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ROLE OF MONOAMINERGIC HYPOTHALAMIC STRUCTURES IN REGULATION OF FUNCTIONS OF THE SYMPATHICO-ADRENAL SYSTEM

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Sudden cooling of the body leads to considerable activation of the sympathico-adrenal system (SAS), which is manifested as elevation of the blood adrenalin (A) and noradrenalin (NA) levels accompanied by a small decrease in the body temperature [3].

Since the body temperature is controlled in the hypothalamus through the reciprocal actions of NA and serotonin [7], the investigation described below was carried out to study the effect of pharmacologic destruction of monoaminergic terminals in the hypothalamus on basal and cold-stress-induced secretion of neurohormones by the SAS.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 180-200 g in the fall and winter. The rats were divided into six groups: 1) intact; 2) control (receiving 0.5% ascorbic acid in physiological saline); 3) receiving 6-hydroxydopamine (6-HDA); 4) receiving demethylimipramine (DMI); 5) receiving DMI + 6-HDA; 6) receiving 5,6-hydroxytryptamine (HTA). The 6-HDA preparation (from "Regis Chemical"), in a dose of 200 μg in 20 μl of solvent, was injected once into the lateral ventricles of the rats (group 2). The animals of group 3 were given DMI (from "Geigy") intraperitoneally in a dose of 5 mg per rat 30 min before injection of 6-HDA into the lateral ventricles. The rats of group 4 received an injection of 5,6-HTA (from "Regis Chemical") in a dose of 75 μg in 20 μl of solvent per rat by injection into the cerebral ventricles.

After injection of 6-HDA into the cerebral ventricles in a dose of 200 μg, terminal portions of noradrenergic and dopaminergic fibers of the hypothalamus are known to be selectively destroyed [9]. Injection of DMI prevents destruction of noradrenergic fibers by 6-HDA but does not prevent injury to dopaminergic terminals [8]; after injection of 5,6-HTA into the cerebral ventricles, terminal portions of serotoninergic fibers in the hypothalamus are selectively destroyed [5].

The injection into the cerebral ventricle was given in a stereotaxic apparatus under hexobarbital anesthesia (10 mg/100 g body weight). Before the beginning of the experiment, all the rats were adapted to the chamber for 3-4 days. All the rats were kept for 1 h in a special chamber, with an air temperature of 22 ± 1 and 5 ± 1°C 7 days after injection of the preparation. The animals were then decapitated, the hypothalamus was removed, and blood was collected. Catecholaminergic structures in the hypothalamus were investigated by a fluorescence histochemical method [6]. The content of dopamine (DA) and NA in the hypothalamus and of NA and A in the blood was determined by the trihydroxyindole method [4]. Serotonin in the hypothalamus was analyzed by a fluorometric method [2]. Values obtained in rats kept at 5°C were compared with the corresponding values for rats kept at 22°C.

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TABLE 1. Effect of Intraventricular Injection of 6-HDA, 5,6-HTA, and DMI on Concentrations (M ± m) of NA and DA in the Hypothalamus and of NA and A in Peripheral Blood Plasma of Rats Exposed to Temperatures of 22 ± 1°C (control) and 5 ± 1°C (cold)

Group No.	Procedure	Hypothalamus, μmoles/kg				Blood, μmoles/liter			
		NA		DA		NA		DA	
		control	cold	control	cold	control	cold	control	cold
1	Intact (12 + 12)	9,81±0,25	—	6,23±0,72	—	27,95±1,99	—	19,68±1,30	—
2	Control (22 + 32)	9,69±0,58 $P_{1-2}>0,5$	10,34±0,24	5,84±0,28 $P_{1-2}>0,5$	5,51±0,10	24,71±2,04 $P_{1-2}>0,05$	34,22±2,30	20,14±1,11 $P_{1-2}>0,5$	28,87±1,11
3	6-HDA (12 + 12)	3,01±0,19 $P_{2-3}<0,001$	3,80±0,37 $P_{2-3}<0,001$	2,49±0,25 $P_{2-3}<0,001$	2,75±0,16 $P_{2-3}<0,001$	39,60±1,57 $P_{2-3}<0,001$	41,96±1,95 $P_{2-3}<0,001$	30,18±0,84 $P_{2-3}<0,01$	26,57±2,49 $P_{2-3}>0,5$
4	Control + DMI (12 + 12)	9,45±0,33 $P_{2-4}>0,5$	9,69±0,71 $P_{2-4}>0,05$	6,82±0,33 $P_{2-4}>0,05$	7,61±0,41 $P_{2-4}<0,05$	24,82±1,24 $P_{2-4}>0,5$	37,23±2,01 $P_{2-4}>0,05$	21,06±0,72 $P_{2-4}>0,5$	31,04±2,09 $P_{2-4}>0,5$
5	DMI + 6-HDA (12 + 12)	6,07±0,36 $P_{4-5}<0,05$	7,03±0,26 $P_{4-5}<0,01$	3,34±0,23 $P_{4-5}<0,001$	3,94±0,50 $P_{4-5}<0,001$	24,12±0,76 $P_{4-5}>0,5$	23,99±1,33 $P_{4-5}<0,001$	18,37±1,04 $P_{4-5}>0,05$	20,34±1,16 $P_{4-5}<0,05$
6	5,6-HTA (12 + 12)	9,51±0,59 $P_{2-6}>0,5$	12,94±0,73 $P_{2-6}<0,01$	5,57±0,09 $P_{2-6}>0,05$	5,25±0,16 $P_{2-6}>0,5$	22,63±0,71 $P_{2-6}>0,5$	23,11±1,42 $P_{2-6}<0,01$	20,73±1,37 $P_{2-6}>0,5$	21,19±0,39 $P_{2-6}<0,05$

Legend. Number of rats used for analysis of hypothalamus and blood plasma respectively shown in parentheses.

