DYNAMIC STUDY OF POST-NATAL THYROID FUNCTION IN THE RAT

By

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ABSTRACT

The thyroid function in development was investigated in post-natal rats. The thyroid iodine content rapidly increased from birth (137 ± 26 ng iodine/mg thyroid) up to day 10 (338 ± 42 ng iodine/mg thyroid) then increased more slowly up to day 30 (425 ± 34 ng iodine/mg thyroid). The maximal plasma concentration of thyroxine was observed on day 16 (56.9 ± 3.5 ng T4/ml) and of iodide on day 10 (110.2 ± 12.6 ng I/ml). The turnover rate constant of extrathyroidal thyroxine was higher at birth (8.0 ± 2.3%/h) than at any older age studied (average 6%/h). Thyroxine secretion by the thyroid was more intense before weaning (37 ng hormonal iodine/h/100 g body weight on days 10 and 20) than after weaning (22 ± 6 ng hormonal iodine/h/100 g body weight in 30 days old rats). The peripheral deiodination rate of thyroxine represented about 90% thyroxine secretion rate in newborn and 10 days old rats and only 40% in adult females. In pre-weaning rats, after a single injection of both [131I]L-T4 and [125I]Na, extrathyroidal radioactivity disappeared more slowly than in 30 days old rats and adult animals. This suggests that iodide concentrations of extrathyroidal tissues are higher before than after weaning.

In the rat, during the 2 first post-natal weeks, the number, size and colloid content of the thyroid follicles increase (Legait et al. 1954; Phillips & Gordon 1955; Mitro et al. 1969). Simultaneously and as a result of these changes, iodine and thyroxine accumulate in the thyroid gland (Florsheim et al. 1966;
Vigouroux 1972a; Stolc et al. 1973). Furthermore, the plasma thyroxine concentration increases after birth and reaches a maximal level during the third post-natal week (Vigouroux 1972a; Wysocki & Segal 1972). These data seem consistent with a higher thyroid activity at the age of 2 or 3 weeks than at birth or after weaning.

In view of the results obtained with radioiodine, the gland of the newborn rat has been considered to be either hyperactive (Florsheim et al. 1966) or hypoactive (Beltz & Reineke 1968) or even inactive (Hommes et al. 1969) in comparison with that of the 3 weeks old rats.

The aim of the present paper which is a part of a so far unpublished thesis (Vigouroux 1974) was to measure the thyroid activity during the first post-natal month of life in the rat. At each investigated age, several parameters were simultaneously determined and combined in order to obtain quantitative data. Results in young rats were compared with those in the adult female.

MATERIALS AND METHODS

Animals

Wistar rats were used. They were fed a laboratory diet (UAR 1.03) containing from 0.8 to 1.5 μg iodine/g and tap water. The age of young rats was expressed as days post partum (birth was day 0).

Assay methods

i) Plasma thyroxine. – It was determined on 0.1 ml of plasma by a method previously described (Vigouroux 1972b) and adapted from the competitive binding assay of Murphy & Jachan (1965). The accuracy of the technique was tested: 9 determinations on a sample rat serum gave 24.6 ± 1.5 ng T₄/ml and 6 determinations on another one, 45.0 ± 2.6 (means ± fiducial intervals, P = 0.05).

ii) Total thyroid iodine. – The whole or parts of thyroid glands, weighing up to 7 mg, were put in 0.05 or 0.1 ml 5 N NaOH (Merck) in small glass tubes. Other tubes with an equal quantity of NaOH but without thyroid tissue were also prepared. After alkaline ashing during 16 h in an oven at 190°C, all the residues were dissolved in 1 or 2 ml 0.45 N HCl (Merck). Determination of thyroidal iodine was performed on aliquots of these solutions. As standard 0–25 μl from a 1 μg iodine (KI)/ml solution was diluted in volumes of the non-thyroidal acid solution equal to the aliquots. Iodide analysis was performed by the ceric-arsenite reaction (Malkin 1965; Pileggi & Kessler 1968).

