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 (T3) is produced by the thyroid and locally, by monodeiodination of thyroxine (T4), in the peripheral tissues. During pregnancy the thyroid hormone status in rats is altered: plasma and tissue levels of T4 and T3 are decreased. We investigated the effects of pregnancy on the contribution of T3 produced locally in the maternal tissues by administering a continuous infusion of [125I]T4 and [131I]T3. The transport of T4 to almost all maternal organs diminished. Less T3 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 T3 decreased, despite the known increase in deiodinase type II activity in the brain while in liver the contribution of locally produced T3 remained constant, despite a known increase in deiodinase type I activity during pregnancy. This discrepancy between deiodinase activities and locally produced T3 can be explained by an insufficient availability of T4. Thus, we conclude that in the rat a decrease in maternal T4 concentration, together with the transport of T4 to the feto-placental compartment, results indirectly in a diminished availability of T3 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 (T3) (2). T3 is produced not only by the thyroid but also locally in peripheral tissues by monodeiodination of thyroxine (T4). In liver, kidney and the thyroid monodeiodination of T4 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 T4 to T3 (3).

Some tissues can adapt to alterations in plasma thyroid hormone status, and regulate intracellular T3 by changing the deiodinase enzyme activities and thus the amount of locally derived T3. 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 T4 is the main source of intracellular T3. Therefore, when the amount of T3 available from plasma is decreased this can be compensated for, to some extent, by an increase in the local conversion of T4 (6).

In the near-term pregnant rat this condition is associated with decreased T4 and T3 levels in plasma and tissues (7–9). From earlier studies of T4 and T3 kinetics it has been suggested that in the near-term pregnant rat T4 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 T4 for the maternal tissues. No changes were found in the transport of T3.

T4 and T3 concentrations in maternal tissues are decreased at the end of gestation (7, 8). However, it is not known how pregnancy influences the amount of T3 produced locally in several tissues. An indication of the amount of locally produced T3 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 T3 produced locally in maternal tissues of the non-pregnant and near-term pregnant rat. By administering a continuous simultaneous infusion of [125I]T4 and [131I]T3 (6, 10–12), T4 and T3 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 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 administrated 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 3,5,3’-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 (Lt(T₃)T₄) and plasma-derived T₃ (p(T₃)T₃) were calculated (6, 10–12). In short:

\[
\text{Tissue} \ T₄ (\text{pmol/g wet wt}) = \frac{\text{tissue} [¹²⁵I]T₄(\% \text{ dose/g})}{\text{plasma} [¹²⁵I]T₄(\% \text{ dose/ml})} \times \text{plasma } T₄(\text{pmol/ml; RIA})
\]
The concentration of $[^{125}I]T_4$ in the tissue was corrected for trapped plasma (5). 

Let $T_3(T_4)$ be calculated as follows:

$$
tissue [^{125}I]T_4 \times plasma [^{125}I]T_4 \\
= tissue [^{125}I]T_4 derived from plasma (% dose/g)
$$

Then tissue $Lc^{[125]}T_3(T_4)$ was calculated as follows:

$$
tissue Lc^{[125]}T_3(T_4) = total tissue [^{125}I]T_3 (% dose/g) - tissue [^{125}I]T_3 derived from plasma (% dose/g)
$$

Thus tissue $Lc^{[125]}T_3(T_4)$ (pmol/g) =

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

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:

$$
tissue T_3 derived from plasma (pmol/g) =
$$

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

The total level of $T_3$ in a tissue is the sum of the values calculated for tissue $Lc^{[125]}T_3(T_4)$ 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

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

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

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

and

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

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

All results are expressed as means ± S.E.. Data were analyzed using the Statistical Package for Social Sciences (19). Statistical analysis was performed by the Student’s t-test.

### 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

<table>
<thead>
<tr>
<th>Control</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>229 ± 2.7</td>
</tr>
<tr>
<td>Number of fetuses</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>$T_4$ (nmol/l)</td>
<td>30.7 ± 3.2</td>
</tr>
<tr>
<td>$T_3$ (nmol/l)</td>
<td>0.62 ± 0.04</td>
</tr>
<tr>
<td>TSH (ng/ml)</td>
<td>0.70 ± 0.04</td>
</tr>
</tbody>
</table>

*P < 0.01, pregnant vs controls.

