RELATIONSHIP BETWEEN CHANGES IN MITOTIC ACTIVITY OF THE CORNEAL EPITHELIUM AND BODY WEIGHT OF FASTING ANIMALS

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Although some research has been done on the role of energy metabolism in the regulation of the mitotic activity of the body tissues [5, 6] much remains to be explained. In the study of this problem it is advisable to carry out experiments during fasting, when the energy reserves of the body are considerably depleted.

The course of various physiological processes during starvation has been studied in adequate detail. We know, in particular, that in young animals whose weight is small, the sharp decrease in the gas exchange (on account of a decrease in the amount of oxidizable material in the body) takes place much sooner than in adult animals, in which this decrease is preceded by a long (7-8 days) period of stable gas exchange [4]. These differences in the time of the decrease in gas exchange in small and large animals during fasting are the result of differences in the expenditure of energy: the expenditure of energy per unit body weight and surface area is much greater in young animals than in adults [4].

Studies of the mitotic activity of the epidermis, the intestinal epithelium and the liver of certain mammals [7, 8, 9] have shown that the number of dividing cells falls during starvation. The question of a connection between the mitotic activity and the character of the processes taking place in the starving animal, however, has not yet been investigated.

In a previous communication [2] we showed that the decrease in mitotic activity taking place on the third day of starvation in rats of small body weight (60 g) was preceded by a considerable increase in the number of dividing cells in the corneal epithelium. In mice, which are characterized by a higher level of the basal metabolism, the fall took place 24 hours earlier than in rats [3].

The object of the present investigation was to study the changes in mitotic activity, taking into account differences in the expenditure of energy in animals of the same species but of different body weight and age, during total and prolonged fasting.

METHOD

Experiments were carried out on male white rats of different body weight: 1) on young, sexually immature animals weighing 55-60 g (low body weight group); 2) on sexually mature animals weighing 157 g (average body weight group); 3) on old animals weighing 332 g (high body weight group).

*Deceased.

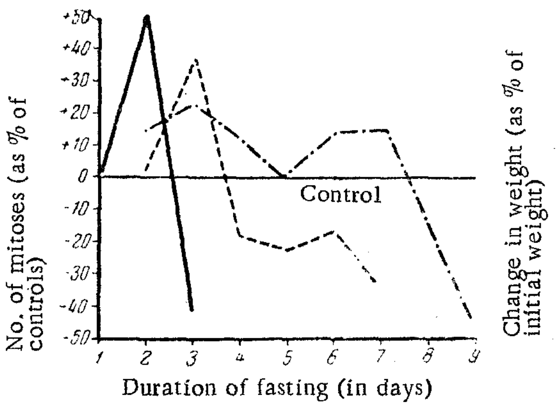

Fig. 1. Changes in the mitotic activity of the corneal epithelium and in the body weight of fasting rats kept at an optimal temperature.

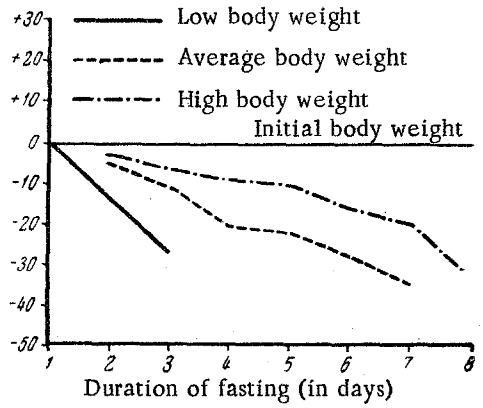

Fig. 2. Changes in body weight and mitotic activity of white rats during fasting

Before the experiment started, the rats were kept under standard conditions for several days. The air temperature in the experimental room varied between 20° and 24°. Control and experimental groups comprised five animals in each variant of the experiment. Fasting in our experiments lasted for one to nine days. The fasting animals received nothing but water. The rats were weighed during the experiments. The control and experimental animals were sacrificed in turn, and always at the same time of day.

