Anabolism versus Catabolism of [5-³H]Uridine and its Relationship to Ribonucleic Acid Labelling in Mouse Liver after Partial Hepatectomy

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The balance between anabolism and catabolism of [5-³H]uridine was studied in the mouse after partial hepatectomy. Labelling of RNA and UDP-glucose was determined and evaluated in relation to changes in the specific radioactivity of UTP. The amounts of labelled catabolic products of uridine were increased several-fold in liver and blood after partial hepatectomy. The specific radioactivity of RNA decreased to about 60% of the control value at 6 h and was in the same range as that of control liver at 24 h after operation. Decreased labelling of RNA and UDP-glucose was attributable to decreased specific radioactivity of UTP. No changes in the size of the UTP pool or in the balance between uridine anabolism and catabolism were found that could explain the decreased specific radioactivity of UTP. Rather, the alterations in the labelling of this metabolite induced by the partial hepatectomy may be related to decreased phosphorylating capacity in the liver cells and/or dilution of the labelled precursor in an expanded uridine pool. The enhanced amounts of uridine catabolic products in liver and blood were probably a consequence of accumulation and altered incorporation of the metabolites from the blood into the liver cells. Despite the increased amounts of labelled catabolic products and the decreased labelling of RNA, the results reported here actually suggest decreased uridine catabolism and slightly increased RNA synthesis in mouse liver after partial hepatectomy. The results stress the importance of proper controls in determination of nucleic acid synthesis and in metabolic studies by use of labelled precursors.

Numerous reports have been published dealing with the anabolic utilization of labelled RNA precursors in rat liver after partial hepatectomy and by changes in the activity of enzymes along the 'de novo' and salvage pathways for pyrimidine nucleotide biosynthesis. Although both routes contribute actively to the nucleotide synthesis in liver cells, available information about the salvage pathways, i.e. re-utilization of pyrimidine bases and nucleosides produced by nucleic acid breakdown, is fragmentary. The scarce information about the importance of the salvage pathways for pyrimidine nucleotide synthesis may be explained by the far better utilization of orotate than of uridine by both normal (Yu & Feigelson, 1970; Witschi, 1972) and regenerating (Čihák *et al.*, 1972a) rat liver. Intact mouse liver, however, seems to utilize well both the 'de novo' and the salvage pathways for synthesis of uracil nucleotides and RNA (Yngner *et al.*, 1977). Differences between tissues and animal species should be assigned to differences in uptake (Lea *et al.*, 1976) and to a diversity in enzymic equipment for metabolism of the administered precursors (Reichard & Sköld, 1958; Sköld, 1960). The importance of such differences is

obvious and must be taken into account in comparison of data on RNA-synthetic activity obtained by use of labelled pyrimidine bases and nucleosides (Hill *et al.*, 1974).

An increased uptake and incorporation of labelled precursors into RNA of regenerating rat liver has been demonstrated in several studies, thus indicating an increased RNA synthesis (for reviews see Bresnik, 1971; Bucher & Malt, 1971; Lewan *et al.*, 1977). The most commonly used precursor in these studies has been orotate, incorporated into the nucleotides by biosynthesis *de novo*.

The turnover and availability of administered precursors for incorporation into nucleotides and RNA is regulated by simultaneous synthesis and degradation. The balance between the pathways for anabolism and catabolism provides a means for regulating the supply of nucleotides for RNA synthesis and may be of importance for the process of liver regeneration after partial hepatectomy. An inverse relationship exists between the capacity of a tissue to synthesize RNA and its capacity to degrade uracil; the rate of uracil breakdown decreases in rat liver slices immediately after partial hepatectomy and

remains low during the period of increased RNA-synthetic activity (Canellakis, 1957; Canellakis *et al.*, 1959).

Reports dealing with uridine uptake and phosphorylation (Plagemann *et al.*, 1969; Plagemann, 1971) suggest that the pattern of uridine incorporation into RNA is dependent on the rate of uridine entry into the cell and is not simply due to changes in the rate of uridine phosphorylation. Attempts have been made to find relevant methods for quantification of the rate of RNA synthesis (Bucher & Swaffield, 1969; Kramer *et al.*, 1972; Cooper, 1972; Puckett & Darnell, 1977), but none of the methods presently available is without drawbacks (Goody & Ellem, 1975; Wieggers *et al.*, 1976).

