Contribution of 3,5,3'-tri-iodothyronine produced locally from thyroxine in several maternal tissues of the near-term pregnant rat

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Abstract

3,5,3'-Tri-iodothyronine (T_3) is produced by the thyroid and locally, by monodeiodination of thyroxine (T_4), in the peripheral tissues. During pregnancy the thyroid hormone status in rats is altered: plasma and tissue levels of T_4 and T_3 are decreased. We investigated the effects of pregnancy on the contribution of T_3 produced locally in the maternal tissues by administering a continuous infusion of [125 I] T_4 and [131 I] T_3 . The transport of T_4 to almost all maternal organs diminished. Less T_3 was transported from the plasma to brown adipose tissue (BAT), liver, kidney and pituitary, in contrast to the ovary where an increase was found. In BAT and brain the amount of locally produced T_3 decreased, despite the known increase in deiodinase type II activity in the brain while in liver the contribution of locally produced T_3 remained constant, despite a known increase in deiodinase type I activity during pregnancy. This discrepancy between deiodinase activities and locally produced T_3 can be explained by an insufficient availability of T_4 . Thus, we conclude that in the rat a decrease in maternal T_4 concentration, together with the transport of T_4 to the feto-placental compartment, results indirectly in a diminished availability of T_3 in the maternal organs.

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Introduction

During pregnancy maternal thyroid hormones are exceedingly important for normal development of the fetal central nervous system (1). The biologically active form of thyroid hormone is 3,5,3'-tri-iodothyronine (T_3) (2). T_3 is produced not only by the thyroid but also locally in peripheral tissues by monodeiodination of thyroxine (T_4). In liver, kidney and the thyroid monodeiodination of T_4 is catalyzed by the deiodinase type I enzyme (ID-I), while in the pituitary, central nervous system and brown adipose tissue (BAT) deiodinase type II enzyme (ID-II) is responsible for the conversion of T_4 to T_3 (3).

Some tissues can adapt to alterations in plasma thyroid hormone status, and regulate intracellular T_3 by changing the deiodinase enzyme activities and thus the amount of locally derived T_3 . During hypothyroidism a decrease in hepatic ID-I activity, and an increase in brain ID-II activity have been described (4, 5). This is in agreement with the contribution of the local conversion found in those organs; in liver and kidney local conversion is decreased, whereas in brain an increase has been found (6).

Especially in the central nervous system local conversion of T_4 is the main source of intracellular T_3 .

Therefore, when the amount of T_3 available from plasma is decreased this can be compensated for, to some extent, by an increase in the local conversion of T_4 (6).

In the near-term pregnant rat this condition is associated with decreased T_4 and T_3 levels in plasma and tissues (7–9). From earlier studies of T_4 and T_3 kinetics it has been suggested that in the near-term pregnant rat T_4 is transported from the plasma to the feto-placental compartment at a very fast rate (9). This leads to a decrease in the availability of T_4 for the maternal tissues. No changes were found in the transport of T_3 .

T_4 and T_3 concentrations in maternal tissues are decreased at the end of gestation (7, 8). However, it is not known how pregnancy influences the amount of T_3 produced locally in several tissues. An indication of the amount of locally produced T_3 in several tissues is based only on measurements of deiodinase activities. It has been found that in the near-term pregnant rat hepatic ID-I and brain ID-II activity are increased (7, 9). The aim of this study was to compare the contribution of T_3 produced locally in maternal tissues of the non-pregnant and near-term pregnant rat. By administering a continuous simultaneous infusion of [125 I] T_4 and [131 I] T_3 (6, 10–12), T_4 and T_3 concentrations in

maternal tissues, the relative contribution of plasma-derived vs locally produced T₃, thyroidal T₄ and T₃ secretion, and the plasma-to-tissue ratios of T₄ and T₃ were determined.

Materials and methods

Animals

Three-month-old female Wistar rats (CPB/WU, Iffa Credo, Brussels, Belgium) were used. The rats were individually housed in metabolic cages at 22 °C, with alternating periods of 14 h light and 10 h darkness. The animals were fed a semisynthetic American Institute of Nutrition diet (13). The dry food was mixed with distilled water (60% dry weight, 40% water) containing 10 mg/l potassium iodide. This high dose of iodide was used to prevent re-utilization of ¹²⁵I and/or ¹³¹I.

