THE DAILY RHYTHM OF MITOTIC ACTIVITY IN MICE ON A MODIFIED FEEDING PROGRAM

N. V. Krasil'nikova

Department of Histology (Scientific Director, Professor I. A. Alov), Khabarovsk Medical Institute
(Presented by Active Member AMN SSSR, A. V Lebedinskii)
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In previous communications we have demonstrated a relationship between the daily rhythm of mitosis and the functional activity of the organ [2, 4]. At the same time, differences were observed between the pattern of mitosis in different organs. In contrast to the epithelium of the skin, the digestive organs gave curves of mitotic activity which were bimodal in character. Analysis of these results suggests that the second maximum and minimum of mitotic activity of the digestive organs are associated with the feeding of the animals in the morning (9 A. M.), i.e., with the stimulation of digestive activity at that time.

If the daily rhythm of mitosis is, in fact, associated with the functional activity of the organ [1, 4, 5], it might be expected that a change in the feeding program would lead to a change in the daily rhythm of mitosis of the digestive organs. The present research was to test this hypothesis.

EXPERIMENTAL METHOD

Experiments were carried out on albino mice aged 2.5 months. The animals (in groups of 5 or 6) were sacrificed at different times of day and night: 8 and 11 A. M., 2, 5, 8, and 11 P. M., and 2 and 5 A. M.

The intensity of cell multiplication was determined at these different times in the epithelium of the duodenum, in the serous and mucous portions of the submandibular salivary gland, in the exocrine portion of the pancreas, in the epithelium of the principal divisions of the kidney, and in the epithelium of the cornea and skin. The intensity of mitotic activity was judged by the number of dividing cells in a constant area (for the kidney, salivary gland and pancreas – 3.3 mm^2, for the remaining objects – 1.65 mm^2), by the relative percentages of the various phases of mitosis, and by the phase coefficient.

During the two months before they were sacrificed, the animals received food and water strictly at the same time of day – 9 P. M.

For the two weeks before sacrifice and on the day of the experiment, certain functional indices of the test organs were determined. The intensity of digestion was measured in the mice by the amount of food taken by the animals and the number of visits made to the feeding bowl. Every 3 h the food left in the feeding bowl was weighed. Visits to the feeding bowl (and at the same time the general activity of the mice) were recorded in a special cage with electrical contacts and a counter, marking every run made by the mouse to the bowl. The volume of water drunk by the mouse was also recorded every 3 h by means of a special floating marker with lever transmission.

EXPERIMENTAL RESULTS

A change in the feeding program of the mice completely altered the mitotic rhythm of the digestive organs. When they took food at 9 P M., the curves of the daily mitotic rhythm of the duodenal epithelium, the salivary gland, and the pancreas of the mice became unimodal in character [4]. The maximum of mitotic activity was found at 8 A. M. The intensity of multiplication of the cells then fell to a minimum at 8-11 P. M., after which the number of cell divisions began to increase. The differences between the levels of the maximum and minimum of mitotic activity were well defined ($P = 0.001$-0.01).

Comparison of the daily mitotic rhythm with the functional activity of the digestive organs (Fig. 1) revealed that these criteria were inversely related to each other. Like the daily mitotic rhythm, the curves of the functional

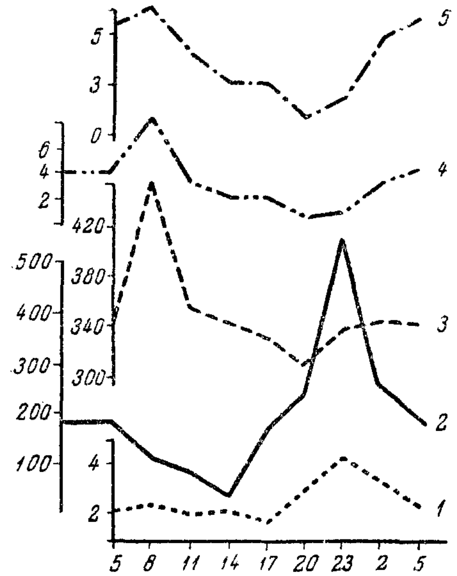

Fig. 1. Curves of the daily mitotic rhythm and functional activity of the digestive organs. Along the axis of abscissas—time of dat; along the axis of ordinates—indices of functional and mitotic activity. 1) Amount of food eaten; 2) No. of visits to feeding bowl; 3) mitotic activity in duodenal epithelium; 4) mitotic activity of pancreas; 5) mitotic activity of salivary gland.