iii) Plasma iodide. – The proteins of 0.1 ml of plasma were precipitated by 0.06 ml 40 % HClO₄ (Merck). 0.1 ml of the supernatant, containing 62.5 % of plasma iodide as determined on samples of plasma labelled with [¹²⁵I]Na, was digested by a sulphonitroperchloric acid mixture according to Lachiver (in Daugeras & Lachiver 1972). Tubes for standard curves (0–10 ng iodine in 0.1 ml 15 % HClO₄) were treated in the same way. Iodide in the ashes was determined by the ceric-arsenite reaction.
A) Three compartment model for metabolism of $^{125}$I and $^{131}$I during the 24 h following a single injection of $[^{125}$I]Na and $[^{131}$I]L-T₄ mixture into young rats. Compartment 1 represents extrathyroid iodide, Compartment 2 is total thyroid iodine and Compartment 3 is extrathyroid hormonal iodine. Thick arrow represents alimentary iodide ingestion. Dotted arrows show initially labelled compartments. $k_{21}$, $k_{01}$, $k_{18}$ and $k_{03}$ are transfer rate constants (see text).

B) Disappearance curves of plasma $[^{125}$I]iodide and PB$^{131}$I (radioactive concentrations extrapolated to 0 time, $c_1(0)$ and $c_3(0)$, are indicated with crosses and arrows) and thyroid accumulation curves of $^{125}$I and $^{131}$I in newborn rats. The best plasma curves and the best thyroid $^{125}$I curve were calculated by an iterative least-square method and the thyroid $^{131}$I curve by using the equation 9 in the text. Vertical bars delimit fiducial intervals ($P = 0.05$). Numbers of rats near points.

iv) Iodine in the diet. – This was measured using the same technique as plasma iodide, except that the material (10–20 mg) was directly digested by a sulphonitroperchloric mixture without previous perchloric acid treatment.

Kinetic study of iodine metabolism
This was performed in rats aged 0, 10, 20 and 30 days and adult female according theoretical model (Fig. 1) modified from Brownell (1951). Taking into account the short interval of time (24 h) selected for the experiments, two approximations were done: 1) the system was in steady state so that peripheral thyroxine turnover rate ($R₃$) equalled thyroxine secretion rate (TSR) by the thyroid gland; 2) the radioiodine released from the gland as thyroxine after administration of tracers was such a small fraction of the injected dose that the transfer from compartment 2 to 3 was negligible.
i) **Radioactive materials.** – [\(^{125}\)I]Na (specific activity \(> 13 \text{ Ci/mg}\)) and [\(^{131}\)I]L-thyroxine (specific activity: \(25-75 \text{ mCi/mg}\)) were purchased from the C.E.A. (Saclay, France). One ml from the radioactive thyroxine solution was diluted in 2 ml rat plasma and dialyzed for the night preceding injection into animals against 1 l of 0.15 m sodium phosphate buffer pH 7.4 at \(4^\circ\text{C}\) to remove contaminants. The resulting solution by paper electrophoresis was found to contain less than 1% of radioactivity as iodide.

ii) **Procedure.** – Intravenous injections were made (jugular vein at birth; saphenous vein in the older rats) under light anaesthesia (cooling of the newborn and ether anaesthesia in the older animals). The animals received in a 0.9% NaCl solution (2-25 \(\mu\)l) a mixture of dialyzed \([^{131}\text{I}]\text{L-T}_4\) (0.2-0.3 ng/g body weight) and \([^{125}\text{I}]\text{Na}\) (0.03 \(\mu\text{Ci/g b.w.}\)). Each adult female was put in a metabolism cage for collection of stool and urine and young rats were given back to their mother up to sacrifice. At each time 4, 8, 16 and 24 h after injection, 8-11 young animals of each relevant age and 4 adult females were bled (brachial artery in young; abdominal aorta in adult) under ether anaesthesia. The thyroid glands and other organs (livers, stomachs, intestines and kidneys) were dissected out and counted for radioactivity, as well as the remaining carcasses. Plasma labelled thyroxine and iodide content were determined according to Geloso & Bernard (1967) as \(\text{PB}^{131}\text{I}\) and \([^{125}\text{I}]\)iodide after trichloroacetic precipitation. For this the quantity of plasma were measured by weighing and adjusted to 0.5 ml with non-radioactive plasma of adult rats. Radioactivity was expressed as per cent of the injected dose.