It was decided to determine *in vivo* whether the enhanced uptake of labelled precursors known to occur in the liver cells after partial hepatectomy (Ord & Stocken, 1972, 1973) was of importance for nucleotide and RNA synthesis and whether the incorporation of a labelled nucleoside such as [³H]-uridine into RNA gives a valid estimate of changes in RNA synthesis after the operation. The purpose of this study was also to examine whether an increased demand for RNA precursors in the regenerating mouse liver could be met by changes in the degradative activity and to what extent the balance between the pathways utilizing UTP for RNA and UDP-glucose synthesis were affected by partial hepatectomy. The acute need for energy in the regenerating liver should make the production of UDP-glucose for glycogen synthesis less important (Bauer *et al.*, 1976) and make more UTP available for RNA synthesis.

The ability of the mouse liver to incorporate uridine effectively (Yngner *et al.*, 1977) made it suitable for an examination of the uridine metabolism during liver regeneration.

Materials and Methods

Animals

Young adult male NMRI mice, weighing 26–28 g (SPF quality, Anticimex, Uppsala, Sweden), were used for the experiments. The animals were kept under constant conditions of light and temperature and had free access to standard laboratory diet.

Partial hepatectomy

Partial hepatectomy and sham operation were performed under ether anaesthesia between 08:00 and 12:00 h, by the method of Higgins & Anderson (1931). The hepatectomized animals were killed 6 or 24 h after removal of two-thirds of the liver.

Chemicals

[5-³H]Uridine (specific radioactivity 30 mCi/mmol) was purchased from The Radiochemical Centre,

Amersham, Bucks., U.K. UDP-glucose dehydrogenase (EC 1.1.1.22), UDP-glucose pyrophosphorylase (EC 2.7.7.9) and nucleoside 5'-diphosphate kinase (EC 2.7.4.6) were from Boehringer, Mannheim, Germany. All other chemicals were of reagent grade.

Radioactive labelling

Non-hepatectomized, sham-operated and partially hepatectomized animals were injected intraperitoneally with 75 μ Ci of [5-³H]uridine dissolved in 75 μ l of 0.9 % NaCl. The uridine was administered with a repeating dispenser (Hamilton Co.) during 10 s.

All determinations of radioactivity were carried out with Insta-Gel scintillation fluid (Packard) in a Packard Tri-Carb liquid-scintillation counter. Quenching was measured with an internal standard.

Tissue sampling

At 90 s before being killed the animals were anaesthetized in a diethyl ether/oxygen atmosphere (Bucher & Swaffield, 1966). The liver was rapidly excised, and frozen within 2 s between precooled aluminium blocks and immersed in liquid N₂. Blood, collected in the peritoneal cavity after liver excision, was frozen in liquid N₂. Liver and blood were stored in liquid N₂ until analysis.

Assay of blood acid-soluble fraction

Frozen blood was homogenized in ice-cold 0.8 M-HClO₄ and after centrifugation at 3000 g the acid-soluble fraction was neutralized with 7 M-KOH/2 M-KHCO₃, with Phenol Red as indicator. The precipitated KClO₄ was sedimented by centrifugation and the total radioactivity determined in the supernatant. Portions of the neutralized acid-soluble fraction were applied on precoated poly(ethyleneimine)-impregnated cellulose thin-layer plates (0.1 mm thick, 10 cm $\times$ 10 cm). The uridine, uracil, dihydrouracil, β -alanine and β -ureidopropionic acid were separated by two-dimensional chromatography (Raaen & Kraus, 1968): the first dimension was with water to 8 cm from the point of application, and the second dimension was with butan-1-ol/methanol/water/conc. NH₃ (60:20:20:1, by vol.) to the upper edge of the chromatogram. The radioactively labelled metabolites were identified by the corresponding marker compounds under u.v. light, with ninhydrin treatment or with acidified *p*-dimethylaminobenzaldehyde (Fink *et al.*, 1956). Uracil and β -alanine were not always quantitatively separated from dihydrouracil and β -ureidopropionic acid respectively by the chromatographic system used. Therefore the radioactivity of uracil was determined together with that of dihydrouracil, whereas that of β -alanine was determined together with that of β -ureidopropionic acid. The metabolites were eluted from the cellulose with 0.7 M-MgCl₂/20 mM-Tris/HCl,

pH 7.4 (Gonzales & Geel, 1975), and the radioactivity in the eluate was determined.

