ON THE RESTORATIVE PROCESSES IN AN OVARY SUBJECTED TO THE ACTION OF THIO-TEF

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Many anti-tumor preparations are capable of suppressing a diverse group of proliferative processes, including regenerative ones [3, 4]. On the basis of this, L. F. Larionov [1, 2] postulated that preparations which inhibit the development of a tumor in a given organ will suppress the regenerative processes of that same organ. Thus, studying the effect of these preparations on regeneration can aid in the orientation about the problem of their therapeutic action. We studied the action of one of the anti-tumor preparations (Thio-TEF) on regeneration of the ovary, since it is known that Thio-TEF inhibits the development of cancer in that organ.

EXPERIMENTAL METHOD

We used 100 white female rats, weighing 100 grams, in the experiments. Three experimental series and one control group were set up, with 25 animals in each.

The first series consisted of unoperated animals, which were injected intraperitoneally with Thio-TEF in physiological saline; a dose of 6 mg per kg of body weight was administered every 72 hours.

The second series was made up of animals in which a half of the left ovary was removed, with simultaneous complete removal of the other ovary.

The third series included animals which underwent the same operation as the animals in the second series, but were also subjected to the action of Thio-TEF following the same schema as for the animals in the first series.

The control consisted of normal rats, which were not subjected to any kind of procedure.

Part of the animals in the first and third series were injected with Thio-TEF for 2 weeks, and part—for a month; at the end of these periods, the animals of all series were sacrificed. The rats were weighed, and the ovaries were taken for histological investigation. Fixation was carried out in a 10% formalin solution, and the preparations were stained with hematoxylin and eosin.

EXPERIMENTAL RESULTS

Table 1 shows the data depicting the changes in the weight of the animals and their ovaries. The administration of Thio-TEF (first and third series) showed a decided action on the general state of the animals, reflected, in particular, by an inhibition of their growth. In addition, the weight of the ovaries fell sharply. With 2 week administration of Thio-TEF, the weight of the ovaries decreased more than 50%, but with injection of Thio-TEF for a month, the weight drop of the ovaries was manifested to a lesser degree. It may be postulated that a certain adaptation to this action occurs in the organism.

In studying the histological changes in the ovaries subsequent to the action of Thio-TEF, we counted the generative elements in 10 ovaries from all the experimental and control animals. They were counted in every fifth section of the ovaries, which were serially cut into 7 micra sections. The results of the count are presented in Table 2.

The marked drop in weight of the ovary subsequent to the action of Thio-TEF was explained by the pronounced structural changes in the sex gland. We observed massive atresia of the follicles, and the overwhelming majority of the follicles were in a state of degeneration. The processes of maturation of the follicles and ovulation were

TABLE 1. Weight of the Rat Ovaries Subsequent to the Action of Thio-TEF

Experiment series	Duration of the experiment	Weight of the rat (in grams)	Weight of the ovary (in mg)		Ratio of the weight of the ovary to the body weight (in %)	
			right	left	right	left
Control	2 weeks	118.6	11.8	12.6	0.09	0.09
First (injected with	1 month	147.3	26.3	27.3	0.17	0.17
Thio-TEF)	2 weeks	94.4	5.4	5.8	0.05	0.05
Second (right ovary and	1 month	105.4	17.3	16.3	0.15	0.13
hald of left removed)	2 weeks	144.5	-	31.3	-	0.21
Third (right ovary and	1 month	147.6	-	31.8	-	0.21
half of left removed;	2 weeks	104.7	-	18.1	-	0.16
injected with Thio-TEF)	1 month	102.9	-	13.3	-	0.13

sharply disrupted, and the number of maturing follicles had decreased by approximately four times; it should be emphasized that yellow bodies were almost completely absent. Along with the signs of atresia and death of the structural components of the ovary, we noted a considerable increase in the amount of primary follicles. Their number rose to 9.5 per section, and the total number of primary follicles in an entire ovary—to 257, while in the ovaries of the control animals, there were only 3.7 per section, and 160 in the entire ovary, i.e. $1\frac{1}{2}$—2 times fewer.

TABLE 2. Relationship of the Generative Elements in Rat Ovaries Following the Action of Thio-TEF

Experimental series	No. of primary follicles in the entire ovary	Average number in one section				
		follicles			yellow bodies	total number of generative elements
		primary	maturing	atretic		
Control[1]	159.7	3.7	8.3	8.1	2.3	23.9
First (injected with Thio-	256.8	9.5	2.1	16.0	0.9	38.7
TEF)	117.6	3.3	5.0	12.9	4.5	25.7
Second (right ovary and half	54.4	1.7	5.4	1.5	6.8	15.4
of left removed)	73.0	2.0	2.7	8.8	3.9	17.0
Third (right ovary and half	74.0	0.9	4.3	2.3	2.7	10.3
of left removed; injected	83.7	1.6	3.1	10.9	1.3	17.1
with Thio-TEF)						

[1]Since the relationship of the generative elements in the ovaries of the control rats was the same after 2 weeks and 1 month from the beginning of the experiment, these data are combined in the table.