iii) **Calculation of kinetic parameters.** – A mathematical formulation for iodine metabolism model (Fig. 1) was done with the help of Laplace transformation. Most of the symbols used were taken from Atkins (1969):

\[
t = \text{time (hour)};
\]

\[
Q_1 \text{ and } Q_3 \text{ were amounts of iodine in compartments 1 and 3 (ng iodine), respectively (Fig. 1)};
\]

\[
C_1 \text{ and } C_3 \text{ were plasma concentrations of iodide and hormonal iodine (ng iodine/ml). } C_3 \text{ was the product of plasma concentration of thyroxine by 0.654 in order to convert thyroxine into iodine;}
\]

\[
V_1 \text{ and } V_3 \text{ were apparent distribution volumes of iodide and hormonal iodine (ml), respectively;}
\]

\[
q_1(0) \text{ and } q_3(0) \text{ were injected doses of } [^{125}\text{I}]\text{Na} \text{ and } [^{131}\text{I}]\text{L-T}_4, \text{ respectively. Each of them is equal to 100%};
\]

\[
q_0^{[125]\text{I}]} \text{ and } q_0^{[131]\text{I}] \text{ were thyroidal radioactivities at a given time (% of injected dose);}
\]

\[
c_1 \text{ and } c_3 \text{ were plasma concentrations of } [^{125}\text{I}]\text{iodide and } [^{131}\text{I}]\text{thyroxine, respectively (% of injected dose/ml);}
\]

\[
c_1(0) \text{ and } c_3(0) \text{ were } c_1 \text{ and } c_3 \text{ at zero time;}
\]

\[
k_{21}, k_{01}, k_{13} \text{ and } k_{03} \text{ were rate constants of iodide thyroidal uptake, iodide urinary excretion, thyroxine peripheral deiodination and thyroxine faecal excretion, respectively (%/h);}
\]

\[
K_{125} \text{ and } K_{131} \text{ were disposal rate constants of total extrathyroidal radioactivity } [^{125}\text{I}] \text{ and } [^{131}\text{I}], \text{ respectively (%/h);}
\]

\[
\lambda_1 \text{ and } \lambda_3 \text{ were turnover rate constants of extrathyroidal iodide and thyroxine, respectively (%/h);}
\]

\[
R_1 \text{ and } R_3 \text{ were turnover rates of extrathyroidal iodide and thyroxine, respectively (ng iodine/h);}\]
$r_{21}$ and $r_{13}$ were rates of iodide thyroidal uptake and thyroxine peripheral deiodination, respectively (ng iodine/h).

$\lambda_1$ and $\lambda_3$ were calculated with equations:

$$c_1 = c_1(0) \ e^{-\lambda_1 t}$$  \hspace{1cm} (1)

$$c_3 = c_3(0) \ e^{-\lambda_3 t}$$  \hspace{1cm} (2)

describing the disappearance of plasma $^{125}$I iodide and $^{131}$I, respectively, as illustrated in Fig. 1.

$$V_1 = q_1(0)/c_1(0).$$  \hspace{1cm} (3)

$$V_3 = q_3(0)/c_3(0).$$  \hspace{1cm} (4)

Thyroxine turnover rate was:

$$R_3 = \lambda_3 \times V_3 \times C_3 = \lambda_3 \times Q_3.$$  \hspace{1cm} (5)

$k_{21}$ was obtained from the thyroid incorporation curves of $^{125}$I iodide (Fig. 1) described by:

$$q_{2[1^{25}I]} = \frac{q_1(0)}{\lambda_1} \left(1 - e^{-\lambda_1 t}\right).$$  \hspace{1cm} (6)

$$r_{21} = k_{21} \times V_1 \times C_1 = k_{21} \times Q_1.$$  \hspace{1cm} (7)

