For instance, a relative decrease was noted in G-6-PDH activity in the zona glomerulosa and zona reticularis (to 0.780 ± 0.008 relative unit compared with 1.080 ± 0.050 relative units in the control). There was also a significant decrease in 3-β-HSDH activity in the zona fasciculata (down to 0.440 ± 0.004 relative unit compared with 0.880 ± 0.006 relative unit in the control) and in NADPH-dehydrogenase activity in the zona glomerulosa (0.420 ± 0.007 relative unit compared with 0.870 ± 0.008 relative unit in the control).

Experiments thus showed that injection of thymarin is followed by a decrease in the linear dimensions of the cells in the zonal glomerulosa, zona fasciculata, and zona reticularis and also a decrease in the volume of these zones of the adrenal cortex. Considering that an increase in the lipid content and a decrease in activity of oxidation–reduction enzymes are observed at the same time in the cytoplasm of cells of the zona glomerulosa and zona reticularis, it can be concluded that under the influence of thymarin the synthetic function of the adrenals is repressed. This applies evidently above all to the production of proantiinflammatory hormones. This explains the fact that administration of thymarin to patients with chronic inflammatory conditions, burns, trauma, and certain other cases, leads to improvement in the clinical course of the disease [6].

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MITOTIC ACTIVITY OF THE REGENERATING RAT LIVER DURING STIMULATION OF α- AND β-ADRENORECEPTORS

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UDC 612.35:612.6.03].014.46:615.217.22

KEY WORDS: regeneration of the liver; propranolol; mitotic activity.

Previous investigations showed that two injections of propranolol (a β-adrenoblocker) increased the mitotic activity of regenerating liver cells, whereas phentolamine, an α-adrenoblocker, inhibited proliferation [1]. It was suggested that under natural conditions stimulation of β-adrenoreceptors ought to inhibit regeneration, whereas excitation of α-adrenoreceptors should stimulate it. To test this hypothesis experiments were carried out with stimulators of α- and β-adrenoreceptors. It was expected that administration of phenylephrine, a stimulator of α-adrenoreceptors, would intensify regeneration in the liver whereas excitation of β-adrenoreceptors by isoproterenol, on the other hand, would inhibit it.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 200-250 g. About 70% of the weight of the liver was removed from all animals. Some animals were given

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(Presented by Academician of the Academy of Medical Sciences of the USSR A. P. Avtsyn.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 91, No. 3, pp. 355-357, March, 1981. Original article submitted May 15, 1980.

0007-4888/81/9103-0374$07.50

TABLE 1. Effect of Phenylephrine, an α-Adrenoreceptor Stimulator, on Mitotic Activity in the Regenerating Liver

Index	Injection of phenylephrine 1 h before resection	Injection of phenylephrine after resection		
		30 min	8 h	2 h
Mitotic index, ‰				
C	8,17±2,93	9,35±2,77	9,55±1,71	7,89±3,06
E	16,95±1,54	16,56±0,64	11,82±1,25	20,54±1,24
	$P>0,025$	$P<0,01$	$P>0,4$	$P<0,005$
Phase coefficient				
C	3,11±0,57	3,24±0,25	3,21±0,27	3,42±0,36
E	4,17±0,19	3,26±0,35	4,48±0,44	3,66±0,39
	$P>0,05$	$P>0,5$	$P<0,001$	$P>0,5$
Binuclear cells, %				
C	2,02±0,35	1,95±0,31	2,00±0,16	1,93±0,29
E	2,32±0,28	2,47±0,16	2,38±0,23	2,53±0,26
	$P>0,5$	$P>0,5$	$P>0,4$	$P>0,05$
Glycogen, mg/g				
C	27,68±3,93	27,47±3,62	27,60±2,78	29,32±0,64
E	38,90±3,00	23,07±3,57	67,80±3,40	4,93±1,44
	$P<0,025$	$P>0,5$	$P<0,001$	$P<0,001$
Number of animals				
C	13	11	10	11
E	11	11	12	11

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

a single intraperitoneal injection of phenylephrine 1 h before or 30 min, 8 h, or 24 h after resection of the liver. The others received isoproterenol or physiological saline (control group) at the same times. The drugs were injected in a dose of 0.2 mg/kg. All the animals were decapitated 30 h after resection, which was always performed at 3-4 p.m. Histological sections (fixation in Carnoy's fluid, embedding in paraffin wax, staining with hematoxylin) were prepared. In each section at least 100 fields of vision were examined under a magnification of 40 × 16. The mitotic index (in promille), the phase coefficient (ratio of the sum of prophases and metaphases, in %, to the sum of anaphases and telophases, in %), and the number of binuclear cells were counted. The glycogen content also was determined in a liver homogenate. The weight of the adrenals and thymus were recorded.

