The present investigation thus shows that nonspecific (i.e., developing also in other pathological processes and in other cells) changes in the nucleolus take place in damaged epithelial cells, in the form of segregation, degranulation, fragmentation, and hypertrophy. None of these changes are fatal, and after cessation of the action of the damaging agent, they can undergo regression with restoration of the normal structure of the nucleolus [3, 4].

It must be particularly emphasized that comparison of the data described above with our previous observations [1] leads to the conclusion that the destructive changes described in the nucleolus, in the same way as partial necrosis while some normal mitochondria and part of the protein-synthesizing apparatus in the cytoplasm remains intact, do not prevent the cells with partial necrosis from embarking upon a phase of DNA synthesis. New DNA formation is the initial phase of development of intracellular regeneration, namely hyperplasia of the genome. The latter, in turn, brings about hyperplasia of intracellular structures at the early stage, and an increase in the number of cells at a later stage. In other words, our results demonstrate that injury, if not too severe, acts as a stimulus activating a regenerative response which, in the epithelial cells of the tubules, is exhibited in both intracellular and cellular form.

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SEASONAL DIFFERENCES IN EFFECT OF THYROID HORMONE DEFICIENCY ON INDOLEAMINE METABOLISM IN THE RAT PINEAL GLAND

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An excess and deficiency of thyroid hormones in the body are known to cause diametrically opposite effects on indoleamine metabolism in the rat pineal gland: saturation of the body with thyroxine activates melatonin formation in the pinealocytes, whereas thyroidectomy inhibits this process [1]. It has been shown that in the presence of an excess of thyroid hormones, serotonin utilization in the pineal is disturbed predominantly toward N-acetylation and subsequent O-methylation, with the formation of N-acetylserotonin (N-aS) and melatonin, whereas in thyroid deficiency, it is shifted toward relative predominance of oxidative deamination, against the background of marked inhibition of methoxyindole biosynthesis. In other words, thyroid hormones affect mainly processes of N-acetylation and O-methylation of pineal indoles. Subsequently, in a study of seasonal differences in the effect of thyroxine on the metabolic pathways of serotonin in the rat pineal gland [3] it was shown that excessive saturation of the body with thyroid hormone causes biochemical disturbances aimed at stimulating the production of pineal melatonin independently of the season, although under conditions of short daylight (winter) these changes were much more marked [3].

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TABLE 1. Seasonal Differences in Effect of Bilateral Thyroidectomy on Indole Concentrations in Pineal Gland of Mature Male Rats

Time of year	Group of animals	Experimental conditions	Statistical parameters	Indole concn. in pineal gland, mg/organ			
				serotonin	N-aS	melatonin	5-HIAA + 5-MOIAA
Winter	1	Control	n	10	10	10	10
			$x \pm S_x$	30,40±2,80	11,32±3,81	12,92±4,75	44,58±7,92
	2	Thyroidectomy	n	9	9	9	8
			$x \pm S_x$	25,77±4,16	2,58±0,27	0,26±0,16	31,81±5,51
			p_{1-2}	--	<0,05	<0,02	--
Summer	3	Control	n	10	10	10	10
			$x \pm S_x$	33,81±3,02	7,93±1,72	4,13±0,16	28,28±6,57
	4	Thyroidectomy	n	10	10	10	11
			$x \pm S_x$	37,60±1,85	5,96±0,59	3,80±0,19	6,37±1,25
			p_{3-4}	--	--	--	<0,01

The aim of this investigation was to study seasonal differences in serotonin metabolism in the pineal gland in the presence of thyroid hormone deficiency induced by thyroidectomy.

EXPERIMENTAL METHOD

Experiments were carried out on 78 mature male Wistar rats in the summer and winter. The animals were kept in the animal house with natural lighting and a normal diet. The lighting schedule was 16 h of daylight and 8 h of darkness (long photoperiod) and 8 h of daylight and 16 h of darkness (short photoperiod). Thyroid hormone deficiency was induced by bilateral thyroidectomy, the animals being used in the experiments not earlier than 3 weeks after removal of the thyroid gland. Intact rats served as the control. Decapitation was carried out at night (between midnight and 3 a.m.), at a time of maximal pineal activity, and in red light. Serotonin and its metabolic products (N-aS and melatonin) and also the total fraction including 5-hydroxy and 5-methoxyindoleacetic acid (5-HIAA and 5-MOIAA) were determined by a fluorometric method [4] in the pineal gland, so that it was possible to judge the different pathways of serotonin metabolism in the pineal gland. Fluorescence of the test substances was measured on a BIAN-130 fluorometer at wavelengths of 365 and 470 nm. The concentration of indoles was expressed per single organ.

EXPERIMENTAL RESULTS

The content of individual indole fractions in the pineal gland of intact and thyroidectomized rats is shown in Table 1, from which it follows that the levels of serotonin and its derivatives in the pineal gland of the control animals is largely determined by the time of year. For instance, in winter the N-aS concentration was 42.7% higher than in summer, whereas the melatonin concentration was increased fourfold under these conditions, but the level of the total fraction of 5-HIAA and 5-MOIAA was reduced (from 44.58 ± 7.92 to 28.28 ± 6.57 ng/organ).

Removal of the thyroid gland caused a decrease in the total indoleamine concentration in the pineal gland in both summer and winter, but definite seasonal differences were found. Thus, if thyroidectomy was performed in winter it led to a decrease in content of all indole components of the pineal gland, the lowering of the melatonin and N-aS levels being most demonstrative. Under long daylight conditions, under the influence of thyroidectomy there was a significant decrease in the content only of the 5-HIAA and 5-MOIAA fraction in the pineal gland (on average by 75%), whereas fluctuation of the levels of all remaining detectable indoles, including N-aS and melatonin, was on a very small scale. Since the varied decrease in indoleacetate formation in summer was not accompanied by corresponding changes in serotonin concentration, it can be tentatively suggested that in thyroid hormone deficiency, serotonin biosynthesis itself is not impaired.

Analysis of the results showed that thyroidectomy in the dark time of the year inhibits the conversion of serotonin along the pathway of its N-acetylation and subsequent O-methylation, whereas thyroidectomy in the light time of the year, while inhibiting serotonin metabolism along the oxidative deamination pathway, has virtually no effect on the processes mentioned above.

These data suggest that under conditions of thyroid hormone deficiency, and in the dark period of the year, activity predominantly of pineal N-acetyltransferase (N-AT) is depressed. Considering the degree of reduction of the melatonin content

in the pineal gland, it can be tentatively suggested that activity of hydroxyindole-O-methyltransferase (HIOMT) falls simultaneously. In the light period of the year, the decrease in pineal monoamineoxidase activity is much more marked than in winter, but it is not accompanied, however, by changes in N-AT and HIOMT activity.

We discussed above some previous data indicating that an excess of thyroxine affects processes of N-acetylation and O-methylation of indoles particularly, and the effect is manifested mainly in the period of short daylight. In this connection it is a perfectly legitimate fact that a thyroid hormone deficiency has an opposite effect on the pathway of serotonin metabolism that is connected with the formation of N-aS and melatonin. It is an interesting fact that the observed effect is exhibited also in the dark period of the year.

Seasonal differences in the realization of the action of thyroid hormones on indole metabolism in the pineal gland can be most logically explained by rhythms of sensitivity of the target organ which, in this case, is the pineal gland for thyroid hormones. The correctness of this hypothesis is confirmed by the results of our previous investigations [2], which demonstrated conclusively seasonal differences in the effect of pineal methoxyindoles on the thyroid gland. Thus we are dealing with a seasonal rhythm of function of the pineal — thyroid gland system.

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