Dependence of Protoveratrine-induced Hypotension on the Hypothalamus.* (23754)

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Through numerous studies (see Martini and Calliauw(1) for the literature) it has been established that certain veratrum derivatives including protoveratrine produce a hypotension through the excitation of the baroreceptors of the sino-aortic area. In a series of papers from this laboratory(2-9) the relation of baroreceptor reflexes to the hypothalamus was investigated by determining the action of hypotensive drugs (acetylcholine, mecholyl, histamine) and hypertensive agents (noradrenaline and adrenaline) before and after the excitability of the hypothalamus had been altered by various procedures. The resulting changes particularly in the cardiovascular action of these substances indicated that: 1. the noradrenaline-induced pulse slowing reflex depends, other conditions being equal, on excitability of the anterior hypothalamus; 2. intensity of sympathetic reflexes elicited by peripheral action of acetylcholine and related drugs depends on excitability of sympathetic division of the hypothalamus involving lateral and posterior hypothalamic nuclei.

Whereas noradrenaline and acetylcholine and related drugs cause a change in intensity of the baroreceptor discharges through variations in blood pressure and consequently in pressure of the sino-aortic area, protoveratrine alters these discharges directly. Injection of veratrum derivatives into the adventitial layer of the bifurcation of the carotid artery(10) or local application of this drug(11) elicits a fall of the blood pressure provided the baroreceptors are intact. The experiments here described were designed to determine whether the protoveratrine-induced baroreceptor reflexes depend likewise on the state of excitability of the hypothalamus.

Methods. The experiments were performed on 21 cats prepared under local anesthesia supplemented by thiopental i.v. Hess electrodes were inserted permitting either injection of pentobarbital or coagulation of a part of the hypothalamus through high frequency currents. The blood pressure was recorded from the femoral artery. EEG records were taken at the same time. Protoveratrine, kindly supplied by E. R. Squibb and Sons, was injected i.v. 1-2 hours after the operation while the cat was under artificial respiration and intocostrin. For further details see the above cited papers. Coagulation and histology as in our earlier work(12).

Results. Table I shows that the average fall of blood pressure following injection of Protoveratrine was 37 mm Hg in the control group, 4.5 mm after injection of 0.02 cc pentobarbital intrahypothalamically, and 8 mm after bilateral coagulation in the hypothalamus. The 2 experimental groups (10 cases) were combined and compared with the control group (11 cases). The difference is statistically highly significant ($\chi^2 = 9.39$; $p < 0.01$). Testing the difference between the means yields $t = 4.26$; $p < 0.001$.

Fig. 1 shows the sites of the injections projected on the median sagittal plane although

TABLE I. Fall of Blood Pressure (in mm Hg) after Intravenous Injection of Protoveratrine (.0005 mg/kg).

A Controls	After inj. of Nembutal* in lateral hypothalamus	After bilateral coagulation in lateral hypothalamus	After inj. of Dial intraper.
56	0	8	6
27	25	10	−8
22	0	6	8
86	−3	8	5
54	5		
10	0		
35			
10			
30			
27			
50			
† 37	4.5	8.0	2.8

* .02 cc 6%. † Avg.

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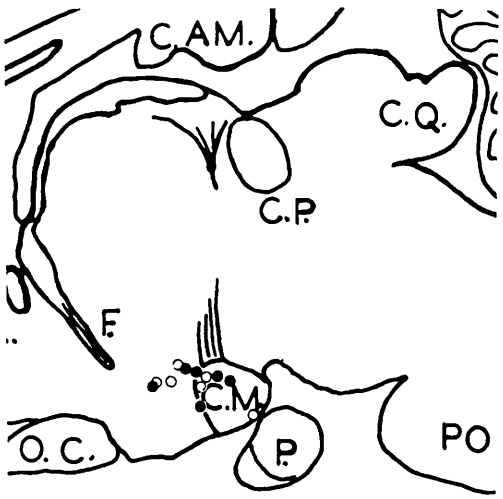

FIG. 1. Sagittal section through brain of cat. Black dots indicate site of inj. at left side, circles on right side. Site of inj. was 1-3 mm lateral to the median plane. O.C., optic chiasma; C.M., mammillary body; P., pituitary; F., fornix; PO., pons.

they were 1-3 mm lateral to it. They are closely related to the mammillary bodies and affect chiefly the lateral hypothalamic nuclei. The sites are similar to those which caused a fall of the blood pressure and pulse rate on intrahypothalamic injection of barbiturates or procaine(5).

