MORPHOLOGICAL INVESTIGATION OF THE HYPOTHALAMO-HYPOPHYSEAL NEUROSECRETORY SYSTEM AND THYROID GLAND DURING INTESTINAL CARCINOGENESIS

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The pathomorphology of the hypothalamo-hypophyseal neurosecretory system and thyroid glands of 150 rats of both sexes was studied during intestinal carcinogenesis induced by 1,2-dimethylhydrazine. The latent period of carcinogenesis was shown to coincide with inhibition of neurosecretion in the paraventricular and supraoptic nuclei and with atrophic changes in the thyroid gland. With the appearance of tumors in the intestine, hypertrophy of the neurons and their nuclei and a decrease in the content of neurosecretory substance were found, accompanied by a tendency toward normalization of the structure of the thyroid gland. The period of spredding cancer was accompanied by increasing hypertrophy of the neurons and a decrease in the content of neurosecretory substance, as well as by marked atrophic changes in the thyroid gland.

KEY WORDS: intestinal carcinogenesis; hypothalamo-hypophyseal neurosecretory system; thyroid gland; 1,2-dimethylhydrazine.

Experimental and clinical oncology has provided evidence that disturbance of the hormonal balance of the body has a significant effect on the formation and development of tumors [1, 3, 4, 7, 14, 15]. There is little information in the literature on structural changes in the hypothalamic-hypophyseal neurosecretory system (HHNS) and thyroid gland during the development of induced tumors [3, 5, 8, 10, 11, 13], and no information whatever on such changes during intestinal carcinogenesis. For that reason the results of a morphological study of HHNS and the thyroid gland during experimental chemical intestinal carcinogenesis may be of definite interest.

EXPERIMENTAL METHOD

Intestinal carcinogenesis was induced in 150 rats of both sexes by weekly subcutaneous injection of 1,2-dimethylhydrazine in doses of 21 and 40 mg/kg. The animals were killed in groups at monthly intervals for 6 months. Material from 20 intact rats served as the control.

Brain tissue was fixed in Bouin's fluid and embedded in paraffin. The paraventricular (PVN) and supraoptic nuclei (SON), the neurosecretory fibers of the hypothalamo-hypophyseal tract (within the hypothalamus) the median eminence, and the posterior lobe of the pituitary were studied in histological sections stained by Gomori's method in Maiorova's modification [9]. Neurosecretory substance was determined quantitatively by the method suggested by Es'kov [6]. The neurosecretory cells were subjected to cytometry and karyometry.

The thyroid glands were weighed and studied in histological sections stained with hematoxylin-eosin, by Mallory's method, by Brachet's method with ribonuclease control, by the McManus–Hotchkiss method, with aldehyde-fuchsin, and with Sudan black. The height of the follicular epithelium and the diameter of the nuclei of the thyroid epithelium were measured and the relative proportions of follicles of different sizes were calculated. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

After the study of the morphogenesis of intestinal carcinoma the present writer [12] dis-

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TABLE 1. Morphology of Hypothalamic Neurosecretory Nuclei Studied during Experimental Chemical Intestinal Carcinogenesis

Period of intestinal carcinogenesis	Sex of rat	No. of rats	Sessional dose, carci., mg/kg	Paraventricular nuclei			Supraoptic nuclei		
				mean diameter of neurons, μ	mean diameter of nuclei of neurons, μ	content of neurosecretion points	mean diameter of neurons, μ	mean diameter of nuclei of neurons, μ	content of neurosecretion points
Control	Male	10		20,7±0,2	10,2±0,2	206±11	20,0±0,3	10,8±0,3	104±6
	Female	10		20,0±0,2	10,4±0,2	196±10	20,4±0,3	10,8±0,2	112±4
Latent period	Male	12	21	20,5±0,3	9,9±0,3	239±8*	20,3±0,2	10,4±0,2	222±9*
	Female	18	21	20,6±0,3	10,2±0,2	234±6*	20,2±0,5	10,7±0,2	231±13*
	Male	20	40	20,3±0,3	10,1±0,2	244±7*	20,1±0,4	10,7±0,2	224±12*
	Female	12	40	20,2±0,2	10,2±0,3	247±6*	20,2±0,3	10,6±0,2	230±14*
Period of tumor growth within intestinal mucosa	Male	11	21	22,3±0,2*	11,3±0,2*	157±11*	23,8±0,2*	11,3±0,2	116±8
	Female	11	21	22,5±0,2*	11,1±0,2*	139±9*	24,1±0,3*	11,2±0,2	111±8
	Male	12	40	23,0±0,3*	11,1±0,2*	162±11*	23,6±0,4*	11,3±0,2	122±7
	Female	10	40	23,3±0,4*	11,2±0,2*	164±10*	23,6±0,5*	11,3±0,2	121±8
Period of spreading cancer	Male	6	21	26,6±0,3*	11,5±0,2*	103±6*	27,0±0,3*	11,8±0,2*	85±6*
	Female	11	21	27,0±0,5*	11,9±0,3*	92±5*	26,9±0,3*	12,0±0,3*	81±5*
	Male	15	40	26,0±0,4*	11,8±0,3*	93±8*	27,4±0,3*	11,8±0,2*	80±9*
	Female	12	40	26,9±0,5*	11,7±0,2*	99±12*	27,2±0,4*	11,9±0,2*	86±7*