Assay of liver acid-soluble fraction

Liver tissue from three to five animals was pooled at each point of analysis. Livers from animals with an abnormal amount of total acid-soluble radioactivity in the blood were discarded before pooling. Frozen liver tissue was pulverized under liquid N₂ and homogenized in 6 ml of ice-cold 0.4M-HClO₄/g wet wt. The acid-insoluble material was used for analysis of RNA and DNA. The acid-soluble fraction was collected after centrifugation at 20000g and adjusted to pH 8.0 with ice-cold 7M-KOH/2M-KHCO₃. The precipitated KClO₄ was sedimented by centrifugation. The enzymic determinations of uracil nucleotide content was performed by the method of Keppler *et al.* (1974).

Portions of the liver acid-soluble fraction was concentrated by freeze-drying and the uridine catabolites were separated and analysed as described for the blood acid-soluble fraction. The liver nucleotides were separated by stepwise two-dimensional development in ammonium formate buffers (Lust & Sahud, 1972).

Determination of RNA and DNA

The precipitated acid-insoluble material obtained after homogenization of liver tissue in 0.4M-HClO₄ was used for determination of RNA and DNA (Munro & Fleck, 1966), and for determination of RNA labelling.

In a second series of experiments, liver RNA was isolated as described by Kirby (1965). The radioactivity of the RNA was determined 20 min after injection of the [³H]uridine.

Results

Incorporation and catabolism of [³H]uridine

In accordance with previous results (Yngner *et al.*, 1977), the intraperitoneally administered uridine was

rapidly incorporated into mouse liver, i.e. the uridine radioactivity was at a maximum level within 2 min and that of the total acid-soluble fraction within 10 min after injection (results not shown). From 10 min, the amounts of uridine and total acid-soluble radioactivity in the regenerating livers were increased by about 2-fold compared with the intact and sham-operated controls. The differences decreased during the later part of the pulse period.

Similar but less pronounced changes were also found in the acid-soluble fraction of blood. The ratio of uridine and total acid-soluble radioactivity between liver and blood is demonstrated in Table 1.

The labelled uridine constituted only a small part of the total liver acid-soluble radioactivity at the end of the pulse period. The greater part of the radioactivity could be assigned to different uridine catabolic products.

The time course of labelling of the uridine catabolic products differed between control (i.e. intact and sham-operated) and regenerating liver and between liver and blood of these animals (Figs. 1a, 1b, 2a and 2b). Compared with the intact and sham-operated controls, the radioactivity of liver uracil/dihydro-uracil increased more rapidly in the regenerating livers and remained increased during the pulse period (Fig. 1a). The differences between control and regenerating liver were most pronounced 6 h after operation, i.e. the radioactivity of uracil/dihydro-uracil was increased about 4-fold at 20 min after injection.

As only small changes in the amount of DNA per g of liver occurs during the first 24 h after partial hepatectomy (Lewan, 1972), we have chosen to express the labelling of the liver uridine catabolic products on a per-gram basis.

Labelled uracil/dihydro-uracil accumulated in blood of the partially hepatectomized mice until 5 min and the amounts were enhanced 3–4-fold 20 min after injection (Fig. 2a). In contrast with the animals 6 h after operation, the controls and those 24 h after par-

Table 1. Relative distribution of [³H]uridine and total acid-soluble radioactivity between liver and blood 20 min after injection of [³H]uridine

Mice were injected intraperitoneally with 75 μCi of [³H]uridine 20 min before death. The radioactivity of total acid-soluble fraction and uridine was determined in the neutralized HClO₄-soluble fraction of frozen blood and liver. The ratios are calculated from c.p.m./g wet wt. values. Each value represents the mean of pooled tissue from three to five mice.

Experimental condition	Time after operation (h)	Liver/blood ratio of ³ H radioactivity	
		Acid-soluble fraction	Uridine
Sham-operation	6	3.8	0.8
	24	4.3	1.0
Partial hepatectomy	6	5.1	1.6
	24	6.3	1.6

Fig. 1. Time course of labelling of uridine catabolic products in control and regenerating mouse liver

Radioactivity of (a) uracil/dihydrouracil and (b) β -alanine/ β -ureidopropionic acid is shown. The mice received $75 \mu\text{Ci}$ of $[5\text{-}^3\text{H}]\text{uridine}$ intraperitoneally at zero time and livers were excised and clamp-frozen in liquid N_2 at the times indicated. Frozen tissue was deproteinized in 0.4M-HClO_4 . The neutralized acid-soluble fraction was used for the determination of radioactivity. ○, Normal control; □, 6h after partial hepatectomy; △, 24h after partial hepatectomy; ■, 6h after sham operation; ▲, 24h after sham operation. Three to five livers were pooled for each point of analysis.