EXPERIMENTAL RESULTS

Injection of phenylephrine 1 h before resection or 30 min and 24 h after resection of the liver caused a significant increase in the mitotic index but no change in the phase coefficient (Table 1). Injection of the drug 8 h after resection did not change the mitotic index although the phase coefficient was higher than in the control. The number of binuclear cells was unchanged after injection of phenylephrine at whatever time. A considerable increase in the mitotic index in most groups, combined with no change in the phase coefficient, indicated that phenylephrine stimulated proliferative activity in the regenerating liver.

Absence of correlation between the glycogen content and the character of the changes in mitotic activity was noted.

Stimulation of proliferative activity in the liver of the rats receiving phenylephrine 24 h after resection was accompanied by marked signs of stress (an increase in weight of the adrenals by 22%, a decrease in weight of the thymus by 20.9%, a sharp fall in the glycogen content in the liver).

Injection of isoproterenol into the rats (Table 2) had hardly any effect on the level of the mitotic index at whatever time it was given. Only in the animals receiving the drug 24 h after resection of the liver was the mitotic index sharply increased, on account of a marked increase in the number of telophases (45.15% compared with 14.52% in the control). This led to a marked decrease in the phase coefficient. A decrease in phase coefficient also was observed in animals receiving isoproterenol 30 min and 8 h after resection. In all experimental groups a significant increase was observed in the number of binuclear cells. These changes (a fall in the phase coefficient, an increase in the number of binuclear cells) can be interpreted as a manifestation of the inhibitory action of isoproterenol on proliferative activity.

TABLE 2. Effect of Isoproterenol, an β-Adrenoreceptor Stimulator, in Mitotic Activity of the Regenerating Liver

Index	Injection of isoproterenol 1 h before resection	Injection of isoproterenol after resection		
		30 min	8 h	24 h
Mitotic index, %				
C	8,17±1,54	9,35±0,63	9,55±1,25	7,89±1,24
E	7,72±1,37	11,92±2,08	8,62±1,22	17,17±2,57
	$P>0,5$	$P>0,1$	$P>0,5$	$P<0,005$
Phase coefficient				
C	3,11±0,57	3,24±0,253	3,21±0,27	3,42±0,36
E	2,24±0,42	1,62±0,163	2,01±0,28	1,26±0,136
	$P>0,2$	$P<0,001$	$P<0,005$	$P<0,001$
Binuclear cells, %				
C	2,02±0,28	1,95±0,16	2,00±0,23	1,46±0,16
E	3,08±0,46	3,12±0,31	2,97±0,39	2,16±0,19
	$P<0,05$	$P<0,005$	$P<0,05$	$P<0,025$
Glycogen, mg/g				
C	27,68±3,00	27,47±3,57	27,6±3,40	29,32±1,44
E	36,20±7,13	40,70±4,40	53,0±1,27	7,97±1,22
	$P>0,4$	$P<0,05$	$P<0,001$	$P<0,001$
Number of animals				
C	13	11	10	11
E	11	12	13	14

Phenylephrine and isoproterenol, in the above doses, thus had opposite actions on hepatocyte proliferation. The intensity of the stimulating or inhibitory effect of the drug depended on the times of their injection. The least inhibitory effect was observed when isoproterenol was given 1 h before resection of the liver, possibly on account of the more rapid inactivation of the drug by the intact liver than by the regenerating liver. Phenylephrine had a weaker stimulating action when given 8 h after the operation.

The experiments with adrenoreceptor stimulators confirmed the earlier hypothesis that excitation of α- and β-adrenoblockers differs in its effect on mitotic activity of hepatocytes in the regenerating liver. The results are in agreement with those of an investigation of the action of α- and β-adrenoreceptor blockers and stimulators on proliferation in the liver during chemical carcinogenesis [2].

The increase in the number of binuclear cells in the regenerating liver under the influence of isoproterenol, found in the present experiments, deserved particular attention. Since binuclear cells have a higher intensity of function [3, 4], an increase in their number should lead to an increase in functional activity of the liver after resection. If that is so, it can be tentatively suggested that excitation of β-adrenoreceptors, together with other existing methods [5, 6], is an important way of increasing liver function.

In the writer's view, one factor capable of influencing switching of the cell to division of intensifying functional activity is a difference in the state of the adrenoreceptors. Excitation of α-adrenoreceptors facilitates exhibition of the mitotic activity of the cell, whereas excitation of β-adrenoreceptors, by changing the character of activity of the cell, switches it to more intensive functioning. Catecholamines evidently play an important role in this switching. The view has been expressed [7] that a dynamic redistribution of hepatocytes takes place in the liver after its resection, one group of hepatocytes dividing intensively whereas the other group functions actively and does not take part in division. On the basis of the results of the present experiments this distribution could be determined by differences in the functional state of adrenoreceptors on the hepatocyte cell membranes.

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