*Difference from corresponding values in animals of control group significant (P<0.05).

TABLE 2. Morphology of the Thyroid Gland Studied during Experimental Chemical Carcinogenesis in the Intestinal Mucosa

Period of intestinal carcinogenesis	Sex of rat	No. of cells	Sessional dose of carci., mg/kg	Weight of thyroid gland, mg/100 g	Height of follicular epithelium, μ	Mean diameter of nuclei of follicular epithelium, μ	mean diameter of interfollicular epithelium, μ	Relative proportion of follicles of different diameters, μ		
								under 50	50—100	under 100
Control	Male	10		14±1	13,0±0,6	7,2±0,4	7,5±0,3	69±4	26±4	5±2
	Female	10		14±1	12,9±0,5	7,2±0,3	7,2±0,4	62±5	30±3	8±2
Latent period	Male	12	21	9±1*	6,7±0,7*	4,5±0,3*	8,0±0,5	15±3*	40±6	45±4*
	Female	18	21	10±1*	6,2±0,4*	4,8±0,4*	7,5±0,7	18±2*	40±7	42±4*
	Male	20	40	9±1*	7,5±0,4*	5,0±0,5*	8,3±0,3	17±3*	37±6	46±6*
	Female	12	40	8±1	6,8±0,4*	5,2±0,4*	7,4±0,5	12±2*	44±4*	44±5*
Period of tumor growth within intestinal mucosa	Male	11	21	13±1	10,5±0,8*	7,0±0,5	7,2±0,3	36±5*	43±3*	21±2*
	Female	11	21	13±1	10,7±0,5*	6,5±0,4	7,5±0,4	40±4*	42±4*	18±4*
	Male	12	40	13±1	9,8±0,5*	6,8±0,4	7,6±0,4	30±5*	50±8*	20±4*
	Female	10	40	12±1	10,2±0,6*	6,7±0,2	7,1±0,3	36±3*	46±6*	18±2*
Period of spreading cancer	Male	6	21	8±1*	5,5±0,3*	4,5±0,3*	6,4±0,7	15±2*	23±3	62±7*
	Female	11	21	8±1*	5,2±0,3*	4,7±0,5*	6,2±0,5	11±2*	26±3	63±6*
	Male	15	40	7±1*	7,1±0,7*	4,9±0,4*	7,0±0,2	21±4*	34±4	45±6*
	Female	12	40	8±1*	7,0±0,5*	4,9±0,5*	6,3±0,6	18±3*	31±3	51±4*

*Difference from corresponding values in animals of control significant (P<0.05).

tinguished three stages of its development: the latent period, the period of tumor growth within the intestinal mucosa, and the period of spreading cancer.

The results showed (Table 1) that during the latent period neurosecretory substance accumulates in the neurons of PVN and SON, the neurosecretory tracts, and neurohypophysis in the absence of changes in the diameter of the neurons or of their nuclei. The content of tigroid in the neurons was reduced under these circumstances. The height of the follicular epithelium and the diameter of its nuclei were reduced by almost half in the thyroid gland (Table 2). The number of medium-sized and large follicles increased. They were filled with