The chief site of the lesions was in the same area. The mammillary bodies and the lateral and posterior hypothalamic nuclei were mainly involved. In one instance the lesion extended to a part of the red nucleus and, in another case, to one side of the supraoptic nucleus.

On the basis of earlier work from this laboratory it may be said that these injections and lesions interfere primarily with sympathetic excitability and tonic sympathetic impulses at the hypothalamic level. Since Protoveratrine fails to evoke a hypotension in sympathectomized animals(10) the action of the drug appears to be due to an inhibition of the central sympathetic tone. Our experiments seem to indicate that an important site of this inhibitory action is the sympathetic division of the hypothalamus.

Table II shows the reversibility of the action of the intrahypothalamically injected barbiturates. Whereas Protoveratrine is practically ineffective following this injection, it causes a distinct hypotension one or 2 hours later. At this time the excitability of the hypothalamus to direct stimulation was completely or almost completely restored to the control level.

The experiment on cat 5094 illustrates the fact that although 0.0005 mg Protoveratrine fails to induce a hypotension in a cat with an appropriate hypothalamic lesion, a sufficiently increased dosage (0.003 mg/kg) occasionally evokes a rise in the blood pressure. The central excitatory action of Protoveratrine on the medulla oblongata and spinal cord(10,13,14) which appears in the dog after sino-aortic denervation is retained in the cat in which, due to a lesion in the hypothalamus, the sino-aortic reflexes had been weakened.

Comment. To demonstrate the importance

TABLE II. Effect of Increasing Doses of Protoveratrine on Blood Pressure in Cats with Reduced Hypothalamic Excitability.

Cat #	Protoveratrine (mg/kg intrav.)	Blood pressure Before inj.	After inj.	Difference (mm Hg)	Remarks
5094	.0005	135	108	27	Control
	.0005	112	106	6	Bilateral coagulation*
	.0015	108	100	8	*Idem*
	.003	93	100	−7	"
5120	.0005	125	120	5	Nembutal bilaterally*
	.001	135	125	10	*Idem*†
	.001	120	85	35	" (1 hr later)
	.0005	120	105	15	" (" ")
5121	.0005	122	122	0	Nembutal bilaterally*
	.001	120	120	0	*Idem*†
	.001	136	106	30	" (2 hr later)

* In posterior hypothalamus.

† The first 2 tests on cat 5120 and 5121 were performed within 10 min. after intrahypothalamic inj. of Nembutal.

of the hypothalamus for sino-aortic baroreceptor reflexes it is necessary to use animals in which the effect of the barbiturates administered during the operation had worn off. This was indicated by the absence of slow potentials in the EEG of our animals. If, however, the experiments are performed in deep barbiturate anesthesia, the hypotensive action of Protoveratrine is absent as in the tests done under Dial-urethane anesthesia (Table I). Under these conditions the excitability of the posterior hypothalamus is greatly reduced(15) as in experiments involving lesions or intrahypothalamic injections of thiopental in this area.

The conclusion derived from our earlier studies cited in the introduction that baroreceptor reflexes act on the hypothalamus is confirmed by the experiments on the action of Protoveratrine described in this paper. Previously published data and our own show that small doses of Protoveratrine (0.0005 mg kg i.v.) elicit a hypotensive effect in the "light" cat but not in barbiturate anesthesia. Moreover, lesions in the sympathetic division of the hypothalamus or reduction of its excitability by the injection of minute quantities of barbiturates likewise reduce or eliminate the hypotensive action of Protoveratrine. Bearing in mind the action of Protoveratrine on the baroreceptors, it may be said that the hypothalamus is more sensitive to baroreceptor reflexes than the medulla oblongata.

Summary. In view of the fact that baroreceptor reflexes depend on excitability of the hypothalamus and that Protoveratrine elicits these reflexes, the action of Protoveratrine in relation to hypothalamic excitability was investigated in the cat. It was found: 1. That injection of barbiturates into the lateral and posterior hypothalamus practically abolishes the Protoveratrine-induced hypotension. This effect is reversible. 2. That lesions confined chiefly to the lateral hypothalamus exert a similar but irreversible effect. Such lesions do not interfere with the hypertensive action of larger doses of Protoveratrine. 3. That barbiturates administered intraperitoneally in anesthetic concentrations eliminate the hypotensive action of Protoveratrine.

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