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EFFECTS OF RESERPINE ON BLOOD-PRESSURE RESPONSES EVOKED FROM THE HYPOTHALAMUS

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Different areas of the hypothalamus were stimulated by a stereotaxic technique before and after reserpine in unanaesthetized cats. Reserpine in a dose of 1 mg./kg. body weight increased the threshold of stimulation of hypothalamic areas in cats giving an initial pressor response. It decreased the threshold of stimulation of areas of the hypothalamus in animals giving an initial depressor response. Reserpine thus appeared to affect the hypothalamus directly in two ways. It depressed the sympathetic centres in the diencephalon and facilitated the parasympathetic ones.

Experimental pharmacological investigations by various workers (Bein, 1953; Tripod and Meier, 1954; Barrett, Rutledge, and Rogie, 1954) have revealed that in therapeutic doses reserpine does not possess any significant peripheral actions on the cardiovascular system. The ability of the drug to block certain reflex vasopressor responses (those obtained from carotid occlusion, stimulation of the central end of the cut vagus or of the sciatic nerve (Bein, 1953; Ray, Roy, Dasgupta, and Werner, 1953; Trapold, Plummer, and Yonkman, 1954), together with its clinical effects (hypotension, bradycardia, miosis, and tranquillizing action), certainly point to a central action, but they do not offer unequivocal support for the hypothesis of a hypothalamic site. Bhargava and Borison (1955) point out that reserpine mainly depresses the supraspinal structures without significantly affecting the spinal vasomotor excitatory state. Schneider (1955) concluded that reserpine caused a central block or inhibition of afferent impulses which normally stimulate the sympathetic activity rather than a direct depression of diencephalic sympathetic centres. Harrison and Goth (1955) observed that hypothalamic pressor response can be diminished in cats by reserpine. All the previous studies have been done on anaesthetized animals. Administration of an anaesthetic in itself may interfere with the nervous responses. The present investigation was therefore undertaken to study the effects of reserpine on hypothalamic stimulation responses in unanaesthetized animals by permanent implantation of electrodes, and to find out its effect on the hypothalamus.

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METHODS

In 22 experiments in cats, electrodes were permanently implanted on both sides of the hypothalamus at different co-ordinates with the help of the Horsley-Clarke stereotaxic instrument according to the method described by Delgado and Anand (1953). The cats were allowed to recover completely. After a period varying from 10 to 15 days, each cat was prepared for carotid blood-pressure recording under light ether anaesthesia, and allowed to regain consciousness fully. Subsequently bipolar stimulation of the hypothalamic region was done in unanaesthetized animals through the implanted electrodes by a square-wave stimulator and blood-pressure responses were recorded on a kymograph. In general, square-wave pulses of frequency of 30/sec. and 0.2 msec. duration were used. Responses were recorded with different intensities of stimulation, differing from one another by 0.5–1 volt. Reserpine ("Serpasil," Ciba), 1 mg./kg. body weight, was then injected into the femoral vein. This produced a generalized fall in blood pressure after about 2 to 3 hours, at the end of which time the same hypothalamic areas were again stimulated with the same parameters as were used before giving reserpine. Blood-pressure responses were again recorded. At the termination of the experiment the animals were killed, the brain specimens fixed in formalin, and the electrode positions verified histologically.

Results

In all 22 experiments were performed. In 16 of these stimulation of different areas of the hypothalamus before reserpine resulted in pressor responses (Table I), whereas in 6 others there were depressor responses (Table II). In 15 experiments out of 16 giving an initial pressor response, the threshold of stimulation for producing the pressor response was markedly increased after reserpine (Fig. 1 and Table I). In one experiment (No. 7, Table I, and Fig. 2), however, the threshold of stimulation for producing a pressor response was decreased after reserpine. In this cat, curiously enough, there was a general rise of blood pressure (30 mm. Hg) during the 1st and 2nd hours after giving reserpine, whereas in all others there was a general fall of blood pressure (30 to 70 mm. Hg) 2 to 3 hours after reserpine. In 6 animals

TABLE I

COMPARISON BETWEEN THE THRESHOLD INTENSITIES OF STIMULATION OF THE HYPOTHALAMIC REGIONS FOR PRODUCING A PRESSOR RESPONSE BEFORE AND AFTER RESERPINE

Serial No.	Threshold Intensity, in Volts, for Pressor Response	
	Before Reserpine	After Reserpine
1	7·7	10·0
2	10·9	14·3
3	12·3	14·3
4	4·9	10·0
5	4·9	5·4
6	4·3	12·2
7	4·35	2·55 After reserpine the general blood pressure was raised
8	2·55	2·55
9	2·55	7·5
10	5·3	7·5
11	4·3	5·3
12	5·3	6·3
13	2·55	3·4
14	1·8	3·4
15	2·55	6·3
16	2·55	No rise even with 7·5 V.