tial hepatectomy showed higher amounts of these products in blood than in liver during the first 10 min after injection. The radioactivities of uracil/dihydro-

Fig. 2. Time course of labelling of uridine catabolic products in blood from control and partially hepatectomized mice

Radioactivity of (a) uracil/dihydrouracil and (b) β -alanine/ β -ureidopropionic acid is shown. The mice received $75 \mu\text{Ci}$ of $[5\text{-}^3\text{H}]\text{uridine}$ intraperitoneally at zero time. Blood was sampled in the peritoneal cavity immediately after liver excision, was frozen in liquid N_2 and deproteinized in 0.8M-HClO_4 . The radioactivity of the metabolites in the neutralized acid-soluble fraction of the blood was determined after separation by t.l.c. ○, Normal control; □, 6h after partial hepatectomy; △, 24h after partial hepatectomy; ■, 6h after sham operation; ▲, 24h after sham operation. Blood from three to five animals was pooled for each point of analysis.

Table 2. Concentration of UTP and UDP-glucose in intact and regenerating mouse liver

Livers were rapidly frozen between metal tongs precooled in liquid N₂. The concentrations of UTP and UDP-glucose were determined in the neutralized HClO₄-soluble liver fraction 5, 10 and 60 min after injection of 75 μ Ci of [³H]-uridine (Keppler *et al.*, 1974). Liver tissue from three to five animals was pooled at each interval. Values represent the means $\pm$ S.D. of the three determinations. *Statistically significant difference by *t* test (*P* < 0.05) compared with intact controls.

Experimental condition	Time after operation (h)	Concn. (μ mol/g wet wt.)	
		UTP	UDP-glucose
Control	—	0.269 $\pm$ 0.052	0.369 $\pm$ 0.035
Partial hepatectomy	6	0.270 $\pm$ 0.041	0.290 $\pm$ 0.037*
Partial hepatectomy	24	0.232 $\pm$ 0.048	0.288 $\pm$ 0.026*

Fig. 3. Specific radioactivity of UTP and UDP-glucose in control and regenerating mouse liver

UTP: $\circ$, normal control; $\square$, 6h after partial hepatectomy; $\triangle$, 24h after partial hepatectomy; $\blacksquare$, 6h after sham operation; $\blacktriangle$, 24h after sham operation. UDP-glucose: $\bullet$, normal control; $\blacksquare$, 6h after partial hepatectomy; $\blacktriangle$, 24h after partial hepatectomy. The mice received 75 μ Ci of [³H]uridine intraperitoneally at zero time and livers were excised and clamp-frozen in liquid N₂ at the times indicated. Frozen tissue was deproteinized in 0.4M-HClO₄. The radioactivity of UTP and UDP-glucose in the neutralized acid-soluble fraction was determined after separation by t.l.c. UTP and UDP-glucose contents were determined as described by Keppler *et al.* (1974). Three to five livers were pooled for each point of analysis.

The β -ureidopropionic acid/ β -alanine radioactivity of regenerating and control liver was 10-fold higher than both that of liver uracil/dihydrouracil (Figs. 1a and 1b) and that of β -ureidopropionic acid/ β -alanine of blood (Fig. 2b). Furthermore, the sham-operation to a certain extent affected the labelling of the uridine catabolic products of both liver and blood, but pronounced differences between intact and sham-operated animals were found only at 5 min after the uridine injection.

Concentration of UTP and UDP-glucose

The size of the liver UTP pool has been reported to increase initially after partial hepatectomy in the rat (Bucher & Swaffield, 1969; Glazer, 1973), thus influencing the amount of labelled precursor available for incorporation into RNA. In contrast with these results, there was no apparent change in the size of the mouse liver UTP pool after partial hepatectomy (Table 2).

The concentration of UDP-glucose was decreased by about 20% at 6 h and 24 h after operation (Table 2).

