Hepatic Extraction and Renal Production of 3,3′-Diiodothyronine and 3′,5′-Diiodothyronine in Man

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ABSTRACT The sequential deiodination of thyroxine (T_4) gives rise to several iodothyronine analogs including 3,3′-diiodothyronine (3,3′-T_2) and 3′,5′-diiodothyronine (3′,5′-T_2). In vitro animal studies suggest that the liver and the kidneys are the main sites of both formation and degradation of 3,3′-T_2 and 3′,5′-T_2. To determine the metabolism of 3,3′-T_2 and 3′,5′-T_2 in human liver and kidneys plasma samples were obtained from (*a*) a brachial artery and a hepatic vein in 20 normal subjects, and from (*b*) a femoral artery and a renal vein in 11 normal subjects. Further, the hepatic plasma flow (*a*) and the renal plasma flow (*b*) were determined.

Both plasma 3,3′-T_2 and 3′,5′-T_2 levels were reduced in the hepatic venous blood as compared to arterial values (1.09±0.40 vs. 1.75±0.74 ng/dl ($P < 0.01$) and 2.02±0.55 vs. 2.44±0.72 ng/dl ($P < 0.01$)) (mean±1 SD). This resulted in a hepatic extraction of both, 3,3′-T_2 and 3′,5′-T_2, which averaged 8.2 and 5.2 μg/d, respectively.

Plasma 3,3′-T_2 as well as 3′,5′-T_2 levels were higher in the renal vein as compared to arterial values, 1.49 ±0.42 vs. 1.39±0.45 ng/dl ($P < 0.05$) and 2.35±0.83 vs. 2.09±0.81 ng/dl ($P < 0.05$), respectively. This positive venoarterial difference implies a net production of 3,3′-T_2 and 3′,5′-T_2 in the kidneys of 1.2 and 3.0 μg/d, respectively.

It is concluded that the liver is an important site of 3,3′-T_2 and 3′,5′-T_2 extraction in normal man. In contrast, the renal production of 3,3′-T_2 as well as 3′,5′-T_2 exceeds the degradation and urinary excretion.

INTRODUCTION

Recent studies have demonstrated that 3,3′-diiodothyronine (3,3′-T_2)[1] and 3′,5′-diiodothyronine (3′,5′-T_2) are normal components of human serum (1–6). They are produced predominantly by extrathyroidal degradation of thyroxine (T_4) (5), which proceeds by serial monodeiodination until all the iodine atoms have been removed (7). Oral administration of 3,5,3′-triiodothyronine (T_3) to normal humans gives rise to 3,3′-T_2, while both 3,3′-T_2 and 3′,5′-T_2 are produced when 3,3′,5′-triiodothyronine (rT_3) is given (5, 8). In vitro studies on rat organ homogenates have suggested that 3,3′-T_2 generation from T_3 and rT_3 is most active in liver and kidneys (9, 10).

Studies of the perfused rat liver have shown that this organ has the capacity to deiodinate 3,3′-T_2 and to a lesser extent to secrete conjugated products in the bile (11). These products seem mainly to be sulfated 3,3′-T_2 and 3′-monoiodothyronine (3′-T_1) (12, 13). In addition, deiodination of 3′,5′-T_2 has been observed in rat liver homogenate, resulting in 3′-T_1 production (14). Recently, Smallridge et al. have shown that intravenous administration of 3′,5′-T_2 to humans results in 3′-T_1 production (15). At least 3,3′-T_2 also seems to be excreted in the urine in the free, unconjugated state (16). Available in vitro data thus implicate the liver as a site of production as well as catabolism of the diiodothyronines. Consequently, the present study was undertaken to examine in man the net exchange of the diiodothyronines across the splanchnic area and the kidney in healthy subjects using intravascular catheter technique.

METHODS

Subjects and procedure. Four different groups of clinically euthyroid subjects were studied after an overnight fast. In group A, which comprised 20 healthy subjects (18 men, 2 women, average age 24 yr, range 18–39 yr) catheters were inserted percutaneously into a brachial artery and a right-sided hepatic vein. The hepatic venous catheter (Cournand No. 7 or 8) was introduced through the femoral vein and posi-

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[1] *Abbreviations used in this paper*: 3,3′-T_2, 3,3′-diiodothyronine; 3′,5′-T_2, 3′,5′-diiodothyronine; 3′-T_1, 3′-monoiodothyronine; T_3, 3,5,3′-triiodothyronine; T_4, thyroxine; TBG, thyroxine-binding globulin; rT_3, 3,3′,5′-triiodothyronine.

tioned 3–4 cm from the wedge position in the hepatic vein during fluoroscopic control. In group B, which included 11 healthy subjects (6 men, 5 women, average age 26 yr, range 21–35 yr) catheters were introduced percutaneously into a femoral artery and a renal vein. The renal venous catheter (Cournand No. 7 or 8) was introduced through the femoral vein and positioned under fluoroscopic control. Group C was made up of 10 healthy subjects (8 men, 2 women, average age 25 yr, range 21–32 yr) in whom catheters were inserted into a femoral artery and vein. The tip of the femoral venous catheter was placed at the level of the inguinal ligament.