$k_{13}$ was calculated by using the $q_{2[1^{25}I]}/q_{2[1^{13}I]}$ ratio of every thyroid in the equation:

$$k_{13} = \frac{q_{2[1^{13}I]}}{q_{2[1^{25}I]}} \left(\frac{\lambda_1 - \lambda_3}{\lambda_3 (1 - e^{-\lambda_1 t})} \right)$$  \hspace{1cm} (8)

where:

$$q_{2[1^{13}I]} = \frac{k_{21} k_{13} q_3(0)}{\lambda_1 - \lambda_3} \left[ 1 + \frac{\lambda_3 e^{-\lambda_1 t} - \lambda_1 e^{-\lambda_3 t}}{\lambda_1 - \lambda_3} \right].$$  \hspace{1cm} (9)

$$r_{13} = k_{13} \times V_3 \times C_3 = k_{13} \times Q_3.$$  \hspace{1cm} (10)

Non-linear parameters in equations 1, 2 and 6 were estimated by an iterative least-square method weighted according to Ottaway (1973).

**Statistics**

Significance of differences between means were analyzed by Student's $t$-test. Products of means were considered significantly different ($P < 0.05$) when their fiducial intervals ($P = 0.05$) calculated by the propagation of errors method (Di Stefano et al. 1973) were not crossing each other.

**RESULTS**

**Thyroid weight and iodine content** (Table 1)

The thyroid weight relative to body weight diminished significantly after the third post-natal week. Thyroid concentration of total iodine was 2.5 times higher at 10 days than at birth ($P < 0.001$). Adult thyroid glands were twice as rich in iodine as glands of 30 days old rats ($P < 0.001$).
**Table 1.**

Thyroid weight relative to body weight and iodine content in rats as a function of age (means ± fiducial limits).

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>Body weight (g)</th>
<th>Thyroid weight (mg/g body weight)</th>
<th>Thyroid iodine (ng/mg tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.3 ± 0.2 (78)</td>
<td>0.14 ± 0.01 (21)</td>
<td>137 ± 26 (21)</td>
</tr>
<tr>
<td>1</td>
<td>5.7 ± 0.2 (54)</td>
<td>0.13 ± 0.03 (19)</td>
<td>186 ± 31 (19)*</td>
</tr>
<tr>
<td>2</td>
<td>7.1 ± 0.4 (25)</td>
<td>0.11 ± 0.02 (16)</td>
<td>165 ± 14 (16)</td>
</tr>
<tr>
<td>5</td>
<td>11.3 ± 0.5 (25)</td>
<td>0.12 ± 0.01 (19)</td>
<td>271 ± 15 (19)*</td>
</tr>
<tr>
<td>10</td>
<td>19.4 ± 0.9 (76)</td>
<td>0.11 ± 0.01 (38)</td>
<td>338 ± 42 (38)*</td>
</tr>
<tr>
<td>16</td>
<td>33.0 ± 1.0 (31)</td>
<td>0.11 ± 0.01 (26)</td>
<td>378 ± 19 (26)</td>
</tr>
<tr>
<td>20</td>
<td>40.7 ± 1.7 (86)</td>
<td>0.11 ± 0.01 (43)</td>
<td>416 ± 32 (43)</td>
</tr>
<tr>
<td>30</td>
<td>70.9 ± 2.3 (72)</td>
<td>0.08 ± 0.01 (39)*</td>
<td>425 ± 34 (39)</td>
</tr>
<tr>
<td>Ad. ♀</td>
<td>258 ± 14 (23)</td>
<td>0.05 ± 0.01 (23)*</td>
<td>864 ± 78 (23)*</td>
</tr>
</tbody>
</table>

* Significant difference from preceding age group ($P < 0.05$).

Number of rats in brackets.

