EFFECT OF SUBTOTAL HEPATECTOMY AND UNILATERAL NEPHRECTOMY ON UBIQUINONE TURNOVER IN THE RAT LIVER AND KIDNEY

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KEY WORDS: regenerating liver; hypertrophied kidney; ubiquinone turnover.

The writer showed previously that partial hepatectomy of unilateral nephrectomy in rats leads to increased biosynthesis of ubiquinones (coenzyme Q) in the residual parts of these organs [3-5]. Considering that the relative constancy of concentrations of biologically active compounds, including ubiquinone, is a function not only of synthesis but also of breakdown, in the investigation described below the velocity constants of degradation and the heal-turnover rate of ubiquinone were determined in the liver and kidneys at different stages after their partial removal.

EXPERIMENTAL METHOD

Experiments were carried out on male noninbred albino rats weighing 200 ± 15 g on an artificial diet consisting of 20% defatted casein, 55% starch, 10% sucrose, 4% mixed salt, 5% animal fat, and vitamins [14]. Three series of animals were studied: I) intact (control), II) after removal of two-thirds of the liver, and III) after unilateral nephrectomy. Ubiquinone was labeled by its immediate biosynthetic precursor, p-hydroxybenzoic acid-^{14}C [13]. This was obtained by alkaline fusion of tyrosine-^{14}C (specific activity 315 mCi/mmole, from Czechoslovakia) [10] and was injected into the caudal vein in a dose of 0.5 μCi in 0.2 ml of 0.9% NaCl solution. Control rats were killed, six at a time, 1, 3, 6, 12, and 18 days after injection of the label, each liver of the animals was investigated separately, and kidneys from two animals were pooled. Subtotal hepatectomy, or right-sided unilateral nephrectomy [3-5] was performed 2 days after injection of p-hydroxybenzoate-^{14}C and the animals were killed six at a time, 1, 2, 3, and 6 days after the operation. Since isolation of ubiquinone from a small weight of tissue is difficult [3], at each time interval organs of rats of series II and III were peeled from two or three animals respectively. The regions of liver or kidney removed also were investigated. The isolation and quantitative determination of ubiquinone-9 were described previously [5]. Its radioactivity was counted in 10 ml of ZhS-107 liquid scintillator on an Isakap/300 counter (Nuclear Chicago) and expressed as the number of counts per minute.

The velocity constants of degradation of ubiquinone and its half-turnover rate were calculated on the basis of the following arguments. Carbon of uniformly labeled p-hydroxybenzoic acid-^{14}C is incorporated chiefly into the benzoquinone moiety of this compound [13, 15] and, consequently, reutilization of the label from it and other lipids is negligible, which means that the constants can be calculated from the kinetics of decrease of radioactivity by the equation:

$$C_t = C_0 \cdot e^{kT} \quad (1)$$

and the half-turnover rate by the equation:

$$T = \frac{\ln 2}{k}, \quad (2)$$

where C_t is the radioactivity of ubiquinone at time T: C_0 the same at zero time; k the velocity constant of degradation; T the time (in days), and $T_{1/2}$ the biological half-decay time. Since the ubiquinone concentration in the remaining lobes of the liver rises rapidly on the

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TABLE 1. Velocity Constants of Degradation and Half-Turnover Periods of Ubiquinone-9 in Liver and Kidneys of Rats after Subtotal Hepatectomy or Unilateral Nephrectomy

Animals	Liver		Kidneys	
	$k \pm 95\%$ confidence interval, day^{-1}	$T_{1/2}$, days	$k \pm 95\%$ confidence interval, day^{-1}	$T_{1/2}$, days
Control	$-0{,}0556 \pm 0{,}0372$ (30)	12,46	$-0{,}0522 \pm 0{,}0362$ (15)	13,27
With subtotal hepatectomy	$-0{,}00038 \pm 0{,}1042$	1820,0	$-0{,}0656 \pm 0{,}070$ (12)	10,56
With unilateral nephrectomy	$-0{,}0598 \pm 0{,}2408$ (10)	11,58	$-0{,}1244 \pm 0{,}0733$ (8)	5,57

Legend. Number of determinations in parentheses.

