THE 24-HOUR RHYTHM OF MITOTIC ACTIVITY DURING REPARATIVE REGENERATION OF THE SALIVARY GLAND, LIVER AND EPIDERMIS IN WHITE MICE AND RATS

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The investigations of a number of authors have shown that the mitotic activity of different organs undergoes regular alterations in the course of the 24 hour day [1, 2, 5]. The data in the literature on the 24 hour rhythm of mitoses during reparative regeneration are contradictory. Thus, Blumenfeld showed that in the epidermis of a healing wound in a rabbit there is a daily rhythm to the mitotic activity [6], while Bullough and Laurence did not observe it in regenerating epidermis in their experiments on mice [7]. M. T. Gololobova showed that the 24 hour mitotic rhythm is retained in the epidermis surrounding the wound, but is absent from the epidermis growing over it [3]. Jaffe [8] demonstrated a clearly manifested 24 hour periodicity to the mitoses in the regenerating liver of rats. L. D. Liozner and coauthors [4] observed periodic changes in the mitotic activity during regeneration of the liver in mice.

The goal of this work was to study the 24 hour regime of mitotic activity during reparative regeneration in organs with high (skin) and low (liver, salivary gland) levels of mitotic activity, and to compare the 24 hour mitotic rhythm in these organs during physiological and reparative regeneration.

EXPERIMENTAL METHOD

In the first series of experiments, we studied the regime of mitotic activity in the submaxillary salivary gland and in the epidermis of the skin during regeneration. The experiments were carried out on white mice, 3 months of age, in which half the left submaxillary gland was resected. The uninjured right salivary gland of the same animals served as the control. In order to study the mitotic activity of the epidermis, fragments of skin were taken (measuring 5 x 10 mm), adjacent to the cutaneous incision through which we removed the salivary gland. Three days after the operation, the animals (6 in each group) were sacrificed over the course of a 24 hour period, at 8, 11, 14, 17, 20, 23, 2 and 5 hours. The mitotic activity was determined in the regenerating and non-regenerating salivary glands, and also

The 24 Hour Fluctuation in Mitotic Activity Within the Epidermis, Liver and Salivary Gland During Physiological (Control) and Reparative (Experimental) Regeneration

Organ studied	Group of animals	Mean number of mitoses in interval of fixation (time of day)							
		5	8	11	14	17	20	23	2
Skin	Control	10.5	16.5	10.0	7.8	6.1	5.8	5.3	8
	Experimental	17.1	33.6	15.0	14.1	13.5	12.5	12.0	15.1
Liver	Control	—	4.5	—	1.1	—	0.8	—	1.5
	Experimental	—	22.2	—	5.3	—	4.0	—	7.8
Salivary gland	Control	4.0	6.8	3.0	2.0	1.5	1.5	1.1	2.0
	Experimental	12.6	18.0	11.0	10.8	9.0	8.0	6.0	9.5

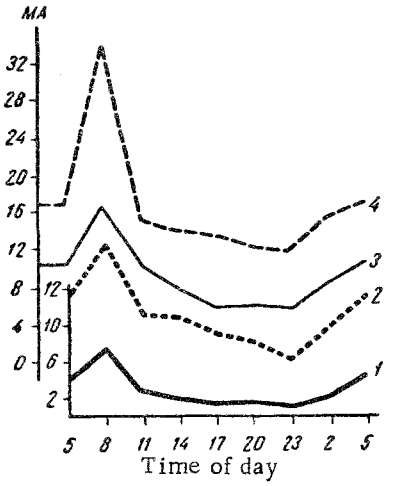

Fig. 1. The 24 hour rhythm of mitotic activity (MA) in an uninjured (1) and regenerating (2) salivary gland, and in normal (3) and regenerating (4) cutaneous epidermis.

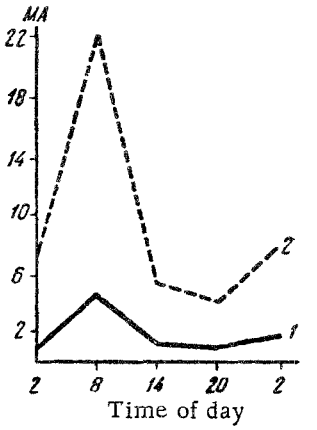

Fig. 2. The 24 hour rhythm of mitotic activity (MA) in uninjured (1) and regenerating (2) liver.

in the regenerating cutaneous epidermis, and, for a control – in the skin of an intact ear of the same animals.