Fig. 1

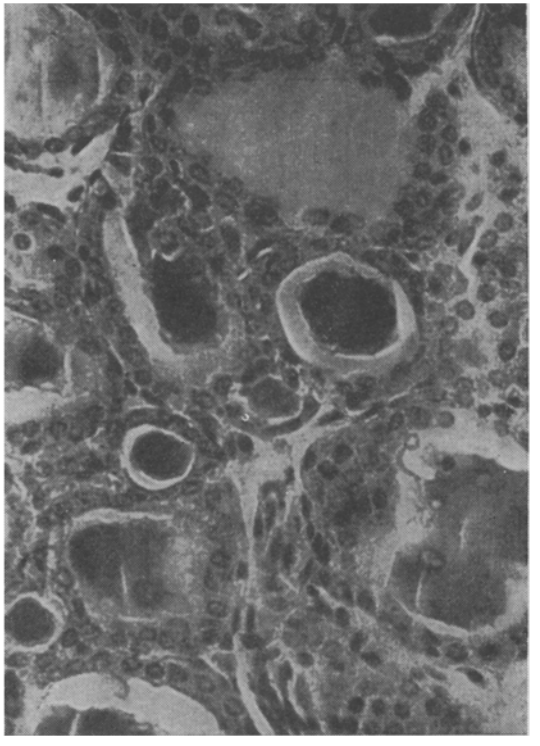

Fig. 2

Fig. 1. Large and medium-sized follicles of thyroid gland filled with thick colloid with a high content of PAS-positive material. Latent period of carcinogenesis. McManus—Hotchkiss, 144×.

Fig. 2. Increased RNA content in cells of follicular epithelium and in colloid of thyroid gland. Period of tumor growth confined to intestinal mucosa. Brachet, 144×.

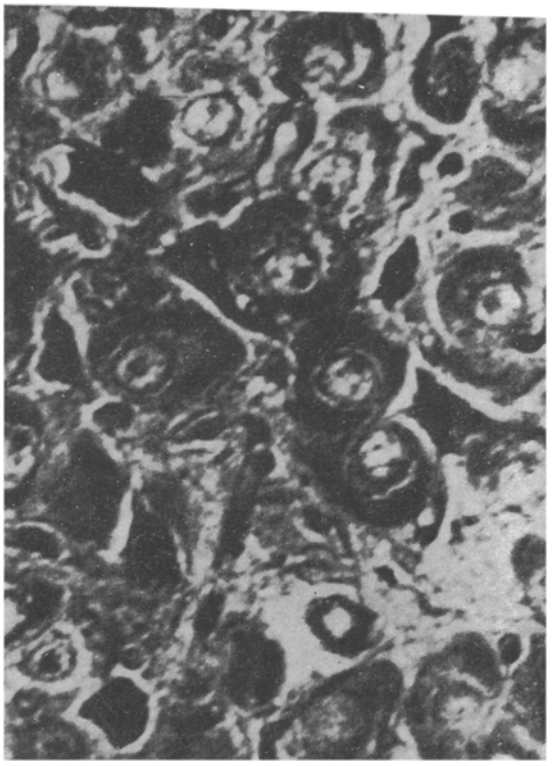

Fig. 3. Increased number of pycnomorphic and dying neurons in paraventricular nucleus. Period of spreading intestinal cancer. Maiorova's modification of Gomori's strain, 450×.

thick colloid, with a high content of PAS-positive substances (Fig. 1). The RNA content in the cytoplasm of the follicular cells and in the colloid was reduced.

In the period of tumor growth confined to the intestinal mucosa, hypertrophied pale neurons with a reduced content of neurosecretory substance were numerically predominant in PVN and SON. The number of pycnomorphic and dying neurons not containing tigroid or neurosecretory substance increased. Minimal amounts of neurosecretory material were contained in the axons. In the neurophyphophysis it was distributed as small concentrations around the congested blood vessels. In the thyroid gland at this period, compared with the latent period, the follicular epithelium and the diameter of its nuclei were significantly increased (Table 2). The number of small follicles with liquid colloid also was increased, but in the medium-sized follicles signs of resorption of colloid appeared, in the form of peripheral vacuoles. The pyroninophilia of the cells of the follicular epithelium and of the colloid was intensified (Fig. 2).

During the period of spreading cancer neurons of PVN and SON were considerably hypertrophied, with enlarged nuclei and nucleoli and with a low content of neurosecretory substance (Table 1). Pycnomorphic and dying neurons also were observed (Fig. 3), ranging in number from 21 to 28%. The neurosecretory pathways and the neurohypophysis were poor in neurosecretory material. This period was characterized by a considerable reduction in the weight of the thyroid gland, marked flattening of the follicular epithelium, and increase in the relative percentage of large follicles (Table 2) filled with thick colloid, a decrease in its pyroninophilia, and a decrease in the RNA content in the follicular epithelium. The number of interfollicular epithelial cells was increased and the diameter of their nuclei was the same as in the control.

In the latent period of intestinal carcinogenesis morphological signs of inhibition of neurosecretion in the hypothalamic nuclei and of hypofunction of the thyroid gland thus appear. The period of tumor growth confined to the intestinal mucosa is accompanied by activation of the neurosecretory process and by a tendency toward restoration of the normal thyroid gland structure. In the period of spreading cancer further activation of the neurosecretory process is observed, whereas marked atrophic changes are found in the thyroid gland.

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