NEUROPHARMACOLOGICAL REGULATION OF THE CARCINOGENIC ACTION OF 1,2-DIMETHYLHYDRAZINE

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A model of tumors of the large intestine in experimental animals, consisting of administration of 1,2-dimethylhydrazine (DMH), constituting an adequate model of human tumor pathology, was developed previously and has been subjected to morphological study [5, 7]. However, the role of the systemic factors of the host organism in the realization of the effect of this carcinogen has hardly been investigated at all [4, 6].

The aim of this investigation was to study the role of the autonomic nervous system in the mechanism of the carcinogenic action of DMH, for which purpose pharmacological agents acting on the adrenergic or cholinergic mechanisms of regulation of homeostasis were used during chronic administration of DMH.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 100 noninbred male albino rats obtained from the Rappolovo Nursery. The method of administration of the carcinogen and of analysis of the experimental data was described previously [1, 5]. Depending on the nature of the modifying factors, the animals were divided into five groups. Besides DMH, animals of the control group (group 1) were given subcutaneous injections of physiological saline 3 times a week. The rats of groups 2 and 3 were given subcutaneous injections of guanethidine (octadin) in a dose of 5 mg/kg and butyroxan (a pyrroxan analog) in a dose of 25 mg/kg with the same frequency. Rats of groups 4 and 5 were given noradrenalin (1 mg/kg) and atropine (10 mg/kg) by the same route. The number of tumor nodules in the large and small intestine was counted 6 months after the beginning of the experiments and their maximal diameter was measured. After fixation in formalin, the experimental material was studied under the microscope, using various histological techniques.

TABLE 1. Effect of Drugs on Carcinogenesis in Large and Small Intestine of Rats

Group of rats	Number of animals		Number of tumor nodules per animal in group according to results of macroscopic study					
			in large intestine					in small intestine (M ± m)
			distribution by mean diameter, mm				$M \pm m$	
	beginning of experiment	end of experiment*	under 6	under 11	under 16	over 16		
1	20	12	9,2	1,0	0,23	0,07	10,6±2,5	1,3±0,2
2	20	10	11,2	0,23	—	—	9,3±1,9	0,6±0,04
3	20	12	8,3	0,73	—	—	7,3±2,0	0,4±0,02
4	20	11	2.6	0,05	—	—	3,2±1,3†	—
5	20	13	3,4	0,07	—	—	4,5±1,8†	0,12±0,01

*The other animals died in the early stages of the experiment from infectious diseases with no sign of tumor pathology.

†Differences from control (group 1) statistically significant ($P < 0.01$).

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EXPERIMENTAL RESULTS

Under the influence of DMH all the rats of groups 1-3 developed tumors of the large intestine, mainly in its descending portion. The tumors were multiple, macroscopically they varied in shape, and they were characterized by both exophytic and endophytic growth. Up to 90% of the tumors, as histological study showed, belonged to different varieties of adenocarcinoma. Single tumors also were found in the small intestine. None of the drugs used had any effect on the morphological structure of the tumors. The sympatholytic guanethidine (group 2) and the α-adrenoblocker butyroxan (group 3) had no effect on the number of tumors or the size of the tumor nodes (Table 1). Consequently, the action of drugs potentiating the functional role of cholinergic processes proved to be ineffective in this experimental model. In the rats of groups 4 and 5 the effect of the opposite action on carcinogenesis was studied — pharmacological stimulation of adrenergic processes by chronic administration of noradrenalin and potentiation of their functional role by administration of atropine. The use of these drugs led to significant inhibition of carcinogenesis in the large and small intestines: Both the number of tumor nodes detected macroscopically and their size were reduced by 2-3 times. These data are evidence of the influence of the nervous system on carcinogenesis in the small intestine [9]; the unique features of the action of DMH are determined, in the writer's view, not only by the character of innervation of the large intestine (absence of vagal innervation), but also by the pharmacological activity of the carcinogen itself.

These results can be explained on the basis of the view that, by contrast with the esophagus, stomach, and liver [2, 3, 8], proliferative activity in the large intestine is controlled by cholinergic mechanisms. During chronic administration of DMH, as a result of its inhibition of adrenergic processes the regulatory role of the parasympathetic division of the autonomic nervous system is considerably increased. Evidence of this is given, in particular, by the prolonged dyspeptic disorders arising in the rats while taking DMH. Under these conditions the state of dynamic equilibrium is disturbed in the neurotropic regulation of homeostasis, and proliferative activity of the epithelium of the mucous membranes of the large intestine is stimulated. Since DMH, in the dose used, gives rise to multiple tumors in all rats of the control group, further intensification of cholinergic processes by means of drugs (groups 2 and 3) has no stimulating effect on carcinogenesis. The use of pharmacological agents weakening cholinergic mechanisms and strengthening the functional role of the adrenergic components of the autonomic nervous system leads to inhibition of carcinogenesis.

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