TABLE II

COMPARISON BETWEEN THE THRESHOLD INTENSITIES OF STIMULATION OF THE HYPOTHALAMIC REGIONS FOR PRODUCING A DEPRESSOR RESPONSE BEFORE AND AFTER RESERPINE

Serial No.	Threshold Intensity of Stimulation, in Volts, for Depressor Response	
	Before Reserpine	After Reserpine
1	7·7	3·5
2	7·7	3·4
3	10·0	5·4
4	10·0	3·4
5	3·4	0·83
6	5·3	4·35

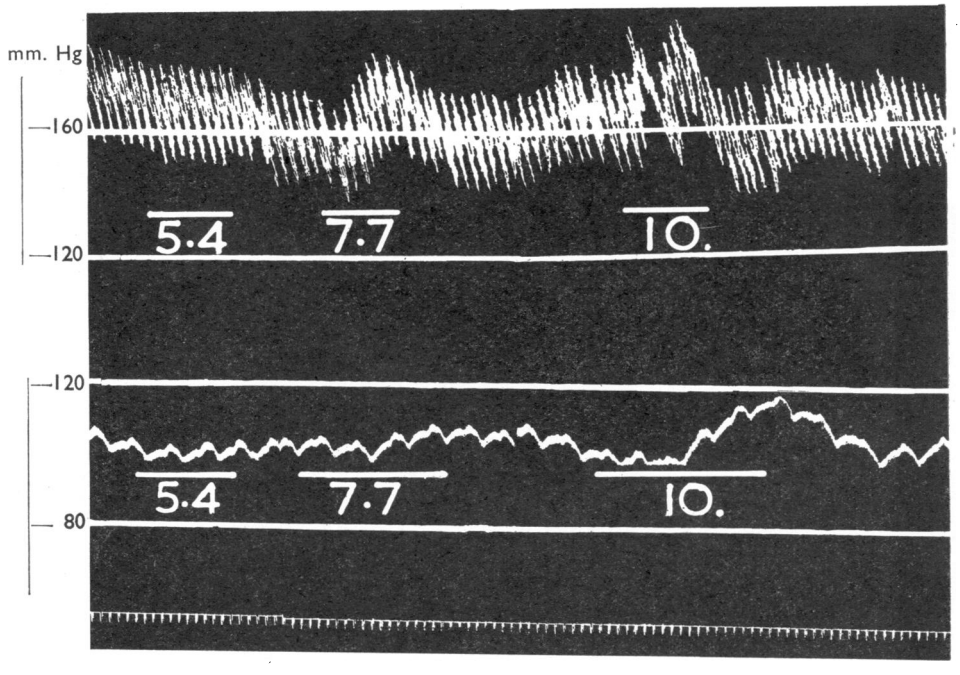

FIG. 1.—Blood-pressure responses produced by stimulation of hypothalamus, before (upper curve) and 2¼ hr. after giving reserpine (lower curve). Note the increase in the threshold of stimulation for pressor response from 7.7 V. to 10 V. after reserpine. Time signal 30/min. The horizontal line denotes the duration and the numerals the voltage of the stimulation.