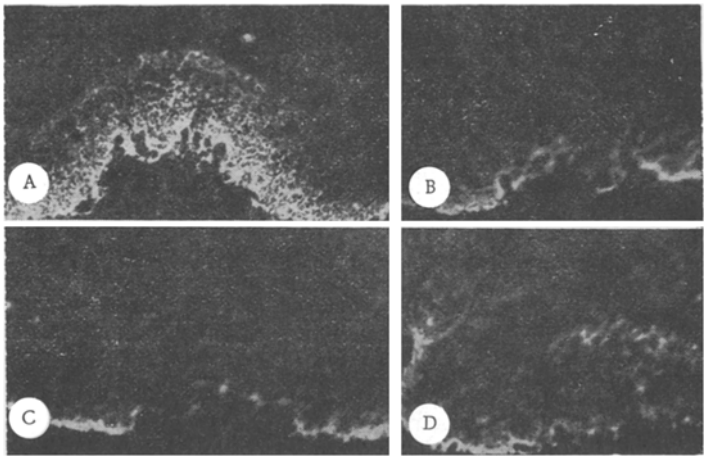

Fig. 1. Median eminance (ME) of rat hypothalamus in control (A) and one week after injection of 6-HDA (B, C) and of DMI + 6-HDA (D). A) Intensive fluorescence of noradrenergic and dopaminergic fibers and terminals in ME; B, C) fluorescence has disappeared in inner zone (B) and is reduced in outer zone of ME (C); D) fluorescence in ME is weaker than in control but stronger than after 6-HDA. Fluorescence photomicrograph; Falck's method; 160×.

EXPERIMENTAL RESULTS

Seven days after injection of 6-HDA into the cerebral ventricle under thermoneutral conditions (22°C) the NA concentration in the hypothalamus fell by two-thirds and the DA level fell by half (Table 1). Histochemical analysis showed that fluorescence of noradrenergic and dopaminergic structures of the hypothalamus did not differ in the rats of groups 1 and 2. In the region of the supraoptic and paraventricular nuclei of the control rats many terminals of noradrenergic fibers formed a dense network with bright green fluorescence. After injection of 6-HDA single terminals were found with tiny varicose thickenings and indistinct fluorescence. Fluorescence disappeared around the vessels in the meninges by the supraoptic nucleus. The effect of 6-HDA on the supraoptico-neurohypophyseal system was described by the writers previously [1]. In the control, single dopaminergic neurosecretory cells and fibers with intensive fluorescence were found in the arcuate nucleus. After injection of 6-HDA their fluorescence decreased. In the inner zone of the median eminence, where in the control (Fig. 1A) mainly noradrenergic fibers were concentrated, fluorescence was virtually

absent (Fig. 1B). In the outer zone of the median eminence where mainly terminals of dopaminergic fibers were concentrated, the intensity of fluorescence was considerably reduced, especially around the capillaries of the portal system (Fig. 1B). Cooling of the rats after injection of 6-HDA into the cerebral ventricles (1 h at 4°C) did not alter the picture of fluorescence of noradrenergic and dopaminergic structures of the hypothalamus compared with that observed in animals kept for 1 h at 22°C.

Consequently, seven days after intraventricular injection of 6-HDA a marked fall was observed in the NA and DA levels in the hypothalamus and a sharp decrease in the intensity of fluorescence and in the quantity of fluorescent noradrenergic and dopaminergic structures was noted. A short exposure to cold did not change the concentrations of catecholamines or the pattern of fluorescence of these structures in the hypothalamus.

After injections of DMI+6-HDA under thermoneutral conditions the NA concentration in the hypothalamus fell, but not to the same extent as after injection of 6-HDA (Table 1); fluorescence in the inner zone of the median eminence increased somewhat (Fig. 1C). Exposure to cold did not change the picture described above. The DA content in the hypothalamus after injection of DMI+6-HDA also fell, irrespective of the ambient temperature, just as after injection of 6-HDA alone (Table 1).

The results of histochemical analysis of various regions of the hypothalamus particularly rich in noradrenergic and dopaminergic structures thus correlate well with the biochemical data.

After intraventricular injection of 5,6-HTA the serotonin level in the hypothalamus fell from 13.6 to 6.2 μmoles/kg, evidence of destruction of terminals of serotoninergic fibers in the hypothalamus. Cooling was accompanied by a distinct increase in the NA concentration in the hypothalamus. In the absence of special pharmacological procedures, Falck's histochemical method does not enable serotoninergic fibers to be detected in the hypothalamus.

The results of experiments to study the action of 6-HDA, 5,6-HTA, and DMI+6-HDA on functional activity of the SAS are given in Table 1. Intraventricular injection did not affect the blood A and NA levels after 7 days. The A and NA levels in the plasma rose clearly after injection of 6-HDA at 22°C; injection of DMI+6-HDA did not change the blood NA level, but the A level was lowered somewhat under these circumstances. After cooling of the control animals the blood NA and A levels rose. In rats receiving 6-HDA, DMI+6-HDA, and 5,6-HTA the action of cold did not affect the blood A and NA levels.

Blocking the majority of noradrenergic fibers of terminals in the hypothalamus under thermoneutral conditions thus caused activation of the function of SAS. After short-term cold stress no further increase in hormone secretion by the SAS was observed. Destruction of dopaminergic and serotoninergic terminals of the hypothalamus did not significantly change the basal secretion of SAS hormones and made it impossible for the SAS to respond to cold.

The results are evidence that the noradrenergic fibers of the hypothalamus evidently play an inhibitory role, whereas dopaminergic and serotoninergic fibers play a stimulating role in the regulation of functional activity of the SAS.

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