In one series of experiments an increase in the intensity of metabolism was brought about in the starving animals. For this purpose the rats were kept at a lowered temperature (16°). The control group was kept at 24-25°.

The mitotic activity was investigated in histological preparations of the corneal epithelium, stained by Carazzi's hematoxylin.

The mitotic index was taken to be the number of divisions taking place on the average in 100 fields of vision, corresponding to 1 mm^2 surface area of the cornea.

RESULTS

1. Starvation of rats of different body weights in optimal temperature conditions.

The weight of the experimental animals and the mitotic indices of the corneal epithelium during fasting changed consistently. The mean figures showing these changes are given in Table 1, and in Figs. 1 and 2. The changes in the mitotic activity of the corneal epithelium and in the body weight of the starving animals are shown graphically. It can be seen that the changes in the mitotic activity were closely related to the changes in body weight observed in the 55-60g rats during three days of starvation. We noted a maximum increase in the number of mitoses in these animals on the second day of starvation (to 51%) and a sharp fall in the number of mitoses at the end of the experiment.

In rats weighing 157g, the fall in body weight was less pronounced and the increase in the number of mitoses observed in these animals on the third day of fasting did not exceed 39%. A fall in mitotic activity was observed only after the fourth day of the experiment. This fall continued to progress until the seventh day inclusive.

In the rats weighing 332g the loss of weight during fasting was least marked. The maximum increase in mitotic activity did not exceed 24%, but a tendency towards an increase in the number of mitoses took place at a much later period (until the seventh day of starvation). After nine days of fasting the mitotic activity also fell in the animals of this weight category.

2. Starvation of rats at a lowered temperature.

The results of these experiments provided a basis for the hypothesis that the intensity of mitotic activity and the degree of depletion of the energy resources of the body are correlated. In order to verify this hypothesis we carried out experiments to increase the expenditure of energy during starvation. For this purpose the fasting and control animals were kept in a room at a lowered temperature (16°). At the same time an experiment was conducted in a room where the temperature was maintained at the optimal level (23-24°). The mean values of the mitotic indices obtained in these experiments are shown in Table 2.

TABLE 1

Changes in the Body Weight and Mitotic Activity of Rats During Fasting

Duration of experiment (in days)	No. of animals	Mitotic index	Control series			Experimental series		
			change in body wt (as % of original)	no. of animals	mitotic index	change in no. of mitoses (as % of controls)	change in body wt (as % of original)	probability of chance difference in mitotic index compared with controls
Low body weight group of rats								
1	10	347	no change	10	346	no change	no change	
2	10	292	+8	10	441	+51	−13.7	P = 0.018
3	10	306	+12	10	181	−41	−27.7	P = 0.027
Average body weight group of rats								
2	10	274	no change	10	279	no change	− 6	
3	10	231	no change	10	321	+39	−12	P = 0.061
4	10	300	+3	10	247	−18	−20	
5	5	284	+2	5	218	−23	−23	
6	5	273	no change	5	230	−16	−28	P=0.0000
7	5	275	+7	5	182	−34	−35	
High body weight group of rats								
2	10	264	no change	10	301	+14	− 3	
3	10	221	no change	10	275	+24	− 7.5	
4	5	250	+3	5	280	+12	− 9	P = 0.0000
5	5	141	no change	5	139	− 1	−11	
6	10	231	+4	10	265	+14	−16.5	
7	5	218	+5	5	252	+15	−20	
9	5	326	+1	5	177	−46	−29	P = 0.027

TABLE 2

Mitotic Activity of the Corneal Epithelium of White Rats on the Third Day of Fasting at Different Temperatures

Temperature of room	Average body wt, (in g)	Mitotic index		Change in mitotic index as % of control	Fall in body wt. as % of initial, after 2 days of experiment
		control animals	experimental animals		
24—25°	200	260∓37,9	315∓19,1	+20	—9
	57	444∓47,9	311∓30,8	—30	—16
16°	200	428∓51,6	276∓11	—36	—22
	57	437	2	in 218 times	—39

[1] The animals were not weighed on the day they were sacrificed.

