EFFECT OF THE ENTEROTROPIC CARCINOGEN 1,2-DIMETHYLHYDRAZINE ON THE HYPOTHALAMIC BIOGENIC AMINE LEVEL IN RATS

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Subcutaneous injection of 1,2-dimethylhydrazine (DMH) in a dose of 21 mg/kg into male rats is followed after 24 h by a substantial fall in the hypothalamic levels of noradrenalin (NA), dopamine (DA), serotonin (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA). During the first 3-12 h after injection of DMH the NA level was lowered and the intensity of 5-HT metabolism increased in the hypothalamus. The hypothalamic histamine level rose only 30 min after injection of the carcinogen. No significant change took place in the biogenic amine levels in the brain stem and cerebral hemispheres under the influence of DMH. It is suggested that an essential link in the mechanism of the carcinogenic action of DMH in rats is the hormonal metabolic disturbances caused by the selective action of DMH at the level of the hypothalamic biogenic amines.

KEY WORDS: *1,2-dimethylhydrazine; biogenic amines; hypothalamus.*

1,2-Dimethylhydrazine (DMH) causes intestinal tumors in rats selectively and with high frequency [4]. The leading role in the mechanism of its carcinogenic effect is ascribed to methylation of nucleic acids and proteins in the enterocytes [6]. At the same time there is evidence of substantial disturbances of homeostatic interrelations in the reproductive and energy producing systems developing under the influence of DMH [2, 5]. These changes are in harmony with views regarding the role of elevation of the hypothalamic threshold of sensitivity to regulatory factors in carcinogenesis [3].

In this connection it is interesting to study the effect of DMH on the brain level of biogenic amines which, as neuromediators, determine the functional state of the hypothalamus and, consequently, of the neuroendocrine system [9, 10].

EXPERIMENTAL METHOD

Experiments were carried out on 192 male rats (weight 120-140 g) obtained from the "Rappolovo" nursery, Academy of Medical Sciences of the USSR. DMH was injected subcutaneously in a dose of 21 mg/kg. The rats were decapitated 30 min and 3, 12, and 24 h after injection of the carcinogen. The animals' heads were frozen instantaneously with acetone cooled to −70°C. The brain was removed from four animals and the content of biogenic amines in the hypothalamus, brain stem, and cerebral hemispheres was determined in each sample. Noradrenalin (NA) and dopamine (DA) were determined by the trihydroxyindole method [11] and serotonin (5-HT) fluorimetrically [7]; 5-hydroxyindoleacetic acid (5-HIAA) was isolated on Sephadex G-10 and the intensity of fluorescence measured in 3 N HCl solution; histamine was isolated together with 5-HT on Amberlite CG-50, type II, and fluorescence was measured after interaction with o-phthalic aldehyde [7].

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TABLE 1. Content of Biogenic Amines in Hypothalamus, Brain Stem, and Cerebral Hemispheres of Rats at Different Times after Injection of DMH (M ± m)

Time after injection of DMH, h	Noradrenalin, μg/g	Dopamine, μg/g	Serotonin, μg/g	5-HIAA, μg/g	Histamine, μg/g
			Hypothalamus		
0	1,67±0,08	0,75±0,20	0,99±0,12	0,79±0,11	1,01±0,16
0,5	1,05±0,08*	0,60±0,12	0,84±0,07	0,95±0,20	1,56±0,19*
3	1,39±0,09*	0,55±0,18	0,57±0,05	1,27±0,15*	0,81
12	1,32±0,08	0,60±0,33	0,66±0,08	0,83±0,08	1,15
24	1,11±0,06*	0,24±0,02*	0,70±0,09	0,45±0,17	0,85±0,11
			Brain stem		
0	0,51±0,05	0,17±0,06	0,44±0,04	0,42±0,08	0,32±0,03
0,5	0,52±0,04	0,14±0,05	0,66±0,11	0,55±0,17	0,69±0,21
3	—	—	0,57±0,07	0,56±0,08	0,64±0,17
12	0,49±0,08	0,10±0,04	0,44±0,04	0,40±0,07	0,54±0,16
24	0,50±0,06	0,12±0,05	0,51±0,10	0,44±0,11	0,48±0,18
			Cerebral hemispheres		
0	0,31±0,03	1,18±0,11	0,21±0,02	0,13±0,03	0,17±0,02
0,5	0,29±0,03	1,17±0,17	0,31±0,02*	0,22±0,06	0,24±0,07
3	—	—	0,38±0,03*	0,22±0,05	0,20±0,06
12	0,27±0,04	1,13±0,24	0,28	0,10	0,16
24	0,27±0,05	1,15±0,16	0,32±0,04	0,12±0,06	0,18±0,07

Legend. 1. Brain tissue from four animals was used in each determination. 2. Mean results from 3 to 13 determinations shown in table. 3. Data differing significantly ($P < 0.05$) from control marked by asterisk.