Design of the study

Two groups of rats were used in this study, i.e. nonpregnant and pregnant rats. After two regular estrous cycles the rats were mated. The day that sperm appeared in the vaginal smear was taken as day 0 of gestation. At the start of the infusion the rats weighed 211 ± 4 g (controls) and 237 ± 3 g (pregnant, day 8).

The continuous intravenous infusion of [¹²⁵I]T₄ (11 MBq/rat/day (30 µCi)) was started on day 8 of pregnancy; 4 days later [¹³¹I]T₃ was added to the infusion fluid. The labeled iodothyronines were administered at a constant rate (10 ml/day), via a cannula which was inserted into the right jugular vein and extended to the right atrium (14) at least 4 days before the continuous infusion was started. The rats were unrestrained, and could eat and drink normally.

Urine and feces were collected from the start of the infusion. The ¹²⁵I and ¹³¹I contents were counted and expressed as a percentage of the daily infused radioactivity. The animals were in isotopic equilibrium when the sum of radioactivity in urine and feces was equal to the daily administered dose.

Labeled iodothyronines

High specific activity [¹²⁵I]T₄ and [¹³¹I]T₃ (specific activity ~80 and ~130 MBq/µg (2200 and 3500 µCi/µg) respectively) were prepared in our laboratory (15, 16). Na¹²⁵I and Na¹³¹I were purchased from Amersham International (Aylesbury, Bucks, UK); L-T₃ and 3,5-L-di-iodothyronine, the respective substrates for labeling, were obtained from Sigma (St Louis, MO, USA). Purity of the tracers was assessed by means of high performance liquid chromatography (HPLC). All infusions consisted of a sterile 0.9% NaCl solution

containing 0.2 mg/ml ticarcillin (Ticarpen; Beecham, Heppignies, Belgium) and 0.3 U/ml heparin (Organon, Tilburg, The Netherlands). The stock infusion solutions were stored at 4 °C in the dark. The infusion flasks were protected from light to minimize artifactual deiodination of the tracers.

Analytical procedures

At the end of the infusion period, i.e. day 20 of gestation for the pregnant rats, the rats were bled under light ether anesthesia. Blood was collected in heparinized tubes. To prevent artifactual deiodination, propylthiouracil (PTU) was added to a final concentration of 0.1 mmol/l (17). To free the tissues of trapped blood, the rats were perfused with 40–50 ml of a 0.9% NaCl solution containing 3 U heparin/ml and 0.1 mmol/l PTU; outflow was obtained by puncturing the inferior vena cava. Maternal tissues were then immediately excised and kept on ice. Either whole small organs or weighed portions of the bigger organs were minced and homogenized in a Potter homogenizer (B Braun, Melsungen, Germany) at 0 °C in methanol containing 0.1 mmol/l PTU, carrier T₄ and T₃ and potassium iodide (1 mg/10 ml). The pituitaries were homogenized in 1.5 ml saline containing carrier and PTU.

To determine the iodothyronine concentration a measured aliquot was taken of each tissue homogenate and the plasma and the ¹²⁵I and ¹³¹I contents were counted. The samples were extracted with methanol-ammonia (25%, 197:3 vol/vol) with 0.1 mmol/l PTU. The dried extracts were dissolved in 0.1 ml 0.2 mol/l ammonia containing carrier T₄, T₃ and potassium iodide (1 mg/10 ml) and subjected to HPLC to separate the iodothyronines. The analyses with HPLC were performed according to the method described earlier (11).

After decay (7–8 half lives) of the ¹³¹I initially present in the samples the concentrations of stable T₄ and T₃ in plasma were assessed by a specific radioimmunoassay (RIA) for rats using [¹³¹I]T₄ and [¹³¹I]T₃ as tracers (18). Plasma thyrotropin (TSH) was measured by the specific RIA developed for the rat by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (Bethesda, MD, USA). Reference preparation RP-2 was used as a standard.

Calculations

The levels of T₄, T₃, tissue T₃ derived from T₄ (LcT₃(T₄)) and plasma-derived T₃ (p(T₃)T₃) were calculated (6, 10–12).