On one hand, this is evidence of the known resistance of primary follicles to the action of Thio-TEF. On the other hand, apparently, the formation of new primary follicles takes place here, under conditions of Thio-TEF's unfavorable action on the ovary, it essentially causing atrophy of the organ.

The total number of generative elements per section in the ovary of the animals in the first series reached 38.7, considerably higher than the number per section in the ovaries of the control animals—23.9; however, the overwhelming majority of them were in a state of atresia.

In the second series of experiments, with resection of half of one of the ovaries and simultaneous complete removal of the other, after 2 weeks we observed a considerable increase in the weight of the portion of the ovary remaining after the resection to 31.3 mg (see Table 1). The weight of the regenerating ovary exceeded the weight of both ovaries of control animals (24.4 mg). One month after the operation, the weight difference between the

regenerating ovary (31.8 mg) and the untraumatized ovary of the control animals (27.3 mg) decreased considerably. Thus, the proliferative processes observed in the ovary following resection were especially manifest in the first 2 weeks. Histological study of the ovaries showed that the increase in the weight of the organs basically occurs as a result of the yellow bodies, whose number increased to 6.8 (see Table 2); there were 3 times more of these structures than in the ovaries of the control animals (2.3). The yellow bodies attained larger dimensions. The number of maturing follicles was equal to 5.4, i.e. more than would be present in the portion of ovary that remained after resection, but it still did not reach the number of maturing follicles in the untraumatized ovary of the control animals, where it was equal to 8.3. We did not observe an increase in the number of primary follicles in the regenerating ovaries (1.7), while in the control it was equal to 3.7; the number of atretic follicles was considerably smaller (1.5) than in the control (8.1).

The total number of generative elements per section in the regenerating ovary was 15.4, somewhat higher than would have been present in the half of the ovary, but it still did not reach the number present in the intact, untraumatized ovary (23.9). Even after a month it still didn't reach this level, although there were a somewhat greater number of generative elements (17) in comparison with the 2-week observations. The relationship of the generative elements in the regenerating ovary one month after the operation was somewhat different; there was a small increase in the number of yellow bodies—to 3.9, and primary follicles—to 2. The number of maturing follicles was somewhat smaller (2.7), while the number of atretic follicles increased to 8.8.

The course of the restorative processes in the rat ovary that was half resected, with simultaneous complete removal of the other ovary, was somewhat different under conditions of Thio-TEF administration. We noted a suppression, or some inhibition, of these processes. The increase in weight of the regenerating ovary was smaller than that seen in the animals of the second series, both at the 2-week observation (18.1 mg) and after a month (13.3 mg). However, in comparing these weight characteristics with the weight of the untraumatized ovaries from the animals of the first series (5.8 mg after 2 weeks, and 16.3 mg after a month), exposed to the action of Thio-TEF, it is obvious that the restorative processes took place, and apparently, were sufficiently intense if the general, unfavorable action of Thio-TEF on the sex glands is taken into consideration. As was shown by the histological study and the count of the number of structural components (see Table 2), the total number of generative elements per section was small; it was equal to only 10.3. However, the relationship of the elements was similar to that observed in the regenerating ovary from the animals of the second series. We noted some intensification in the processes of follicular maturation, the number of these follicles being equal to 4.3 and their conversion into ova taking place; the number of yellow bodies was 2.7. The number of follicles undergoing atresia was small-2.3. Proliferation of the primary follicles was suppressed; the number of primary follicles was equal to only 0.9 (single ones in a visual field).

After a month, in the traumatized ovaries exposed to the action of Thio-TEF the total number of generative elements per section increased to 17.1, but this does not indicate an intensification of the proliferative-restorative processes, since this increase basically occurred as a result of increased atresia of the follicles. Also, the number of maturing follicles (3.1) and yellow bodies (1.3) decreased, i.e. the processes of maturation and ovulation were depressed. In addition, we noted a similar relationship of the generative elements in the ovaries from the animals of the first series (subjected to the action of Thio-TEF).

The observed phenomena of follicular atresia and suppression of the other processes in the ovary subjected to the action of Thio-TEF are apparently the basis of the preparation's therapeutic action against ovarian cancer. The same thing is observed in association with the action of other therapeutic agents, such as roentgen rays.

Thus, we established that Thio-TEF, which processes therapeutic activity against a tumor of the ovaries, actually causes both atrophy of the intact ovary and depression of its regeneration. Therefore, studying the effects of new anti-tumor preparations on the regeneration of normal organs can be useful in making initial judgments on the potential spectrum of their anti-tumor activity.

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