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EFFECT OF ADRENORECEPTOR FUNCTION ON MITOTIC ACTIVITY OF THE REGENERATING RAT LIVER

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Analysis of the recent literature [2-6] shows that the regenerative activity of the liver depends to a definite extent on the original functional state of the adrenoreceptors. The present writer showed previously in rats [1] that administration of two doses (1 h before and 24 h after resection of the liver) of the α-adrenoblocker phentolamine considerably reduced the mitotic index, whereas administration of the β-adrenoblocker propranolol at the same times increased the mitotic index in the regenerating liver. Neither adrenoblocker had any marked effect on the ratio between early and late phases of mitosis. The aim of the present investigation was to discover the effect of administration of a single dose of the adrenoblockers at different times after partial hepatectomy.

EXPERIMENTAL METHOD

Noninbred male albino rats weighing 200-250 g were used. About 70% of the liver by weight was removed from the animals. Some animals were given a single intraperitoneal injection of phentolamine, others a single dose of propranolol, 20 mg/kg in both cases. The drugs were given 1 h before, or 30 min, 8, and 24 h after resection of the liver. Control rats received physiological saline in the same volume at the same times. The animals were decapitated 30 h after the operation, in all cases at 3-4 p.m. Histological sections were prepared from the liver (fixation in Carnoy's fluid, embedding in paraffin wax, staining with hematoxylin).

The regenerative activity of the liver was estimated from the mitotic index (in promille), the phase coefficient (the ratio of early and late phases of mitosis, in %), and the number of binuclear cells (in %). At least 100 fields of vision of the microscope under a magnification of 40 × 16 were examined in each section. The glycogen content in the liver also was determined by the method of Vertar and Wenner.

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TABLE 1. Effect of a Single Dose of Propranolol on Mitotic Activity of the Regenerating Liver (M ± m)

Parameter	Time of injection of propranolol			
	before resection		after resection	
	1 h	30 min	8 h	24 h
Mitotic index:				
C	8,8±0,83	7,1±1,35	8,4±0,6	6,1±0,54
E	12,6±1,14	10,9±1,37	18,8±0,71	16,0±0,43
	$P<0,01$	$P>0,05$	$P<0,001$	$P<0,001$
Phase coefficient:				
C	3,37±0,7	2,47±0,4	3,10±0,36	2,42±0,49
E	4,94±0,81	5,8±0,4	4,58±0,39	4,2±0,4
	$P>0,02$	$P<0,001$	$P<0,025$	$P<0,005$
Number of binuclear cells, %				
C	2,63±0,33	2,76±0,2	2,77±0,28	3,28±0,39
E	2,08±0,15	2,38±0,32	2,64±0,14	2,37±0,92
	$P>0,2$	$P>0,4$	$P>0,5$	$P<0,05$
Glycogen, mg/g:				
C	4,1±0,74	5,46±0,54	6,26±1,19	7,18±0,92
E	4,7±0,5	7,3±1,76	7,4±0,77	3,1±0,44
	$P>0,5$	$P>0,2$	$P>0,4$	$P<0,005$
Number of animals:				
C	6	6	6	6
E	7	10	10	10

Legend. Here and in Table 2: C) control, E) experiment.

TABLE 2. Effect of a Single Dose of Phentolamine on Mitotic Activity of the Regenerating Liver (M ± m)

Parameter	Time of injection of phentolamine			
	before resection		after resection	
	1 h	30 min	8 h	24 h
Mitotic index:				
C	8,3±0,65	6,8±0,35	8,5±0,47	9,7±0,45
E	4,2±0,41	2,6±0,25	5,0±0,28	4,2±0,26
	$P<0,001$	$P<0,001$	$P<0,001$	$P<0,001$
Phase coefficient:				
C	3,37±0,25	3,07±0,7	3,86±0,74	3,26±0,39
E	1,1±0,16	1,2±0,15	1,89±0,4	1,26±0,2
	$P<0,001$	$P<0,025$	$P<0,001$	$P>0,001$
Number of binuclear cells, %				
C	2,7±0,36	2,2±0,24	1,99±0,57	2,4±0,17
E	3,9±0,34	2,4±0,29	3,7±0,51	2,9±0,4
	$P>0,5$	$P>0,5$	$P<0,05$	$P>0,2$
Glycogen, mg/g:				
C	4,4±0,4	9,1±1,5	6,1±0,57	7,6±1,2
E	20,0±1,21	21,0—3,7	15,6—1,39	18,0±0,14
	$P<0,001$	$P<0,005$	$P<0,001$	$P<0,001$
Number of animals:				
C	8	8	7	7
E	10	10	8	8

EXPERIMENTAL RESULTS

The experimental results showed (Table 1) that under the influence of the β-adrenoblocker propranolol the mitotic index was increased if the drug was given 1 h before and, in particular, 8 and 24 h after resection of the liver. Injection of the drug 30 min after the operation had no significant effect on the mitotic index (Table 1). An increase in the number of early phases of mitosis under the influence of propranolol was observed when the drug was given at all times after resection, whereas preliminary β-adrenoreceptor blockade did not change the phase coefficient. The number of binuclear cells in the regenerating liver was unchanged after propranolol. Propranolol likewise had no significant effect on the glycogen content.

By contrast with the effect of propranolol, α-receptor blockade by phentolamine caused a decrease in the mitotic index and an increase in the number of late phases of mitosis, regardless of the time of administration of the drug. The number of binuclear cells was unchanged (except in the group of animals receiving phentolamine 8 h after the operation). The liver glycogen content was increased in all the rats, evidence of inhibition of glycogenolysis by phentolamine (Table 2).

Analysis of the occurrence (in %) of the individual phases of mitosis led to the conclusion that propranolol caused a reduction in the percentage of telophases and, in some groups, an increase in the number of prophases and metaphases also. The increase in the mitotic index after propranolol could perhaps be the result of two processes: an increase in the number of cells commencing mitosis and the more rapid course of the late mitotic phases.

The reduction in the phase coefficient under the influence of phentolamine, as analysis showed, was the result of a reduction in the number of early mitotic phases (prophases and metaphases) and an increase in the number of telophases or anaphases. It can be tentatively suggested that the fall in the mitotic index was closely connected with a decrease in mitotic activity of the hepatocytes and also with inhibition of passage through the late mitotic phases.

Comparison of these data with changes in the same indices of regeneration in the liver after administration of two doses of the α- and β-adrenoblockers [1] indicates that the frequency of administration of the drug had no effect on the direction of the changes in the mitotic index: After one and two injections of propranolol the mitotic index increased, whereas after phentolamine it decreased. However, after a single injection of propranolol the phase coefficient increased, whereas after phentolamine it decreased. After two doses of the adrenoblockers the phase coefficient remained within normal limits. Possibly the adrenoblockers are not absolutely specific and, if given in two doses, they may perhaps affect both α- and β-adrenoreceptors, although to different degrees. Under these conditions, the effect of the blockers on the duration of the mitotic cycle was perhaps balanced, and this led to preservation of the phase coefficient at the level observed in experiments in which two doses of the adrenoblockers were given.

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