In short:

$$\begin{aligned} \text{Tissue T}_4 \text{ (pmol/g wet wt)} \\ = \frac{\text{tissue } [^{125}\text{I}]\text{T}_4 \text{ (% dose/g)}}{\text{plasma } [^{125}\text{I}]\text{T}_4 \text{ (% dose/ml)}} \times \text{plasma T}_4 \text{ (pmol/ml; RIA)} \end{aligned}$$

The concentration of [^{125}I]T $_4$ in the tissue was corrected for trapped plasma (5).
Lc T $_3$ (T $_4$) was calculated as follows:

$$\frac{\text{tissue } [^{131}\text{I}]T_3 \text{ (\% dose/g)}}{\text{plasma } [^{131}\text{I}]T_3 \text{ (\% dose/ml)}} \times \text{plasma } [^{125}\text{I}]T_3 \text{ (\% dose/ml)}$$

$$= \text{tissue } [^{125}\text{I}]T_3 \text{ derived from plasma (\% dose/g)}$$

Then tissue Lc [^{125}I]T $_3$ (% dose/g) =

total tissue [^{125}I]T $_3$ (% dose/g) – tissue [^{125}I]T $_3$ derived from plasma (% dose/g)

Thus tissue Lc T $_3$ (T $_4$) (pmol/g) =

$$\frac{\text{tissue Lc } [^{125}\text{I}]T_3 \text{ (\% dose/g)}}{\text{plasma } [^{125}\text{I}]T_4 \text{ (\% dose/ml)}} \times \text{plasma } T_4 \text{ (pmol/ml; RIA)}$$

whereby [^{125}I]T $_3$ was multiplied by 2 to correct for the loss of ^{125}I from the phenolic ring of T $_4$.

The concentration of T $_3$ derived from plasma in the various tissues was obtained as follows:

tissue T $_3$ derived from plasma (pmol/g) =

$$\frac{\text{tissue } [^{131}\text{I}]T_3 \text{ (\% dose/g)}}{\text{plasma } [^{131}\text{I}]T_3 \text{ (\% dose/ml)}} \times \text{plasma } T_3 \text{ (pmol/ml; RIA)}$$

The total level of T $_3$ in a tissue is the sum of the values calculated for tissue Lc T $_3$ (T $_4$) and pT $_3$ (T $_3$).

The rate of infusion of [^{125}I]T $_4$ and [^{131}I]T $_3$ and their respective blood levels were used to calculate the plasma clearance rates (PCR) for T $_4$ and T $_3$. If the plasma concentration is expressed as a percentage of the infused dose (in 1 h/100 g body weight), then

$$\text{PCR}(\text{ml} \cdot \text{h}^{-1} \cdot 100 \text{ g body wt}^{-1})$$

$$= \frac{100}{\% \text{ dose (h} \cdot 100 \text{ g body wt}^{-1} \cdot \text{ml}^{-1})}$$

The production rate (PR) for T $_4$, or the plasma appearance rate (PAR) for T $_3$, is the PCR for T $_4$ or T $_3$ multiplied by their respective plasma concentrations. The production of T $_3$ by the thyroid (ThPRT $_3$) can be calculated as follows:

since the amount of circulating T $_3$ derived from T $_4$ (T $_3$ (T $_4$)) is given by

$$T_3(T_4) = \frac{\% \text{ dose/ml } [^{125}\text{I}]T_3}{\% \text{ dose/ml } [^{125}\text{I}]T_4} \times \text{plasma } T_4 \text{ (pmol/ml; RIA)}$$

and

$$\frac{T_3(T_4) \text{ (pmol/ml)}}{\text{plasma } T_3 \text{ (pmol/ml; RIA)}} \times 100\% = \% T_3(T_4)$$

then $\{100 - [\% T_3(T_4)]\} \times \text{PAR } T_3 = \text{ThPRT}_3$ in picomoles per h per 100 g body weight.

All results are expressed as means $\pm$ S.E.. Data were analyzed using the Statistical Package for Social Sciences (19). Statistical analysis was performed by means of the Student's *t*-test.

Table 1 Body weight and plasma thyroid hormone concentrations in nonpregnant controls and 20-day pregnant rats. Data are expressed as means $\pm$ S.E.

	Control (n = 10)	Pregnant (n = 9)
Body weight (g)	229 $\pm$ 2.7	305 $\pm$ 4.8*
Number of fetuses		12 $\pm$ 1
T $_4$ (nmol/l)	30.7 $\pm$ 3.2	18.9 $\pm$ 4.8*
T $_3$ (nmol/l)	0.62 $\pm$ 0.04	0.52 $\pm$ 0.03
TSH (ng/ml)	0.70 $\pm$ 0.04	0.80 $\pm$ 0.11

**P* < 0.01, pregnant vs controls.

Results

Each rat received the continuous infusion until the individual ^{125}I - and ^{131}I -radioactivities in urine and feces equalled the daily input for at least two days. This occurred in both groups after 10 days [^{125}I]T $_4$ infusion and 7 days [^{131}I]T $_3$ infusion. At this time the rats were assumed to be in isotopic equilibrium as far as the major pools of T $_4$, T $_3$ and their metabolites were concerned.