Specific radioactivity of UTP and UDP-glucose

Labelled uridine was maximally incorporated into liver UTP within 5–10 min after injection. Compared with intact animals, the UTP specific radioactivity was decreased both 6 and 24 h after partial hepatectomy (Fig. 3). However, the difference between sham-operated and regenerating liver was most pronounced 6 h after operation, i.e. 5 and 20 min after injection the specific radioactivities were 25 and 50% respectively of those in sham-operated animals. At 24 h after operation, the 5 min value of the UTP specific radioactivity was decreased by about 30%, whereas at 20 min the value was not significantly different from that of the sham-operated controls.

The effect of partial hepatectomy on the time course of CTP labelling was similar to that of UTP, although the radioactivity was less than one-tenth as much (results not shown).

Administered [³H]uridine is incorporated into UDP-glucose through the UTP pool. The specific

uracil in liver and blood of the intact animals were very similar during the later part of the pulse period (Figs. 1a and 2a).

Also the radioactivity of β -ureidopropionic acid/ β -alanine was enhanced in liver and blood after partial hepatectomy (Figs. 1b and 2b). Compared with control liver, the 20 min values of these metabolites were increased about 10- and 8-fold at 6 and 24 h respectively. The corresponding changes in blood were 4- and 2-fold respectively.

Fig. 4. Incorporation of [^3H]uridine into RNA of control and regenerating mouse liver

Specific radioactivity of the RNA fraction: $\circ$, normal control; $\square$, 6h after partial hepatectomy; $\triangle$, 24h after partial hepatectomy; $\blacksquare$, 6h after sham operation; $\blacktriangle$, 24h after sham operation. Specific radioactivity of isolated RNA: $\bigcirc$, normal control; $\square$, 6h after partial hepatectomy; $\triangle$, 24h after partial hepatectomy. The animals were intraperitoneally injected with $75\mu\text{Ci}$ of [^3H]uridine. The specific radioactivity of RNA was determined either in the acid-insoluble liver fraction obtained after homogenization in 0.4M-HClO_4 (Munro & Fleck, 1966) or after isolation of the RNA by the method of Kirby (1965). Three to five livers were pooled at each point of analysis.

radioactivity of UDP-glucose fluctuated in accordance with that of UTP (Fig. 3), and decreased to about 50% of the control value 6h after partial hepatectomy. The difference between control liver and liver regenerating for 24h was less pronounced.

Specific radioactivity of RNA

The time course of labelling of mouse liver RNA is demonstrated in Fig. 4. The incorporation of uridine into the RNA fraction increased continuously during the first part of the pulse period, but remained relatively constant from 20min after injection. Apart from the first 20min, the specific radioactivity of RNA in the 24h-regenerating liver was in the same range as that of the intact and sham-operated controls. At 6h after operation, however, the RNA specific radioactivity amounted to only about 60% of the control values. During the later part of the pulse period, the relative differences between the RNA specific radioactivity in intact, sham-operated and partially hepatectomized animals were similar, but less pronounced than those of UTP.

Previous reports have indicated that non-specific radioactivity may be released during alkaline hydro-

lysis of RNA (Dahnke, 1975; Yngner *et al.*, 1977). Thus in a separate series of analyses we isolated the liver RNA and compared its specific radioactivity with that of the RNA fraction obtained as described by Munro & Fleck (1966). The two methods revealed the same relative difference between control and regenerating liver, although the specific radioactivity of the isolated RNA was considerably lower (Fig. 4).

Discussion

Livers from partially hepatectomized rats have been shown to possess an increased capacity to incorporate labelled orotate and uridine compared with sham-operated controls (Ord & Stocken, 1972, 1973). In accordance with these results, the regenerating mouse liver also incorporated more labelled uridine per g of tissue, during the first 20min after injection, than did intact liver.

In the present study we found no enhanced labelling of either UTP, or of RNA or UDP-glucose, whether the radioactivity was calculated per g wet wt. of liver or per mg of DNA, despite an almost 2-fold increase in amount of labelled uridine in the regenerating liver. The results thus indicate that the penetration of the precursor into the cells is not directly coupled to its anabolic utilization and its incorporation into the RNA (Ord & Stocken, 1973), or, if a relation exists, that it is obscured by changes in any of the pools of metabolites through which the precursor must pass to be incorporated into the RNA.

The changes in the RNA specific radioactivity after operation can be accounted for by parallel but slightly more pronounced changes in the UTP labelling. The fact that the RNA specific radioactivity of 6h- and 24h-regenerating mouse liver decreased less than that of UTP may be interpreted as indicating an increased RNA polymerase activity at these times after partial hepatectomy (Schmid & Sekeris, 1975; Yu, 1975). The present results do not indicate, however, whether an accretion of RNA in mouse liver after partial hepatectomy is due mainly to increased rate of transcription or to decreased degradation.

