CHANGES IN DIURNAL RHYTHM OF MITOTIC ACTIVITY OF THE CONVOLUTED TUBULES IN COMPENSATORY AND REGENERATION HYPERTROPHY OF THE KIDNEY IN RATS

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Many investigators [1-14] have observed an increase in the number of mitoses in the kidney during compensatory hypertrophy and regeneration. However, it is not known for how long it remains increased. This problem may be solved only by a study of the diurnal rhythm of mitotic activity, and this was done in the present investigation.

EXPERIMENTAL METHOD

Experiments were carried out on 885 male albino rats weighing 90-120 g, of which 295 were controls and 590 experimental. The latter were divided into two groups, with 295 rats in each group. The left kidney was removed from the animals of group 1, while in the rats of group 2 the left kidney was removed and from 1/3 to 1/4 of the right kidney was resected at one operation. The operation was always performed between 9 a.m. and 4 p.m. The experimental and control animals were decapitated 12 and 24 h, 2, 5, and 14 days, and 2, 3, and 6 months after the operation. At each time 40 animals of the control series and of each variant of the experiment, i.e., 120 rats altogether, were sacrificed, but 6 months after the operation only 15 animals of each group were sacrificed. At all these times the animals were killed every 3 h during the 24 h period—5 rats each at 6 and 9 a.m., 12 noon, 3, 6, and 9 p.m., 12 midnight, and 3 a.m. The material was treated by the usual histological methods. Mitoses were counted on the average in 26,000 cells for each animal. The mitotic coefficient was expressed in promille. Statistical analysis of the experimental results was carried out by the Fisher—Student method.

EXPERIMENTAL RESULTS

The diurnal changes in the mitotic coefficient (MC) in the kidney undergoing compensatory hypertrophy and in the resected kidney at various times after the operation are given in the table. As the table shows, in compensatory hypertrophy 12 h after the operation the diurnal rhythm of mitosis is disturbed. The MC reaches a maximum at 3-6 a.m. (transgression absent) and a minimum at between 12 noon and 6 p.m. At these times the number of mitoses is much lower than in the control series (for 12 noon $P < 0.001$, for 3 p.m. $P = 0.023$, and for 6 p.m. transgression is absent).

The MC is much higher than in the control 24 h after the operation (by 4.2 times, transgression absent). The diurnal rhythm of mitosis is disturbed. The MC reaches a maximum at 6 a.m. and a minimum at 9 a.m. The MC is also above the control level 2 days after the operation, on the average by 1.8 times, and the diurnal rhythm of mitosis is disturbed. The MC reaches a maximum at 12 midnight and between 6 a.m. and 12 noon, and a minimum at between 3 and 9 p.m.

At all times of the experiment the MC is increased 5 days after the operation (transgression absent) on the average by twice, and the diurnal rhythm of mitosis is the same as in the control.

Two weeks after the operation the MC shows a statistically significant increase over the control at all times of observation (transgression absent) on the average by twice. From now on the diurnal rhythm is unchanged.

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Changes in MC in Epithelium of Convoluted Tubules during the 24 Hours (in %) in Control and Experimental Rats

Time of day	Period of investigation (in days after operation)							
	0,5	1	2	5	14	30	90	180
Control kidney								
6	0,68	0,53	0,55	0,79	0,66	0,50	0,61	—
9	0,73	0,56	0,65	0,77	0,72	0,57	0,60	0,80
12	0,89	0,76	0,76	0,89	0,87	0,69	0,73	0,94
15	0,83	0,62	0,82	0,70	0,82	0,77	0,82	0,82
18	0,61	0,52	0,70	0,67	0,66	0,60	0,67	—
21	0,53	0,48	0,44	0,60	0,57	0,41	0,43	—
24	0,66	0,50	0,53	0,59	0,61	0,48	0,46	—
3	0,63	0,53	0,47	0,61	0,60	0,49	0,48	—
mean	0,69±0,04	0,56±0,03	0,61±0,05	0,69±0,04	0,69±0,04	0,57±0,04	0,60±0,05	0,85±0,04
Kidney with compensatory hypertrophy								
6	1,62	4,93	1,05	1,29	1,26	0,85	0,75	—
9	0,70	1,45	1,26	1,47	1,37	0,91	0,87	0,83
12	0,47	2,80	1,31	1,73	1,66	1,06	0,93	0,95
15	0,42	2,72	1,05	1,57	1,41	1,11	0,87	0,92
18	0,34	1,79	1,09	1,38	1,37	1,01	0,69	—
21	0,54	1,51	0,84	1,23	1,18	0,77	0,56	—
24	0,80	1,92	1,28	1,25	1,25	0,90	0,68	—
3	1,14	1,70	0,84	1,32	1,27	0,93	0,68	—
mean	0,75±0,15	2,35±0,35	1,09±0,06	1,41±0,06	1,35±0,05	0,94±0,04	0,75±0,04	0,89±0,19
Kidney with regeneration hypertrophy								
6	0,47	0,28	2,62	3,05	1,72	1,01	0,88	—
9	0,60	0,48	3,28	4,32	1,95	1,05	1,00	0,90
12	0,87	0,48	3,46	6,41	2,13	1,14	1,05	1,01
15	0,63	0,60	2,85	4,41	1,85	1,16	1,03	0,97
18	0,87	0,68	2,27	3,99	1,43	1,01	0,90	—
21	1,21	0,69	2,21	2,74	1,33	0,85	0,82	—
24	0,65	0,86	2,85	2,90	1,41	0,98	0,81	—
3	0,90	0,59	2,49	3,03	1,44	1,00	0,85	—
mean	0,78±0,08	0,58±0,06	2,75±0,16	3,86±0,38	1,68±0,10	1,03±0,03	0,92±0,03	0,92±0,13

One month after the operation the mean diurnal MC is increased over the control value at all times of observation on the average by 1.6 times (transgression absent).