Table 1 shows that plasma T $_4$ decreased in pregnant rats. Plasma T $_3$ and plasma TSH did not change significantly. Plasma clearance rates (PCR) and production rates (PR) for T $_4$ and T $_3$ are expressed per total animal and per 100 g body weight (Table 2). No alterations were found in the PCR for T $_4$ and T $_3$ when

Figure 1 Concentrations of (A) T $_4$ and (B) T $_3$ in BAT, brain (Br), cerebellum (Cer), heart (H), kidney (K), liver (Li), muscle (M), ovary (Ov) and pituitary (Pit) from nonpregnant (solid bars) and 20-day pregnant (hatched bars) rats. Values are means $\pm$ S.E.. **P* < 0.05 compared with nonpregnant rats.

Figure 2 Concentrations of T₃ derived from plasma and produced locally in several organs (see Fig. 1) from nonpregnant (solid bars) and 20-day pregnant (hatched bars) rats. Values are means $\pm$ S.E.. * $P < 0.05$ compared with nonpregnant rats. %Lc is the percentage local conversion (i.e. the percentage T₃ locally produced from T₄ in relation to the total T₃) in nonpregnant (C) and 20-day pregnant (P) rats.

expressed per 100 g body weight; however the PCR for T₄ increased significantly per total animal. The production of T₄ remained constant for the total animal. For T₃ the PAR decreased per 100 g body weight but remained constant per total animal. Per total animal the contribution of T₃ produced by the thyroid increased, whereas extrathyroidal T₃ production showed a decrease.

The total tissue concentrations of T₄ and T₃ are shown in Fig. 1. In all tissues the T₄ concentration diminished significantly. The total T₃ concentration decreased in all organs, except in the ovary which exhibited an increase.

Figure 2 shows the contributions of plasma-derived and locally produced T₃ in the organs. The amount of T₃ derived from plasma decreased in BAT, heart, kidney, liver, muscle and pituitary. The amount of T₃ produced locally decreased in BAT and brain. In the ovary an

increase was found for T₃ derived from both plasma and local production. The percentage local conversion (that is the percentage T₃ locally produced from T₄ in relation to the total T₃) was lower in BAT, whereas an increase was found for the ovary. For all other organs the percentage local conversion remained constant.

The tissue-to-plasma ratio for T₄ decreased in all tissues, except the heart and ovary (Table 3). For [¹³¹I]T₃ the tissue-to-plasma ratio decreased in BAT, kidney, liver and pituitary, whereas it increased in the ovary (Table 4). Table 5 shows the ratio of [¹²⁵I]T₃-to-[¹²⁵I]T₄. This ratio increased for the brain, cerebellum, liver, muscle, ovary and pituitary.

Discussion

In this study we were able to determine the contribution of local conversion of T₄ to T₃ in several tissues of the near-term pregnant rat. The method, the surgical procedure to insert the cannula and the subsequent continuous infusion of [¹²⁵I]T₄ and [¹³¹I]T₃ did not have a negative effect on pregnancy. This is demonstrated by the normal body weight and number and weight of fetuses in the near-term pregnant rats.

In accordance with previous reports pregnancy resulted in a decrease in plasma T₄. In contrast, plasma T₃ did not decrease significantly in this study (7–9).

The plasma clearance rates for T₄ and T₃ were not altered significantly. However, when expressed per total animal instead of per 100 g body weight an increase in the PCR for T₄ was found. This is in agreement with the results of kinetic experiments (9).

By expressing the production rates per total animal a more realistic comparison can be made between nonpregnant and near-term pregnant rats. In the pregnant rat the weight of maternal tissues is not increased in proportion to the body weight; the enormous gain in body weight is mainly due to the fetoplacental compartment. However, this compartment does not contribute essentially to the production of maternal T₄ and T₃.