**Fig. 2.**

Plasma thyroxine and iodide concentrations as a function of age in rats. Vertical bars delimit fiducial intervals ($P = 0.05$). Numbers of rats near points.
Thyroxine and iodine levels in plasma (Fig. 2)

Maximal concentration of plasma thyroxine occurred on day 16 and of plasma iodide on day 10. At a given age, plasma thyroxine and iodide levels were rather constant. Nevertheless, in 10 days old rats, plasma iodide ranged from 35 to 172 ng/ml. Table 2 shows that on day 10 plasma iodide concentration increased as did the amount of iodine in the diet. In other respects the thyroidal $^{131}$I-uptake and the plasma $[^{131}$I]thyroxine concentration, 24 h after a single injection of $[^{131}$I]Na, increased as the plasma iodide levels decreased, while the thyroid $[^{127}$I]iodide uptake did not seem to change appreciably.

Iodine metabolism as a function of age (Table 3)

Iodide turnover rate constant $\lambda_1$ was significantly lower during the 3 first post-natal weeks than after weaning. Thyroxine turnover rate constant $\lambda_3$ was high at birth and remained rather constant later on. At all stages, the iodide distribution volume $V_1$ and $V_3$ when expressed per 100 g body weight were observed at birth. Afterwards, $V_1$ progressively decreased. $V_3$ was reduced by half between 0 and 10 days. Between 10 and 30 days, it decreased significantly ($P < 0.05$) but more slowly than $V_1$.

The thyroid iodide uptake rate constant $k_{21}$ was lower during the 3 first weeks than after weaning. Thyroxine deiodination rate constant $k_{13}$ decreased from birth up to adulthood when $k_{13}$ was lower than $\lambda_3$ ($P < 0.05$).

During the 3 first weeks, the pool of extrathyroidal iodine $Q_1$ equilibrated with plasma iodide exceeded the pool of hormonal iodine $Q_3$ by 5–7 times.

Table 2.

Results obtained 24 h after injection of a $[^{131}$I]Na tracer dose to 10 days old rats as a function of diet iodine content. A) 1.6 $\mu$g iodine/g diet; B) 0.3 $\mu$g iodine/g diet (means ± fiducial limits).

<table>
<thead>
<tr>
<th></th>
<th>Plasma iodide (ng I/ml)</th>
<th>Thyroidal $^{131}$I uptake (% dose)</th>
<th>Thyroidal $^{127}$ uptake (ng I/ml plasma)</th>
<th>Plasma $[^{131}$I]thyroxine (% dose/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (6)</td>
<td>146 ± 22</td>
<td>4.5 ± 0.6</td>
<td>6.6 ± 1.3</td>
<td>0.09 ± 0.01</td>
</tr>
<tr>
<td>B (7)</td>
<td>49 ± 9*</td>
<td>18.4 ± 1.8*</td>
<td>9.0 ± 1.9</td>
<td>0.31 ± 0.06*</td>
</tr>
</tbody>
</table>

* Significant difference from upper value ($P < 0.001$). Thyroidal $^{127}$I uptake is the product of plasma iodide level by thyroidal $^{131}$I uptake.