In groups A, B, and C patency of the catheters was maintained by saline flushing. Blood samples for analyses of 3,3'-T_2, 3',5'-T_2, rT_3, T_3, T_4, and thyroxine-binding globulin (TBG) were collected after a basal period of 30 min.

Group D included 10 patients (1 man, 9 women, average age 57 yr, range 31–74 yr) who had undergone elective cholecystectomy 8 d before the study. At the time of the surgical procedure the umbilical vein was dilated and a catheter (baby feeding tube) was inserted into the portal vein. The catheter was maintained patent by constant rate infusion of heparinized saline. At the time of the study all patients were ambulatory and had normal intestinal, hepatic and renal function. Function of the main bile duct was ensured by direct cholegraphy performed postoperatively through a catheter, which was subsequently withdrawn. Blood samples were collected simultaneously from the portal vein and an antecubital vein and analyzed for 3,3'-T_2 and 3',5'-T_2 concentrations.

All healthy subjects and patients were informed of the nature, purpose, and possible risks involved in the study before giving their voluntary consent to participate.

Hepatic plasma flow was estimated in group A with the continuous infusion technique (17) using indocyanine green dye (18). Indocyanine green concentration was determined spectrophotometrically in plasma. Renal plasma flow was determined in group B with the use of paraaminohippuric acid. Paraaminohippuric acid was infused at a constant rate and plasma concentrations were determined as described by Brun (19).

The hepatic net production of the diiodothyronines was calculated as the product of the difference between the arterial and hepatic venous plasma concentrations and the hepatic plasma flow. Similarly the renal net production was calculated using the difference between arterial and renal venous plasma concentrations and the renal plasma flow.

Analyses. Plasma levels of the iodothyronines were measured using a gel separation (Sephadex G-25, fine)/antibody extraction method as earlier described (6, 20). The intra-assay coefficient of variation of the 3,3'-T_2 radioimmunoassay in a plasma sample with normal (1.7 ng/dl, $n = 15$) concentration of 3,3'-T_2 was 7.1%, the lower detection limit was 0.2 ng/dl. Cross-reactivity of different analogs with the L-3,3'-T_2 antibody (relative potency of the compounds tested was calculated on the basis of the amount that caused 50% inhibition of the ^{125}I-3,3'-T_2 binding to the antibody) was: L-rT_3: 0.074%; 3,5,3'-triiodothyroacetic acid: 0.045%; L-T_3, L-3'-T_1, and L-3-monoiodothyronine: 0.018%; L-T_4, L-3',5'-T_2, L-3,5-T_2, L-diiodotyrosine, L-monoiodotyrosine, and tetraiodothyroacetic acid: <0.001%. The 3',5'-T_2 determination had an intrassay coefficient of variation in a plasma sample with normal (3.9 ng/dl, $n = 10$) contents of 3',5'-T_2 of 5.0%. The lower detection limit was 0.3 ng/dl and the cross-reactivity of the L-3',5'-T_2 antibody was: L-3,3'-T_2: 4.558%; L-3'-T_1: 0.208%; L-rT_3: 0.030%; L-T_4, L-T_3, L-3,5-T_2, L-3-monoiodothyronine, tetraiodothyroacetic acid, 3,5,3'-triiodothyroacetic acid, L-diiodotyrosine, and L-monoiodotyrosine: <0.001%. Studies on human urine before and after enzymatic deconjugation show that cross-reaction of the 3,3'-T_2 antibody with glucuronated and sulfated 3,3'-T_2 is <35 and 36%, respectively, whereas the cross-reaction of the 3',5'-T_2 antibody with conjugated 3',5'-T_2 compounds is <4 and 3%, respectively.[2] The intraassay coefficient of variation of the rT_3, T_3, and T_4 radioimmunoassays was 7–8%. Serum TBG was measured using an immunoelectrophoretic method (21). All samples from each subject were run in the same assay.

Statistical analyses were performed using the Wilcoxon test for paired data with Pratts modification (22) and all results are given as mean±1 SD.