Table 2 Plasma clearance rates for T₄ and T₃, production rate for T₄, plasma appearance rate for T₃ and T₃ production by the thyroid and local conversion from T₄ in nonpregnant controls and 20-day pregnant rats. All values are expressed per total animal and per 100 g body weight. Data are expressed as means $\pm$ S.E.

	Per total animal		Per 100 g body weight	
	Control (n = 10)	Pregnant (n = 9)	Control (n = 10)	Pregnant (n = 9)
PCR T ₄ (ml/h)	2.16 $\pm$ 0.21	3.47 $\pm$ 0.23*	0.95 $\pm$ 0.10	1.14 $\pm$ 0.07
PCR T ₃ (ml/h)	46.7 $\pm$ 3.6	51.7 $\pm$ 2.2	20.4 $\pm$ 1.6	16.9 $\pm$ 0.7
PR T ₄ (pmol/h)	63.3 $\pm$ 6.6	64.1 $\pm$ 5.8	27.7 $\pm$ 2.9	21.0 $\pm$ 1.8
PAR T ₃ (pmol/h)	28.5 $\pm$ 2.4	26.5 $\pm$ 1.3	12.5 $\pm$ 1.2	8.7 $\pm$ 0.4*
ThPR T ₃ (pmol/h)	7.5 $\pm$ 2.3	13.3 $\pm$ 1.6*	3.3 $\pm$ 1.0	4.3 $\pm$ 0.5
T ₃ (T ₄) (pmol/h)	21.1 $\pm$ 2.7	13.2 $\pm$ 0.9*	9.2 $\pm$ 1.2	4.4 $\pm$ 0.3*

T₃ (T₄), production rate of T₃ from local conversion of T₄

* $P < 0.05$, pregnant vs controls.

Table 3 Tissue-to-plasma ratios for T₄ in control and 20-day pregnant rats. Data are expressed as means $\pm$ s.e.

	Control	Pregnant	P value
BAT	0.144 $\pm$ 0.019	0.089 $\pm$ 0.011	< 0.05
Brain	0.091 $\pm$ 0.013	0.049 $\pm$ 0.008	< 0.01
Cerebellum	0.160 $\pm$ 0.027	0.041 $\pm$ 0.007	< 0.001
Heart	0.091 $\pm$ 0.009	0.080 $\pm$ 0.006	ns
Kidney	0.516 $\pm$ 0.062	0.319 $\pm$ 0.025	< 0.05
Liver	1.017 $\pm$ 0.072	0.640 $\pm$ 0.035	< 0.001
Muscle	0.066 $\pm$ 0.007	0.034 $\pm$ 0.002	< 0.001
Ovary	0.283 $\pm$ 0.029	0.253 $\pm$ 0.012	ns
Pituitary	0.145 $\pm$ 0.023	0.052 $\pm$ 0.012	< 0.005

ns, not significant.

Table 4 Tissue-to-plasma ratios for [¹³¹I]T₃ in control and 20-day pregnant rats. Data are expressed as means $\pm$ s.e.

	Control	Pregnant	P value
BAT	2.76 $\pm$ 0.30	1.92 $\pm$ 0.12	< 0.05
Brain	1.67 $\pm$ 0.11	1.80 $\pm$ 0.22	ns
Cerebellum	2.17 $\pm$ 0.19	1.87 $\pm$ 0.11	ns
Heart	3.31 $\pm$ 0.32	2.90 $\pm$ 0.13	ns
Kidney	11.42 $\pm$ 1.13	7.75 $\pm$ 0.53	< 0.05
Liver	7.35 $\pm$ 0.43	6.07 $\pm$ 0.29	< 0.05
Muscle	1.60 $\pm$ 0.15	1.29 $\pm$ 0.08	ns
Ovary	2.41 $\pm$ 0.30	4.13 $\pm$ 0.23	< 0.001
Pituitary	10.14 $\pm$ 0.81	7.31 $\pm$ 0.63	< 0.01

Table 5 Tissue [¹²⁵I]T₃-to-[¹²⁵I]T₄ ratios in control and 20-day pregnant rats. Data are expressed as means $\pm$ s.e.