Three months after the operation the mean diurnal MC was close to the control value. The difference between the experimental and control values is not statistically significant ($P = 0.037$).

Six months after the operation no differences were found between the control and experimental series.

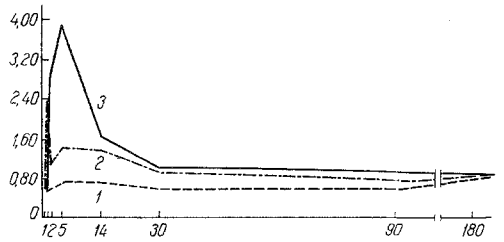
The table shows that 12 h after the operation the MC in the resected kidney is also sharply abnormal. The diurnal rhythm of mitosis is disturbed. The MC reaches its maximum at 9 p.m. and its minimum at 6 a.m. The difference between the experimental and control values at 9 p.m. is statistically significant (transgression absent) and at 6 a.m. it is close to significant ($P = 0.027$). The mean diurnal values of the MC in the experimental and control series do not differ significantly.

Disturbance of the diurnal rhythm of mitosis is also observed 24 h after the operation. The MC reaches its maximum at 12 midnight and its minimum at 6 a.m. The difference between the experimental and control series at these times is statistically significant ($P < 0.01$ in both cases). The mean diurnal value of the MC is the same as in the control.

The diurnal rhythm of mitosis remains disturbed 2 days after the operation. The MC is at its maximum at 12 noon and its minimum at between 6 and 9 p.m. At these, as at other times, the difference between the experimental and control values is statistically significant (transgression absent in all cases). The mean diurnal MC is increased by 4.5 times.

The diurnal rhythm of mitosis is still disturbed 5 days after operation. The MC is at its maximum at 12 noon. At this time it is considerably increased—7 times higher than the control. It reaches its minimum at 9 p.m., but even at this time it is still considerably increased—4.6 times above the control figure. The mean diurnal MC is 5.6 times higher than in the control.

Two weeks after the operation the diurnal rhythm of mitosis is restored. The periods of the maximum and minimum of the MC coincide in the experimental and control series. Throughout the 24 h the MC



Changes in MC in kidney with compensatory hypertrophy and resected kidney. Abscissa) days after operation, ordinate) mitotic coefficient (in %): 1) in control rats; 2) in rats after removal of left kidney; 3) in rats after removal of left kidney and resection of 1/3-1/4 of right kidney.

is increased by a statistically significant margin at all times of investigation (transgression always absent). The mean diurnal MC is 2.4 times higher than in the control.

One month after the operation the MC shows a stastically significant increases throughout the 24 h (at all times transgression absent). The MC reaches its maximum at 3 and its minimum at 9 p.m. The increase in MC from 6 a.m. to 3 p.m. is statistically significant (transgression absent). The mean diurnal MC is increased 1.8 times.

Three months after operation the MC has a maximum at 12 noon. The difference between the experimental and control values at this time is statistically significant. The MC is minimal at 9 p.m. The increase in MC from 6 a.m. to 12 noon and its decrease from noon to 9 p.m. are statistically significant (in both cases transgression absent). However, at 6 a.m. and 3 p.m. the increase of MC is not statistically significant ($P = 0.094$ and $P = 0.110$ respectively). The mean diurnal MC is increased by only 1.5 times over the control value.

Six months after the operation no significant differences are found between the experimental and control series at the times investigated ($P = 0.504$, $P = 0.394$, and $P = 0.347$ respectively).

The changes in the mean diurnal MC in the kidneys with compensatory and regeneration hypertrophy throughout the experimental period are shown graphically in the figure. It is clear that the MC rises 12 h after unilateral nephrectomy, and the increase is particularly sharp at the end of the 1st day after operation. Subsequently the number of mitoses gradually falls by comparison with the control value, but still remains increased, and not until 3-6 months after operation does the difference between the experimental and control values disappear. The diurnal rhythm of mitosis is disturbed for 12-48 h after operation.

In the solitary resected kidney an increase in MC is found 2 days after the operation, reaching its maximum on the 5th day of the experiment. By one month after the operation the MC falls appreciably, although it does not equal the control level until after 6 months. The diurnal rhythm of mitosis, which is disturbed 12 h after the operation, is restored after 2 weeks.

It may be noted that in experiments carried out on albino rats, the MC in the regenerating kidney was also observed to reach a maximum on the 5th day after operation [7].*

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