It can be seen from the figures given in Table 2 that an increase in the basal metabolism of the fasting animals resulting from an increase in the expenditure of energy for the needs of heat production led to a decrease of 36 % in the mitotic activity, even in the rats weighing 200 g, although in the rats of the same weight but kept at a temperature of 23-24° the mitotic activity was increased by 20 %.

The greatest decrease in mitotic activity (218 times greater than in the controls), accompanied by the greatest loss of weight, was found in the rats weighing 57 g, the energy expenditure per unit body weight of which was much greater than in the adult animals. The experimental results described demonstrate the existence of a relationship between the degree of wasting of the animals during starvation and the original weight, and also a connection between the body weight of the animals and the character of the change in the mitotic activity. The smaller the weight of the animals and the higher, although the shorter in duration, the increase in the mitotic activity at the beginning of fasting, the sharper its fall at the end.

In the majority of cases when the fall in the initial weight was 20 % an increase in mitotic activity was observed. With a further decrease in weight, the number of dividing cells also diminished.

In the largest animals, distinguished by the smallest loss of body weight, the mitotic activity was increased until the seventh day of starvation inclusive. Only after nine days of starvation did a significant increase take place in the number of mitoses.

When our results are compared with those in the literature, support is obtained for the claim that the mitotic activity persists during starvation. Hooper and Blair [8], for example, who investigated the mitotic activity of the epithelium of the small intestine of fasting rats, observed a slight fall in the number of dividing cells only on the fifth day of the experiment. Similar results were obtained by A. N. Zorin [1].

Our experiments give evidence of the high proliferative power of the corneal epithelium even during starvation, an indication that synthetic processes continue to take place in this structure at a high level. A decrease in the mitotic activity took place only in the stage of severe emaciation of the animal. We consider that the quicker and more acute fall in the mitotic activity of the smaller rats if related to their more intensive basal metabolism and, consequently, to the more rapid expenditure of energy-producing material, necessary for the maintenance of various physiological processes, including cell proliferation. The latter is confirmed by the experiment in which starving rats of low body weight were kept for three days at a lowered temperature. This led to the rapid expenditure and depletion of the energy resources of the animals for the production of heat, and to the almost complete disappearance of mitoses in the corneal epithelium. In the animals which had fasted for three days, but which were kept at a higher temperature, no such sharp fall in mitotic activity took place anywhere.

We have previously found in white mice [3] that compensation for the expenditure of energy by carbohydrates alone enables the the mitotic activity of the corneal epithelium to be maintained at a normal level until the fourth day of fasting inclusive. This suggests that the energy resources of the body play a most essential part in cell proliferation.

SUMMARY

Fasting for 24 hours did not change the number of dividing cells of the corneal epithelium in rats with the average weight of 55-60 g, whereas 48-hour fasting was accompanied by its intensification; mitotic activity was found to be considerably reduced after 72 hr of the experiment. After an initial rise, observed for up to 72 hr of fasting, the mitotic activity was found to decrease on the 4th, 5th, 6th, and 7th days in rats with an average weight of 157 g. The maximal reduction of mitotic activity (34 %) and of the body weight (35 %) was revealed on the 7th experimental day.

In rats with average weight of 332 g the mitotic activity increased by 13 % on the average (as compared with controls) during fasting from 2 to 7 days. Reduction in the number of dividing cells in this weight group was noted after 9 days of fasting. The most rapid reduction of the weight and mitotic activity occurred in rats with the least weight. In medium-weight and high-weight rats such changes took place later. Intensification of metabolism in the fasting animals, connected with the increased energy expenditure for replenishment of thermal requirements (with the animals kept at 16°C) produced maximal reduction of mitotic activity and the greatest loss of weight in the smallest rats.

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*Original Russian pagination. See C. B. translation.