TOPOGRAPHIC DISTRIBUTION OF DIVIDING HEPATOCYTES IN THE REGENERATING LIVER LOBULE DURING PEAK MITOTIC ACTIVITY

Yu. A. Romanov and T. V. Savchenko

UDC 612.35.014.2:612.6.03+
616.36-003.93-018.15

KEY WORDS: mitotic activity; hepatic lobule; hepatectomy.

Morphological and functional heterogeneity of hepatocytes depending on their location in the hepatic lobule is an urgent biological problem [5-8]. The way in which the ability of the cells to proliferate depends on their intralobular location is very interesting [2-4, 6, 8]. However, this problem has not been adequately studied and data in the literature are contradictory [1-4].

In the investigation described below, the time course of behavior of proliferating hepatocytes in different zones of the lobule was studied during peak mitotic activity in the residual liver after partial hepatectomy.

EXPERIMENTAL METHOD

Experiments were carried out on 20 non-inbred male rats weighing 200 g. Two-thirds of the liver was removed by the usual method between 10 and 11.30 a.m. The animals were killed five at a time 20, 24, 28, and 23 h after the operation. Pieces of liver were fixed and embedded in paraffin wax; sections 4 μ thick were cut and stained with hematoxylin and eosin. The general mitotic index (GMI) was determined by counting 10,000 hepatocytes. The mitotic index (MI) also was calculated in each zone of the lobule. For this purpose lobules were chosen in which the distance from the central vein to the triad included from 20 to 116 cells (radius of the lobule). Three zones were then distinguished in the lobule: peripheral (1), middle (2), and inner (3), all with the same width along the radius [9]. The number of mitoses and the total number of hepatocytes were counted in each zone in a certain number of fields of vision under high power of the microscope, and values of MI_1, MI_2, and MI_3 were calculated for the first, second, and third zones of the hepatic lobule respectively. From 10 to 15 lobules were examined in sections from each animal. MI was expressed per thousand The significance of differences was estimated by the Fisher–Student method at the $P < 0.05$ level.

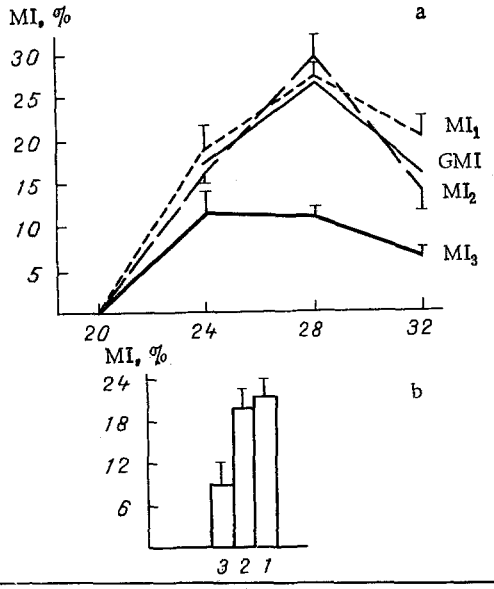

Fig. 1. Change in MI and its mean value in different zones of the rat hepatic lobule after removal of two-thirds of the liver. Abscissa: a) time after operation (in h); b) zones of lobule. Ordinate, MI (in ‰). a) Changes in MI_1, MI_2, MI_3, and GMI at different times after operation; b) average values of MI_1, MI_2, and MI_3.

Chair of Biology, Medical-Biological Faculty, N. I. Pirogov Second Moscow Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR D. S. Sarkisov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 11, pp. 597-598, November, 1986. Original article submitted March 10, 1986.

 0007-4888/86/0011-1580$12.50 © 1987 Plenum Publishing Corporation

TABLE 1. Ratios between Values of MI in Different Zones of the Hepatic Lobule of Adult Rats at Different Times after Partial Hepatectomy

Time after operation, h	MI_2/MI_3	MI_1/MI_3	MI_1/MI_2
24	1,40	1,63	1,16
28	2,72	2,38	0,88
32	2,43	3,49	1,44
Mean	2,10	2,32	1,11

EXPERIMENTAL RESULTS

It will be clear from Fig. 1 that the first dividing cells appeared in the liver 24 h after hepatectomy (GMI = 15.83 ‰). By 28 h their number had increased significantly compared with the previous time, to reach a maximum (26.37‰, $P_{24} = 0.024$). By 32 h GMI had fallen to 15.60 ‰ ($P_{28} = 0.001$). The highest mitotic activity in the regenerative liver, according to data in the literature [2, 4], is observed 24 and 26 h after hepatectomy.

Changes in MI in different zones of the liver also are shown in Fig. 1. Mitoses were present 24 h after the operation in all zones; the values of MI_1, MI_2, and MI_3 at this time, moreover, did not differ significantly from each other. The ratios between values of MI in the different zones were closely similar (Table 1). However, 28 h after the operation the ratios between these parameters in the different zones differed significantly (Table 1). This was because MI_1 and MI_2 at this time of the experiment had significantly ($P = 0.001$-0.033) increased, to reach peak values, whereas MI_3 was virtually unchanged compared with the previous time. By 32 h after the operation values of all MI were significantly reduced, but the ratios between their values differed. MI_1 and MI_2, determined 28 and 32 h after the operation, were 2.5-3.5 times higher than MI_3 (Table 1).

Analysis of correlation between changes in MI in different zones of the lobule in the course of the experiment revealed a high degree of similarity of the cell kinetics in zones 1 and 2 ($r_{MI_2-MI_1} = +0.75 \pm 0.12$) and a weak degree of correlation between MI in these zones and in zone 3 ($r_{MI_3-MI_2} = +0.33 \pm 0.25$ and $r_{MI_3-MI_2} = +0.32 \pm 0.25$).

The reasons for differences in the ability of hepatocytes in different zones of the lobule to proliferate, including those found during reparative regeneration of the organ, have been discussed in the literature [2-4, 8]. Some workers [3] consider that zones 1 and 2 of the hepatic lobule are reserve zones relative to proliferative processes. Our data indicate a higher proliferative potential in hepatocytes of the peripheral and middle zones of the regenerating hepatic lobule during the period of peak mitotic activity in the organ after partial hepatectomy. However, in our view, to explain the principles governing differences in the kinetics of hepatocytes in different zones of the regenerating liver lobule it is necessary to study this problem at other, later stages of regeneration.

The authors are grateful to Dr. Med. Sci. S. G. Mamontov for help with the experiments.

LITERATURE CITED

1. A. Brues and B. Marble, J. Exp. Med., 65, 15 (1937).
2. J. Fabricant, J. Cell Biol., 36, 551 (1968).
3. J. Gricham, Cancer Res., 22, 842 (1962).
4. R. Harkness, J. Physiol. (London), 116, 373 (1952).
5. A. Le Bouton, Anat. Rec., 160, 383 (1968).
6. A. Le Bouton and R. Marchand, Dev. Biol., 23, 524 (1970).
7. J. Melvin, Anat. Rec., 160, 607 (1968).
8. H. Rabes, R. Wirsching, H.-V. Tuczek, and G. Iseler, Cell Tissue Kinet., 9, 517 (1976).
9. A. Rappoport, A. Borowy, W. Lougheed, and W. Lotto, Anat. Rec., 119, 11 (1954).