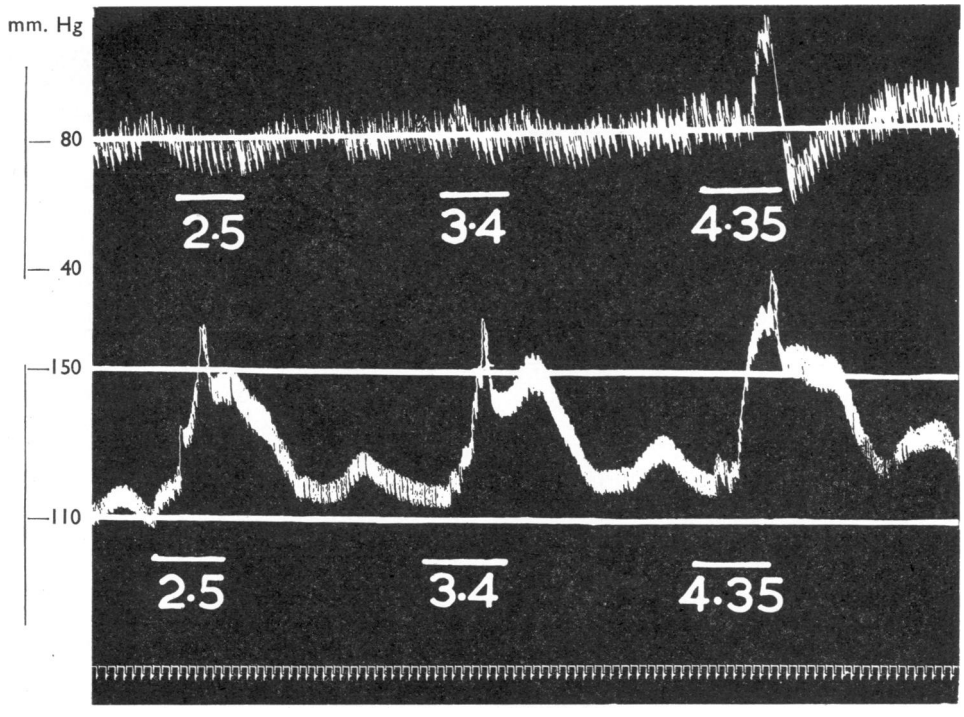

FIG. 2

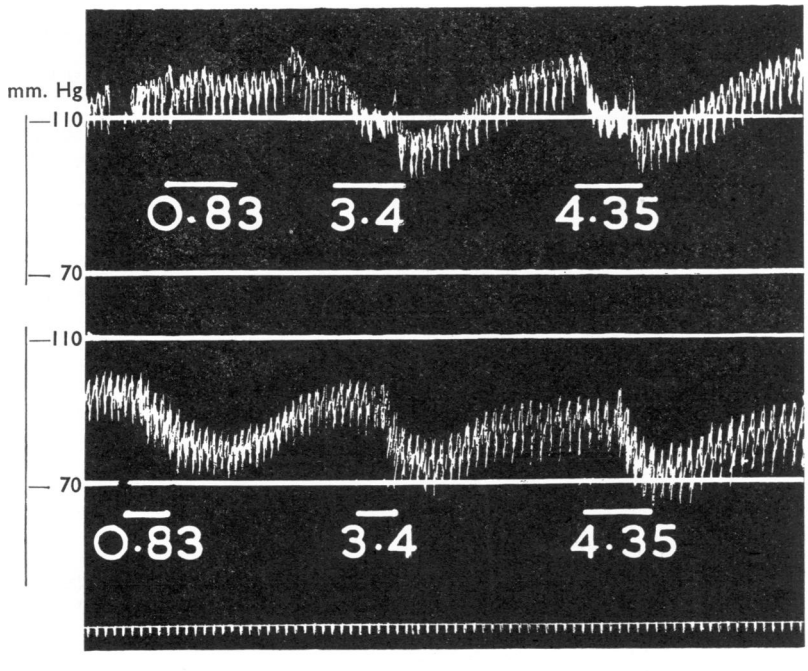

FIG. 3

FIG. 2.—Blood-pressure responses as in Fig. 1 produced by stimulation of hypothalamus, before and 4 hr. after giving reserpine, showing a decrease in the threshold for stimulation for pressor response from 4.35 V. to 2.5 V. after reserpine. Note also a rise of 30 mm. Hg in the general blood pressure after giving reserpine. Time signal 30/min.

FIG. 3.—Blood-pressure responses as in Fig. 1 produced by stimulation of hypothalamus, before and 2¾ hr. after reserpine, showing a decrease in the threshold for stimulation for depressor response from 3.4 V. to 0.83 V. after reserpine. Time signal 30/min.

showing an initial depressor response, there was a marked diminution in the threshold of stimulation for producing the depressor response after reserpine (Fig. 3 and Table II). Two other cats died 3 to 4 hours after giving reserpine, owing to a continuing fall in the general blood pressure.

Discussion

The observations reported here show that after reserpine the threshold of stimulation of the hypothalamic regions giving an initial pressor response is increased. Only in one cat was the threshold of stimulation diminished. In this cat, paradoxically, there was a general rise of blood pressure after reserpine. We have been unable to find any explanation for this anomaly. On the other hand, the threshold of stimulation of those regions which gave an initial depressor response was lowered after reserpine. These observations show that reserpine, in doses of 1 mg./kg. body weight, selectively affects the hypothalamus. In such doses it not only depresses the sympathetic centres in the hypothalamus, but it also facilitates the parasympathetic centres. These results are at variance with those of Schneider (1955) and of Harrison and Goth (1955). This may be due to the fact that these authors experimented with anaesthetized animals. The anaesthetic in itself may depress the hypothalamic areas so much that it may interfere with the nervous responses evoked from the hypothalamus. In this connexion it is interesting to note that after reserpine a typical picture of rage is not obtained (Schneider, 1955). In sham rage experiments, the influence of anaesthetics is absent. It appears that the effects of reserpine are due not only to selective depression of sympathetic centres in the diencephalon but also to facilitation of parasympathetic areas. The active facilitation of parasympathetic areas may also explain the production of bradycardia, miosis, etc., as well as the aggravation of existing bronchial asthma, renal colic, biliary colic, and ulcerative colitis which are observed in some hypertensive patients after reserpine treatment, as reported by Vakil (1954) and by Doyle and Smirk (1955).

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