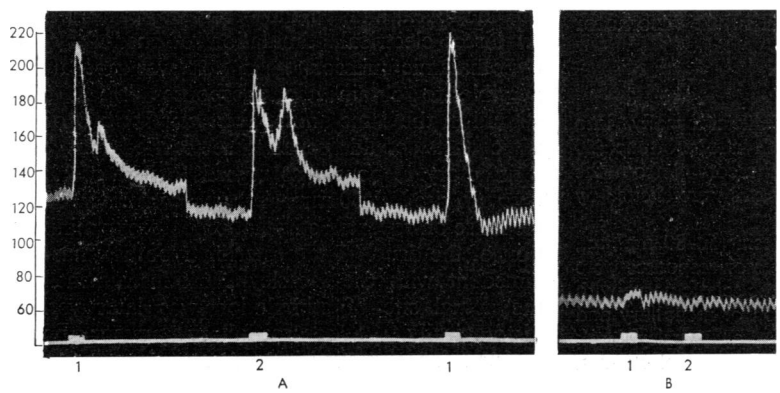

FIG. 1.—Decorticated cat (3.4 kg.); blood pressure in mm. Hg. Signals indicate periods of stimulation (7 sec.) of (1) hypothalamus (4.5 V) and (2) medulla (1.5 V). A before, and B 4 min. after, intravenous injection of 100 μg./kg. chlorpromazine.

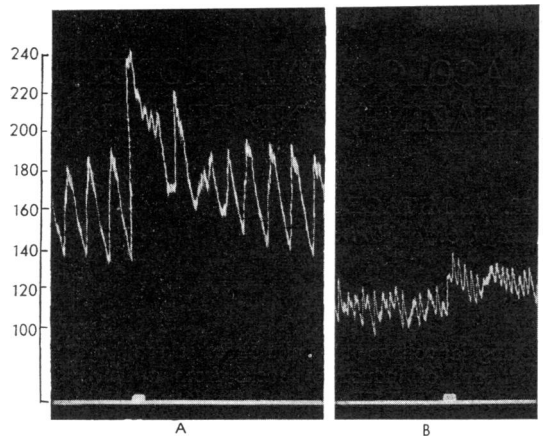

FIG. 2.—Decorticated cat (3.0 kg.); blood pressure in mm. Hg. Signals indicate periods of stimulation of the sciatic nerve (5 sec.; induction coil). A before, and B 6 min. after, intravenous injection of 100 μg./kg. chlorpromazine.

results in decorticate animals supplement our previously reported findings regarding the effect of chlorpromazine on the behaviour of decorticate cats: it is apparent that the effects of direct electrical stimulation of the hypothalamus are suppressed by chlorpromazine in the same way as the signs of sham rage when evoked by reflex stimulation (Dasgupta *et al.*, 1954).

Comparable observations with morphine reveal a different pattern of activity: only the skeletal motor components of sham rage are reduced or abolished in therapeutic doses (Wikler, 1944), whereas effects of direct hypothalamic stimulation are not suppressed (Masserman, 1939). However, before assigning to chlorpromazine any central activity peculiar to this drug only, it will be necessary to compare the pattern of activity of other drugs with central depressant actions under similar experimental conditions.

SUMMARY

1. Intracisternal injection of chlorpromazine to rhesus monkeys causes a fall of blood pressure and suppression of carotid sinus reflexes.

2. Pressor responses elicited by electrical stimulation of hypothalamic or medullary pressor areas, and the sciatic pressor reflex, are specifically abolished in decorticated cats by chlorpromazine in doses of 50–100 μg./kg.

3. Cats under chloralose anaesthesia are considerably less susceptible to such blocking actions of chlorpromazine.

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