	Control	Pregnant	P value
BAT	0.728 $\pm$ 0.171	0.567 $\pm$ 0.075	ns
Brain	0.796 $\pm$ 0.072	1.532 $\pm$ 0.201	< 0.01
Cerebellum	0.473 $\pm$ 0.056	1.916 $\pm$ 0.315	< 0.001
Heart	0.594 $\pm$ 0.062	0.511 $\pm$ 0.041	ns
Kidney	0.390 $\pm$ 0.025	0.444 $\pm$ 0.042	ns
Liver	0.137 $\pm$ 0.010	0.186 $\pm$ 0.012	< 0.01
Muscle	0.407 $\pm$ 0.047	0.574 $\pm$ 0.060	< 0.05
Ovary	0.142 $\pm$ 0.017	0.422 $\pm$ 0.041	< 0.001
Pituitary	1.341 $\pm$ 0.180	3.621 $\pm$ 0.837	< 0.05

ns, not significant.

Despite normal plasma TSH values the production of T₃ by the thyroid is enhanced, in contrast to the thyroidal production of T₄ which remained constant. Therefore, the T₃-to-T₄ ratio for thyroid hormones produced by the thyroid of the pregnant rat is increased. This pattern is also found during iodine deficiency (20), diabetes mellitus and modified fasting (12). On the other hand, the contribution of peripherally produced T₃ entering the plasma decreased. This implies that less T₃ was produced, or reached the plasma, in those organs which contribute to circulating T₃ i.e. liver and kidney (6). The increase in thyroidal T₃ production, and the decrease in peripherally produced T₃ in the plasma together resulted in an unchanged plasma appearance rate.

The amount of T₄ decreased drastically in all organs. For some organs this had already been reported by Calvo *et al.* (7). The tissue-to-plasma ratio for T₄ decreased in all organs except the ovary and heart. Therefore, the transport of plasma T₄ to the maternal organs diminished, resulting in a tissue T₄ concentration which was decreased even more than the plasma T₄ level. In contrast, a marked increase in the transport from plasma to the fast pool has been found in kinetic experiments (9). However, in the normal situation the fast pool consists mainly of liver and kidney (21). We have already suggested that in the near-term pregnant rat the fetoplacental compartment also belongs to the fast pool (9). This implies that less T₄ is available for the maternal organs, an hypothesis which is confirmed by the results of this study: the transport of T₄ to the maternal organs decreased.

For T₃ the total tissue concentration diminished in all organs except the ovary, which exhibited a pronounced increase in the total T₃. This is the result of an increase in both plasma-derived T₃ and locally produced T₃. The ovary is the only organ measured in which the percentage T₃ produced locally from T₄ had increased in relation to the total T₃. This interesting finding could indicate that the ovary is metabolically very active at the end of gestation. It is not clear why this occurs.

The tissue-to-plasma ratio for plasma-derived T₃ ([¹³¹I]T₃) decreased in BAT, liver, kidney and pituitary, which means that less T₃ was transported from plasma to these organs. This is also demonstrated by the decreased amount of plasma-derived T₃ in these organs.

The ratio of [¹²⁵I]T₃-to-[¹²⁵I]T₄ increased in the brain and cerebellum. Since the [¹²⁵I]T₃-to-[¹²⁵I]T₄ ratio is a marker for the activity of deiodinase enzymes, the activity of ID-II must have increased. This was confirmed by measurements of ID-II activity in the brain of near-term pregnant rats (7, 9). However, despite this increase in ID-II in the brain there was a decrease not an increase in locally produced T₃. This has to be explained by the decrease in T₄ in the brain. In BAT the ratio of [¹²⁵I]T₃-to-[¹²⁵I]T₄ remained unchanged, indicating that no alterations in ID-II activity occur in BAT during pregnancy. Therefore, the decrease in the local production of T₃ in BAT has to be the result of a diminished availability of precursor T₄.

The ratio of [¹²⁵I]T₃-to-[¹²⁵I]T₄ also increased in the liver, but not in the kidney which has to be the result of an increase in the activity of ID-I. It is known that the activity of deiodinase type I is increased in the liver of near-term pregnant rats (7, 9), indicating that an increased fraction of T₄ is monodeiodinated to T₃. In this way, despite the decrease in T₄, a normal level of locally produced T₃ could be reached in the liver.

In conclusion normal tissue T₃ values cannot be maintained in the near-term pregnant rat. The tissue T₄ concentrations are decreased so much that normal T₃ values cannot always be reached, not even in those organs in which deiodinase activity was elevated.

Further regulation is not possible because there is not sufficient T₄ available for the local production of T₃. Therefore, the transport of T₄ to the feto-placental compartment results indirectly in a T₃ deficiency in the maternal organs.

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