EXPERIMENTAL RESULTS AND DISCUSSION

Injection of DMH had a selective action on the hypothalamus and caused substantial changes in its content of biogenic amines (Table 1). The NA level in the hypothalamus 30 min after subcutaneous injection of the carcinogen was reduced by 37% and it remained low for 24 h. The DA level in the hypothalamus did not fall significantly until 24 h after injection of DMH (by 68%).

Numerous investigations have established the mediator role of NA and DA in the liberation of hypothalamic gonadotropin releasing hormones. Administration of drugs inhibiting the synthesis or liberation of catecholamines inhibits the secretion of gonadotropins by the pituitary [10]. A fall in the NA and DA content in the hypothalamus under the influence of DMH corresponds to the antigonadotropic effect of this carcinogen discovered previously [2, 5]. In the first 3 h after injection of DMH the fall in the hypothalamic 5-HT level was accompanied by a corresponding increase in the concentration of 5-HIAA, the end product of its metabolism, indicating stimulation of 5-HT metabolism. By the 12th hour after injection of DMH the 5-HIAA level was the same as initially, but by 24 h the hypothalamic content of both 5-HT and 5-HIAA was substantially reduced. By this time the DA level also had fallen. Presumably DMH selectively inhibits hypothalamic activity of the decarboxylase of aromatic L-amino acids; this effect, moreover, is not exhibited until 24 h after injection of the carcinogen. This hypothesis is also confirmed by observations on the effect of other hydrazine derivatives on dopa-decarboxylase [8].

Meanwhile, during the first few hours after injection of DMH the compound evidently had some inhibitory effect also on dopamine-β-oxidase activity in the hypothalamus, for the DA level remained only slightly lowered for a long time despite the considerable fall in the NA level. This effect of DMH could be explained by its ability to be oxidized rapidly to azomethane, and so to inhibit dopamine-β-oxidase activity. The significant increase in the hypothalamic histamine level 30 min after injection of DMH was evidently the result of a stressor response to injection of the carcinogen. Other evidence in support of this conclusion is given by the stimulation of serotoninergic mediation and inhibition of adrenergic mediation in the hypothalamus, both of which are essential for the liberation of corticotropin releasing hormone [9].

These results give a deeper insight into the ability of DMH to raise the threshold of sensitivity of the hypothalamic-gonadotropic system to the inhibitory action of estrogens discovered previously [2, 5]. Blocking of adrenergic transmission in hypothalamic structures regulating the pituitary gonadotropic function has been shown [1] to play an essential role in the development of this disturbance. Besides changes in the function of the reproductive system, DMH also leads to the development of marked disturbances of lipid and car-

bohydrate metabolism [2]. Similar changes in the reproductive and energy producing systems, developing in response to injection of other classes of carcinogens, also arise, it will be noted, during the performance of the neuroendocrine program of development and aging and the formation of age pathology both in animals and in man [3].

It can be postulated from these results that hormonal and metabolic disturbances, creating the conditions necessary for proliferation of the tumor cell, play an essential role in the mechanism of the carcinogenic action of DMH in rats.

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POSSIBILITY OF MIGRATION OF CERTAIN ELEMENTS IN BIOLOGICAL SYSTEMS DURING X-RAY IRRADIATION

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The effect of local x-ray irradiation on the content of certain elements in cell components (nuclei, mitochondria) and blood serum of rats with transplanted sarcoma M-1 in a dose of 250 R during growth of the tumor was shown to lead to a redistribution of Zn from the nuclei into the mitochondria. Statistically significant postradiation changes also were found in the content of Ca, Mg, Cu, and Zn in the blood serum of rats with a transplanted sarcoma M-1 after a single session of local irradiation of the tumor in a dose of 1000 R.

KEY WORDS: *Migration of elements; postradiation changes; neutron-activation and atom-absorption analysis; x-ray irradiation.*

The action of ionizing radiation is known to be accompanied by disturbance of normal metabolic processes taking place in the cell. These disturbances depend on the character of the radiation and on the quantity of absorbed energy. The writers have postulated that changes of concentration of heavy metals can take place in certain structural components of animals with sarcoma under the influence of ionizing radiation [1]. The explanation of the nature of postradiation migration of heavy metals could itself become the key to the study

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