In the second series of experiments, we studied the 24 hour mitotic regime in the regenerating liver. The experiments were performed on white rats, $2\frac{1}{2}$-3 months of age, in which, under ether narcosis, we had removed the left great lobe of the liver, and a fragment of the left median lobe. The mean weight of the resected portion of the organ was equal to 2.2-2.7 grams. Since the weight of the liver was equal to an average of 7-8 grams, approximately a third of the organ was removed.

The control consisted of the liver of animals in which, under ether narcosis, we carried out a laparotomy without injuring the liver. Three days after the operation, the rats (6 in each group) were sacrificed in the course of a 24 hour period, at 8, 14, 20 and 2 hours. The number of mitoses was determined in a fragment taken from the remaining portion of the left median lobe of the liver.

The magnitude of mitotic activity was judged from the number of dividing cells in a constant area; for the salivary gland – 3.3 mm^2 (approximately 14,000 cells), for the liver – 4.28 mm^2 (approximately 10,000 cells), and for the epidermis – 1.65 mm^2. The obtained data were subjected to statistical analysis, according to the method of Fisher-Student. All the animal groups were operated on during morning hours. The animals received their food and water at one time – at 9:00 P.M.

EXPERIMENTAL RESULTS

The curve of mitotic activity in the non-injured submaxillary gland had one peak at 8 o'clock in the morning, and a minimum of mitoses was noted at 11:00 P.M. (see table). In the mucous and serous portions of the submaxillary gland we encountered only single dividing cells. After resection of the salivary gland, the mitotic activity in the remaining half of the organ increased. On the 3rd day after the operation the number of dividing cells in the regenerating salivary gland at all intervals exceeded the number of mitoses in the uninjured organ by several times. In the regenerating submaxillary gland, the mitotic activity also changed regularly in the course of 24 hours. The curve for the 24 hour mitotic rhythm showed a single peak. The maximum mitotic activity was noted in the morning hours (8:00 A.M.), and the minimum – in the night hours (11:00 P.M.) ($P < 0.001$).

The 24 hour fluctuations in mitotic activity within the epidermis adjacent to the wound defect, and within the normal skin (control) showed parallel courses. The curves described a single peak. The maximum mitotic activity was noted at 8:00 A.M., and the minimum – at 11:00 P.M. ($P = 0.001$). The level of mitotic activity in the regenerating epidermis was markedly greater than in the control at all the intervals (Fig. 1).

In studying the regime of mitotic activity in the regenerating liver of white rats, we observed an increase in mitotically dividing cells at 8:00 A.M.; at 8:00 P.M. the number of mitoses decreased to a minimum ($P = 0.001$-0.1)

(Fig. 2). With regeneration of the liver, there occurred a marked increase in the number of cell divisions at all intervals. The number of mitoses in the regenerating liver exceeded the number of mitotically dividing cells in the uninjured organ by 4-5 times. A comparison of the curves for the 24 hour mitotic regime in the salivary gland, liver and cutaneous epidermis during regeneration showed that they run parallel courses, and all bear a single peak. The maximum mitotic activity was observed at 8:00 A.M., and the minimum – at 8:00-11:00 P.M. Thus, despite the significant elevation in mitotic activity during regeneration, the 24 hour rhythm of proliferating cells does not undergo essential changes.

During physiological and reparative regeneration of different organs, one observes general regularities in the changes in mitotic activity of the cells over a 24 hour period, which is apparently caused by a close interrelationship between these processes.

SUMMARY

Comparison of the curves of the 24 hour mitotic rhythm in the submaxillary salivary gland, liver and skin epidermis during regeneration demonstrated that they were parallel and had a single peak. The maximum mitotic activity was observed at 8 A.M. and the minimum at 8-11 P.M. The same changes of the 24 hour mitotic rhythm in the mentioned organs were observed during physiological regeneration. Consequently during physiological and repair regeneration of various animal organs there are general regularities in the 24 hour changes of mitotic activity of the cells evidently caused by the close interrelationship of these processes.

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