Changes in the size of the UTP pool as reported for regenerating rat liver (Bucher & Swaffield, 1969; Glazer, 1973) were not indicated in this study.

The different time courses of incorporation of [^3H]uridine into UTP of the control and regenerating mouse liver would indicate a decreased or unchanged nucleotide synthesis at 6 and 24h after partial hepatectomy. However, uridine kinase has not been reported to change significantly during the first 12h after partial hepatectomy (Čihák *et al.*, 1972b). Furthermore, preliminary results obtained by use of labelled orotate do not indicate an increased biosynthesis of uracil nucleotides *de novo* in the regenerating mouse liver that would compensate for a decreased

UTP synthesis through the salvage pathways (T. Yngner, E. Carlberg, C. Engelbrecht & L. Lewan, unpublished work). Rather, the observed changes in the UTP labelling after partial hepatectomy can probably be accounted for by a decreased phosphorylation and/or increase in the uridine pool. The glycogen and glucose concentrations decrease after partial hepatectomy (Simek *et al.*, 1968; Neville *et al.*, 1970; Lea *et al.*, 1970; Bonney *et al.*, 1973), a fact that may impair the energy status of the liver cells. A decreased phosphorylating capacity (Atkinson, 1968; Farber, 1973; Lewan *et al.*, 1977) may lead to a decreased UTP labelling and perhaps to an increase in the uridine pool that would further decrease the amount of label incorporated into UTP. Besides, if a decreased phosphorylating capacity was accompanied by a decreased catabolic activity (Canellakis, 1957; Canellakis *et al.*, 1959), this would further increase the uridine concentration and decrease the UTP labelling.

Although the increased radioactivity of the uridine catabolic products in both liver and blood after partial hepatectomy in mouse could be interpreted as indicating an increased uridine catabolism, this is certainly not so. The increased amounts are more probably a consequence of an accumulation and an altered flow of metabolites into the liver cells of the partially hepatectomized animals.

The amounts of labelled uridine and uracil/dihydro-uracil registered in blood during the first minutes after injection may to a certain extent be affected by the site of blood sampling (Yngner *et al.*, 1975; Engelbrecht *et al.*, 1977), but the results for the intact, sham-operated and partially hepatectomized animals indicate high uridine phosphorylase activity in tissues other than the liver (Guroff & Rhoads, 1969; Tseng & Gurpide, 1973; Dahnke & Mosebach, 1975). Since the final steps in the catabolism of uridine are considered to be restricted to the liver (Reichard & Sköld, 1958), a decreased catabolism of uracil/dihydrouracil in the regenerating liver would cause an expansion of the pool of these metabolites in both liver and blood. Owing to the presence of such an increased pool, the labelled uracil/dihydro-uracil would accumulate and increase the radioactivity of these products in the blood. Moreover, the fact that the labelled uracil/dihydrouracil in the intact animals was not evenly distributed between blood and liver until 20 min after injection, whereas that of the mice 6 h after partial hepatectomy was so within 2 min after injection, suggests a more efficient incorporation of these metabolites from blood into the regenerating liver. This interpretation of the results is in accordance with the better utilization of uracil known to occur in regenerating liver and hepatoma compared with normal liver (Rutman *et al.*, 1954; Canellakis, 1957; Heidelberger *et al.*, 1957).

Concerning the distribution of labelled uridine

catabolic products between liver and blood, the 24 h-regenerating liver seem to occupy a position intermediate between that of the 6 h-regenerating and intact liver.

The high amount of labelled β -ureidopropionic acid/ β -alanine in liver compared with that of blood, as well as the fact that the peak of radioactivity of these metabolites was obtained later after the uridine injection than that of uracil/dihydrouracil, support the idea that the final steps in the degradation of uridine are confined to the liver (Reichard & Sköld, 1958). The 10-fold difference in β -ureidopropionic acid/ β -alanine radioactivity between blood and liver of both control and partially hepatectomized mice indicates a pronounced accumulation of these products in the liver cells, whereas the same relative difference between blood and liver suggests a similar rate of transport of the metabolites out of the cells. The difference between β -ureidopropionic acid/ β -alanine radioactivity in liver and blood can partly be assigned to the dilution of the metabolites within different tissue volumes.

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