RESULTS

The plasma levels of 3,3'-T_2 and 3',5'-T_2 in arterial and hepatic venous samples in group A are shown in Table I. The hepatic venous concentration of 3,3'-T_2 was 40% lower than the arterial ($P < 0.01$). Likewise the average 3',5'-T_2 concentration was 20% lower in hepatic venous samples compared to arterial ($P < 0.01$). The estimated hepatic plasma flow was 854±171 ml/min. The hepatic clearance calculated as the product of the arterial-hepatic venous concentration difference and the hepatic plasma flow was 8.2±6.4 μg/24 h for 3,3'-T_2 and 5.2±5.5 μg/24 h for 3',5'-T_2. The plasma concentrations for T_3, rT_3, T_4, and TBG were all similar in arterial and hepatic venous samples (Table I).

Arterial and renal venous levels of 3,3'-T_2 and 3',5'-T_2 in group B are shown in Table II. The renal venous

[2] Manuscript in preparation.

TABLE I

Plasma Levels of Iodothyronines and TBG in Samples From an Artery and the Hepatic Vein and Splanchnic Clearance of 3,3'-T_2 and 3',5'-T_2 in Group A (n =20)

	Plasma 3,3'-T_2		Splanchnic clearance of 3,3'-T_2	Plasma 3',5'-T_2		Splanchnic clearance of 3',5'-T_2	Plasma T_3		Plasma rT_3		Plasma T_4		Plasma TBG	
	A	HV		A	HV		A	HV	A	HV	A	HV	A	HV
	ng/dl		*μg/24 h*	*ng/dl*		*μg/24 h*	*ng/dl*		*ng/dl*		*μg/dl*		*mg/dl*	
Mean	1.75	1.09*	8.16	2.44	2.02*	5.22	100.3	103.2	40.7	40.4	6.7	6.8	1.01	1.00
SD	0.74	0.40	6.41	0.72	0.55	5.49	22.8	24.0	9.8	12.0	0.9	0.9	0.16	0.16

A, artery; HV, hepatic vein.

* Significantly different from the corresponding value, $P < 0.01$.

TABLE II

Plasma Levels of Iodothyronines and TBG in Samples From an Artery and the Renal Vein and Renal Production of 3,3'-T_2 and 3',5'-T_2 in Group B (n = 11)

	Plasma 3,3'-T_2		Renal production of 3,3'-T_2	Plasma3',5'-T_2		Renal production of 3',5'-T_2	Plasma T_3		Plasma rT_3		Plasma T_4		Plasma TBG	
	A	RV		A	RV		A	RV	A	RV	A	RV	A	RV
	ng/dl		*μg/24 h*	*ng/dl*		*μg/24 h*	*ng/dl*		*ng/dl*		*μg/dl*		*mg/dl*	
Mean	1.39	1.49*	1.18	2.09	2.35*	3.03	93.3	92.5	32.2	34.1	6.2	6.1	1.25	1.24
SD	0.45	0.42	1.85	0.81	0.83	4.27	16.5	11.5	8.8	8.5	1.2	1.4	0.31	0.30

A, artery; RV, renal vein.

* Significantly different from the corresponding value, $P < 0.05$.

concentration of 3,3'-T_2 exceeded the arterial by 7% ($P < 0.05$). Likewise, the renal vein concentration of 3',5'-T_2 was 12% higher than the arterial ($P < 0.05$). The renal plasma flow was 836±119 ml/min and the calculated renal production of the two diiodothyronines was 1.2±1.9 and 3.0±4.3 μg/d, respectively.

The plasma levels of the two diiodothyronines in arterial and femoral venous samples (group C) are shown in Table III. For both compounds similar levels were observed in arterial and venous samples. In group D, which was studied postoperatively after elective cholecystectomy blood samples were collected from the portal vein and a cubital vein. No differences of statistical significance were observed.

DISCUSSION

The findings in the present study demonstrate that 3,3'-T_2 as well as 3',5'-T_2 are extracted from the circulation by the splanchnic tissues. The positive arterial hepatic venous concentration differences for both diiodothyronines observed in group A may reflect either hepatic metabolism or metabolism in other splanchnic tissues. However, the finding that portal and peripheral vein diiodothyronine concentrations (group D) as well as arterial and femoral venous concentrations (group C) were similar, indicates that portal venous and arterial concentrations are the same. Moreover, the finding that T_4 and TBG concentrations were similar in arterial and hepatic venous samples excludes the possibility that the observed diiodothyronine concentration difference across the splanchnic area may be due to differences in iodothyronine protein binding. It may thus be concluded that the splanchnic uptake of diiodothyronines reflects hepatic rather than extrahepatic hormone extraction. The current observations in intact man thus confirm previous in vitro studies of rat liver homogenate indicating that the liver has the capacity to metabolize the diiodothyronines (11–14).