first day after subtotal hepatectomy [6], to determine the value of k the specific radioactivity of the ubiquinone was not used, but its radioactivity in the regenerating region. Tauber and Reutter [16] used a similar method to calculate k for proteins in regenerating liver. Since the ubiquinone content in hypertrophied kidneys is unchanged, as the writer showed previously [3], in this case the decrease in specific radioactivity in ubiquinone was used for the calculations for the control animals also. The constants and their confidence intervals were calculated with the aid of the MIR-2 computer on a linear regression program [1]. The program was based on transformation of equation (1) into its linearized form:

$$\ln C_t = \ln C_0 - kT \qquad (3)$$

EXPERIMENTAL RESULTS

The experimental results are given in Table 1. It must be pointed out beforehand that the rates of renewal of ubiquinone in the liver and kidneys of rats are low and if they are compared with the rates of DNA renewal in the mitochondria and of renewal of proteins in their inner membranes [7], they do not differ significantly. In the early stages of regeneration of the liver, during the first 6 days, a significant fall was observed in the rate of renewal of the ubiquinone reserves. Evidently the rapid increase in the total quantity of this coenzyme which the writer found previously in the regenerating part of the liver, and also the increase in its radioactivity after injection of labeled precursors [4-6] can be explained both by the more rapid biosynthesis and by the slower breakdown of the compound. In the regenerating liver, incidentally, the rate of degradation of proteins also is reduced [16]. Loss of ubiquinone by the liver cells can be explained: first, by irreversible oxidative conversions of the end fragment of its isoprenoid side-chain [9-11] and, second, by the excretion of unchanged molecules by the cells into the bile [9]. It has been suggested that oxidation of the side-chain of ubiquinone closely resembles in its mechanism the oxidation of the side-chain of sterols, when bile acids are formed from them [11]. Both the bile-excreting and also, evidently, the bile-forming functions of this organ are depressed in the early stages of regeneration [2]. This evidently also causes the marked increase in the half-decay period of coenzyme Q in the early stages of regeneration. Finally, it is interesting to note that some increase in the rate of renewal of the ubiquinone reserves in the kidneys is observed in rats after subtotal hepatectomy.

The half-turnover period of ubiquinone in the remaining kidney after unilateral nephrectomy was reduced by more than half. The writer found previously that, despite increased biosynthesis of this coenzyme in the hypertrophied kidney, its content expressed per gram wet weight of tissue remained constant [3]. The results now obtained explain this fact satisfactorily. Examination of the mechanisms leading to an increase in the turnover rate of this compound in the hypertrophied residual kidney after unilateral nephrectomy must take into account the following facts. Ubiquinone is known to be excreted with the urine [12]. The possibility cannot be ruled out that its elimination from the residual kidney after removal of the other organ is considerably increased on account of an increase in permeability of the cell membranes [8].

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EFFECT OF TOXIC LIVER DAMAGE ON THE GENERATIVE FUNCTION OF RATS

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There is convincing evidence in the literature that hepatitis and cirrhosis arising through the action of infectious or toxic agents are accompanied by marked disturbances of neuroendocrine regulation and metabolism, and by structural changes not only in the liver, but also in other organs and systems, including the reproductive sphere [1, 2, 4, 5, 7-9, 11, 12, 14, 15]. However, the effect of infectious and toxic liver damage on generative function has not yet been adequately studied. Naturally it is not always possible to study this problem fully under clinical conditions, and accordingly experimental investigations can be of definite assistance in this connection.

There are indications in the literature that liver damage caused by the alkaloid heliotrine, contained in the weed *Heliotropium lasiocarpium*, which occurs episodically at the present time, is characterized by a pathomorphological and, to a certain degree, a functional-metabolic picture which in many respects is similar to that of the changes in infectious hepatitis [1, 6, 10]. However, in the accessible literature no studies of the effect of this form of liver damage on reproductive function could be found.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats of both sexes weighing initially 120-140 g. Heliotrine poisoning was produced by subcutaneous injection of a solution of the alkaloid heliotrine in a dose of 25 mg/100 g body weight [1]. There were four series of experiments: I) control (12 females), II) injection of heliotrine into males which were mated with intact females (18 females) on the 25th day from the beginning of the experiment; III) injection of heliotrine into females which were mated on the 25th day with intact males (28 females). IV) Injection of heliotrine simultaneously into females and males, which were mated on the 25th day of poisoning (28 females).

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