![Figure 1](https://example.com/fig1.png)

**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 ± S.E.. *P < 0.05 compared with nonpregnant rats.
shown in Fig. 1. In all tissues the T4 concentration decreased. and locally produced T3 in the organs. The amount of T3 decreased in all organs, except in the ovary which diminished significantly. The total T3 concentration whereas extrathyroidal T3 production showed a local conversion (i.e. 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]T1-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 feto-placental compartment. However, this compartment does not contribute essentially to the production of maternal T4 and T3.

table: 2

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 10)</td>
<td>(n = 9)</td>
</tr>
<tr>
<td>PCR T4 (ml/h)</td>
<td>2.16 ± 0.21</td>
<td>3.47 ± 0.23*</td>
</tr>
<tr>
<td>PCR T3 (ml/h)</td>
<td>46.7 ± 3.6</td>
<td>51.7 ± 2.2</td>
</tr>
<tr>
<td>PR T4 (pmol/h)</td>
<td>63.3 ± 6.6</td>
<td>64.1 ± 5.8</td>
</tr>
<tr>
<td>PAR T3 (pmol/h)</td>
<td>28.5 ± 2.4</td>
<td>26.5 ± 1.3</td>
</tr>
<tr>
<td>ThPR T3 (pmol/h)</td>
<td>7.5 ± 2.3</td>
<td>13.3 ± 1.6*</td>
</tr>
<tr>
<td>T3 (T4) (pmol/h)</td>
<td>21.1 ± 2.7</td>
<td>13.2 ± 0.9*</td>
</tr>
</tbody>
</table>

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

*P < 0.05, pregnant vs controls.
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 feto-placental 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 T₃ 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 [¹²¹I]T₃-to-[¹²¹I]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 mono-deiodinated 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.

### Table 3 Tissue-to-plasma ratios for T₄ in control and 20-day pregnant rats. Data are expressed as means ± S.E.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Pregnant</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAT</td>
<td>0.144 ± 0.019</td>
<td>0.089 ± 0.011</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Brain</td>
<td>0.091 ± 0.013</td>
<td>0.049 ± 0.008</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.160 ± 0.027</td>
<td>0.041 ± 0.007</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart</td>
<td>0.091 ± 0.009</td>
<td>0.080 ± 0.006</td>
<td>ns</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.516 ± 0.062</td>
<td>0.319 ± 0.025</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Liver</td>
<td>1.017 ± 0.072</td>
<td>0.640 ± 0.035</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.065 ± 0.007</td>
<td>0.034 ± 0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.283 ± 0.029</td>
<td>0.253 ± 0.012</td>
<td>ns</td>
</tr>
<tr>
<td>Pituitary</td>
<td>0.145 ± 0.023</td>
<td>0.052 ± 0.012</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

ns, not significant.

### Table 4 Tissue-to-plasma ratios for [¹³¹I]T₃ in control and 20-day pregnant rats. Data are expressed as means ± S.E.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Pregnant</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAT</td>
<td>2.76 ± 0.30</td>
<td>1.92 ± 0.12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Brain</td>
<td>1.67 ± 0.11</td>
<td>1.80 ± 0.22</td>
<td>ns</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>2.17 ± 0.32</td>
<td>1.87 ± 0.11</td>
<td>ns</td>
</tr>
<tr>
<td>Heart</td>
<td>3.31 ± 0.32</td>
<td>2.90 ± 0.13</td>
<td>ns</td>
</tr>
<tr>
<td>Kidney</td>
<td>11.42 ± 1.13</td>
<td>7.75 ± 0.53</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Liver</td>
<td>7.35 ± 0.43</td>
<td>6.07 ± 0.29</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.60 ± 0.15</td>
<td>1.29 ± 0.08</td>
<td>ns</td>
</tr>
<tr>
<td>Ovary</td>
<td>2.41 ± 0.30</td>
<td>4.13 ± 0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pituitary</td>
<td>10.14 ± 0.81</td>
<td>7.31 ± 0.63</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

### Table 5 Tissue [¹²⁵I]T₃-to-[¹²⁵I]T₄ ratios in control and 20-day pregnant rats. Data are expressed as means ± S.E.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Pregnant</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAT</td>
<td>0.728 ± 0.171</td>
<td>0.567 ± 0.075</td>
<td>ns</td>
</tr>
<tr>
<td>Brain</td>
<td>0.796 ± 0.072</td>
<td>1.532 ± 0.201</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.473 ± 0.056</td>
<td>1.916 ± 0.315</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart</td>
<td>0.594 ± 0.062</td>
<td>0.511 ± 0.041</td>
<td>ns</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.390 ± 0.025</td>
<td>0.444 ± 0.042</td>
<td>ns</td>
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<tr>
<td>Liver</td>
<td>0.137 ± 0.010</td>
<td>0.186 ± 0.012</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.407 ± 0.047</td>
<td>0.574 ± 0.060</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.142 ± 0.017</td>
<td>0.422 ± 0.041</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pituitary</td>
<td>1.341 ± 0.180</td>
<td>3.621 ± 0.837</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

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.
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.

Acknowledgements

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References

1 Hetzel BS. Iodine deficiency disorders (IDD) and their eradication. The Lancet 1983 1126–1129.
2 Oppenheimer JH, Schwartz HL, Surks MI, Koerner D & Dillman WH. Nuclear receptors and the initiation of thyroid hormone action. Recent Programme Hormone Research 1976 32 529–565.
10 Doorn van J, Roelfsema F & van der Heide D. Concentrations of thyroxine and 3,5,3’-triiodothyronine at 34 different sites in euthyroid rats as determined by an isotopic equilibrium technique. Endocrinology 1985 117 1201–1208.

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