3,3'-T_2 and 3',5'-T_2 may be metabolized along several different pathways in the liver. Deiodination of both 3,3'-T_2 and 3',5'-T_2 may take place as observed in studies on perfused rat liver and on rat liver homogenates (11–14). A second pathway for metabolism of the diiodothyronines appears to be conjugation and the conjugated products are excreted in the bile (12, 13). However, the similar concentrations in arterial and portal venous blood observed in this study suggest that a possible enterohepatic circulation of the diiodothyronines is of quantitatively minor importance, but direct measurements in bile may be required to further elucidate this question. Finally, it is likely that there is a simultaneous hepatic uptake and production of diiodothyronines, since rat liver homogenate has been shown capable of degrading T_3 and rT_3 to 3,3'-T_2 (9, 10).

The average hepatic clearance of 3,3'-T_2 and 3',5'-T_2 was 7.3 and 4.9 μg/d × 70 kg body wt, respectively. The daily whole body degradation rate for 3,3'-T_2 and 3',5'-T_2 in normal man has been evaluated by single injection tracer technique. It was estimated to be 18 and 10 μg/d × 70 kg body wt, respectively (6).[2] These data thus demonstrate that the liver plays an important role in the metabolism of 3,3'-T_2 and 3',5'-T_2 in man because

TABLE III

Plasma Concentrations of 3,3'-T_2 and 3',5'-T_2 in Groups C and D

	Group C (n = 10)		Group D (n = 10)	
	Femoral artery	Femoral vein	Portal vein	Cubital vein
3,3'-T_2, *ng/dl*	1.94±0.63	1.88±0.71	2.11±0.59	2.17±0.23
3',5'-T_2, *ng/dl*	3.27±0.62	3.52±0.98	4.47±0.32	4.33±0.25

one-third and one-half, respectively, of the total daily degradation of the diiodothyronines is carried out in the liver.

Significant arterial-hepatic venous differences for rT_3, T_3, and T_4 were not observed in the present study. From the knowledge of the degradation rates of the iodothyronines and the hepatic plasma flow maximal arteriovenous plasma concentration differences can be calculated. With regard to rT_3, T_3, and T_4 the arteriovenous differences were too small in relation to the plasma concentrations to be estimated since they were considerable less than the intraassay variation of the respective assays. Thus, the present findings do not exclude the possibility that the human liver participates in the degradation of rT_3, T_3, and T_4. Recent in vitro studies involving rat liver homogenates have demonstrated that T_4 may be deiodinated to T_3 and rT_3 and that these compounds may be further deiodinated in the liver (9, 23–26).

The renal metabolism of the diiodothyronines resulting in a net production may also proceed along several different pathways. 3,3′-T_2 has been shown to be produced from T_3 as well as rT_3 in rat kidney homogenates at rates two to five times greater than in liver homogenate (9, 10). The findings of 5-monodeiodinating enzyme activity in the rat kidney makes it reasonable to assume that also 3′,5′-T_2 is produced in the kidneys (from rT_3), possibly in cells of the renal tubules (9, 27). The presence of these enzymes in the kidneys also makes a deiodination of the diiodothyronines a possibility. A third possibility for renal handling of diiodothyronines seems to be urinary excretion. We have recently demonstrated that the excretion of unconjugated 3,3′-T_2 and 3′,5′-T_2 in urine from normal man averages 0.35 and <0.01 μg/d, respectively. Thus, the total production of 3,3′-T_2 and 3′,5′-T_2 in the human kidneys can be calculated to 1.2 and 2.2 μg/day × 70 kg body wt, respectively, which is one-tenth and one-fourth of the respective total daily production rates.

Although rT_3, T_3, and T_4 deiodinating enzyme activities have been demonstrated in rat kidney homogenate no difference in plasma levels of these iodothyronines in arterial and renal venous blood were observed in the present study. Again, methodological problems in determining a small arteriovenous concentration difference may be of importance but the findings are in accordance with a previous study (28).

The present findings suggest that the liver is an important site of 3,3′-T_2 and 3′,5′-T_2 extraction in normal man. In contrast, the intact human kidney produces 3,3′-T_2 as well as 3′,5′-T_2 in excess of the simultaneous degradation and urinary excretion. This difference between human liver and kidneys may partly be explained by different deiodination activities and capacities and/or the capacity of the liver to conjugate iodothyronines, a metabolic pathway which does not seem to exist in the kidneys (29). However, it shall be emphasized that the hepatic extraction and the renal net production of 3,3′-T_2 and 3′,5′-T_2 probably are results of degradation as well as production in both organs. In addition it appears that other tissues i.e., muscles (9, 23) besides the liver and the kidneys are active in the extrathyroidal metabolism of iodothyronines, and although the deiodinating enzyme activities in these tissues are relatively low (9, 23), the metabolism of the iodothyronines may be quantitatively important due to their relatively large weight.

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