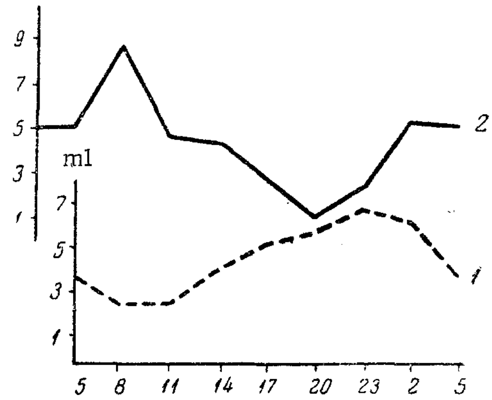

Fig. 2. Curves of the daily mitotic rhythm and functional strain on the kidney. 1) Volume of water drunk; 2) mitotic activity of the kidney.

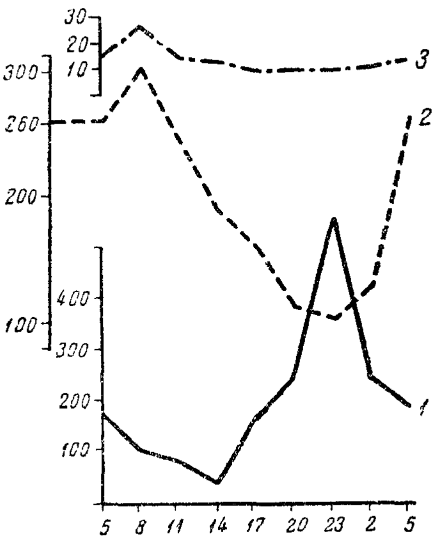

Fig. 3. Curves of the daily mitotic rhythm in the epithelium of the cornea and skin and the general activity of the animals. 1) General activity of mice; 2) mitotic activity of the cornea; 3) mitotic activity of the epidermis.

activity of the digestive organs were unimodal in character. The maximum of ingestion of food and the highest frequency of visits made by the animal to the feeding bowl coincided with the minimum of mitotic activity (11 P. M.). Conversely, the minimal values of functional activity (8 A. M.) coincided with a high intensity of multiplication of the cells. Hence, by altering the animals' feeding time, we abolished the morning rise in digestive activity, which led to the disappearance of the second minimum and maximum of mitotic activity in the digestive organs.

The mitotic activity in the epithelium of the principal divisions of the kidney (Fig. 2), like that of the digestive organs, reached its maximal values at 8 A. M. The maximum absorption of water by the mice at 11 P. M. coincided with the minimal values of the intensity of cell division in the kidney; conversely, high mitotic activity (8 A. M.) corresponded to low indices of absorption of water by the animals. Hence, an inverse relationship between work and cell division was observed in the kidney too.

In our previous experiments we found that increased water intake by animals during the morning was reflected in the daily periodicity of mitosis in the kidney in the form of a second minimum and maximum of cell divisions. By giving fresh water to the animals in the evening we abolished the morning increase in water intake by the mice, and this was reflected in the daily mitotic rhythm of the kidney; the curve of the daily periodicity of cell division became obviously unimodal in character.

The change in the feeding program of the animals had no effect on the mitotic activity in the epithelium of the cornea and skin. The intensity of cell division in the epithelia of the skin and cornea varied synchronously with the daily mitotic rhythm in the digestive organs and kidney. The maximal number of dividing cells was observed at 8 A. M. Comparison between the daily rhythm of mitoses in the corneal epithelium and the epidermis and the general activity of the mice during the 24-hour period (the curve of the frequency of visits to the feeding bowl serves at the same time as an octogram) demonstrated the inverse relationship between these indices.

Confirmation was thus obtained of the earlier findings [2] that the daily periodicity of mitotis in the various organs of albino mice is based on a common daily rhythm, typical for nocturnal animals (maximum in the morning, minimum in the evening or at night). However, this basic rhythm may be modified in various organs by changes in the pattern of their functional activity.

SUMMARY

In this work a daily rhythm of mitotic activity was studied in the intestinal epithelium, in the salivary and pancreatic glands, in the kidney, epidermis, and in the corneal epithelium of albino mice in changed nutritional regimen. Alteration in the feeding time completely changed the character of the daily mitoses curve in the digestive organs. In mice fed at 9 a.m. the daily mitotic rhythm in the digestive organs was characterized by a double-peak curve, whereas in mice fed at 9 p.m., by a single-peak curve. The curve of the daily mitotic periodicity in the kidney also acquired a single-peak character. The rhythm of mitotic activity in the epithelium of the cornea and skin has not altered with changes in the regimen of feeding; it was single-peak and synchronized with the mitotic rhythms of the digestive organs and kidney.

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