Number of rats in brackets.
Parameters of extrathyroidal iodide and hormonal iodine metabolism determined as a function of age in rats during the 24 h following a single injection of both $^{[125]}$I$^{-}$Na and $^{[131]}$I-L-T$_4$ (means ± fiducial limits).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 0 (40)</th>
<th>Day 10 (38)</th>
<th>Day 20 (45)</th>
<th>Day 30 (39)</th>
<th>Adult ♀ (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$</td>
<td>133 ± 22</td>
<td>112 ± 6</td>
<td>72 ± 11*</td>
<td>52 ± 10*</td>
<td>34 ± 11</td>
</tr>
<tr>
<td>$V_3$</td>
<td>46 ± 8</td>
<td>24 ± 5*</td>
<td>20 ± 2</td>
<td>18 ± 2</td>
<td>18 ± 3</td>
</tr>
<tr>
<td>$\lambda_1$</td>
<td>5.2 ± 1.7</td>
<td>4.2 ± 0.2</td>
<td>7.3 ± 1.6*</td>
<td>14.7 ± 3.2*</td>
<td>17.5 ± 5.9</td>
</tr>
<tr>
<td>$\lambda_3$</td>
<td>8.0 ± 2.3</td>
<td>5.5 ± 1.4*</td>
<td>6.1 ± 1.0</td>
<td>6.0 ± 1.2</td>
<td>6.0 ± 1.4</td>
</tr>
<tr>
<td>$k_{21}$</td>
<td>1.1 ± 0.6</td>
<td>0.8 ± 0.5</td>
<td>1.0 ± 0.3</td>
<td>2.5 ± 0.6*</td>
<td>4.4 ± 1.9</td>
</tr>
<tr>
<td>$k_{13}$</td>
<td>7.5 ± 1.2</td>
<td>5.3 ± 0.6</td>
<td>4.8 ± 0.6</td>
<td>4.5 ± 0.5</td>
<td>2.4 ± 0.6*</td>
</tr>
<tr>
<td>$K_{125}$</td>
<td>2.3 ± 0.7**</td>
<td>1.2 ± 0.5**</td>
<td>3.7 ± 0.9**</td>
<td>10.7 ± 2.0</td>
<td>15.5 ± 5.7</td>
</tr>
<tr>
<td>$K_{131}$</td>
<td>1.3 ± 0.5***</td>
<td>1.0 ± 0.4***</td>
<td>2.4 ± 0.5***</td>
<td>4.3 ± 0.7</td>
<td>4.0 ± 1.2</td>
</tr>
<tr>
<td>$C_1$</td>
<td>20 ± 2</td>
<td>43 ± 4*</td>
<td>40 ± 3</td>
<td>21 ± 1*</td>
<td>16 ± 3*</td>
</tr>
<tr>
<td>$C_3$</td>
<td>8 ± 1</td>
<td>28 ± 2*</td>
<td>31 ± 2*</td>
<td>21 ± 2*</td>
<td>19 ± 2*</td>
</tr>
<tr>
<td>$Q_1$</td>
<td>2.7 ± 0.6</td>
<td>4.9 ± 0.5*</td>
<td>2.9 ± 0.5*</td>
<td>1.1 ± 0.2*</td>
<td>0.5 ± 0.2*</td>
</tr>
<tr>
<td>$Q_3$</td>
<td>0.4 ± 0.1</td>
<td>0.7 ± 0.1*</td>
<td>0.6 ± 0.1</td>
<td>0.4 ± 0.1*</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>$R_1$</td>
<td>139 ± 53</td>
<td>203 ± 23</td>
<td>209 ± 56</td>
<td>158 ± 47</td>
<td>92 ± 46</td>
</tr>
<tr>
<td>$R_3$</td>
<td>29 ± 10</td>
<td>37 ± 12</td>
<td>37 ± 7</td>
<td>22 ± 6*</td>
<td>20 ± 6</td>
</tr>
<tr>
<td>$r_{21}$</td>
<td>29 ± 16</td>
<td>38 ± 16</td>
<td>30 ± 11</td>
<td>27 ± 9</td>
<td>23 ± 13</td>
</tr>
<tr>
<td>$r_{13}$</td>
<td>27 ± 7</td>
<td>36 ± 8</td>
<td>29 ± 5</td>
<td>17 ± 3*</td>
<td>8 ± 3*</td>
</tr>
</tbody>
</table>

* Significant difference ($P < 0.05$) from preceding age group.
** Significant difference ($P < 0.05$) from $\lambda_1$.
*** Significant difference from $\lambda_3$ ($P < 0.05$).

For description of symbols see Materials and Methods. $V_1$, $V_3$ expressed as ml of plasma /100 g body weight; $\lambda_1$, $\lambda_3$, $k_{21}$, $k_{13}$, $K_{125}$ and $K_{131}$ as %/h; $C_1$ and $C_3$ as ng iodine/ml plasma; $Q_1$ and $Q_3$ as $\mu$g iodine/100 g body weight; $R_1$, $R_3$, $r_{21}$ and $r_{13}$ as ng iodine/h/100 g body weight.

In the adult $Q_1$ and $Q_3$ were not significantly different and were lower than those in suckling rats ($P < 0.05$).

The hormonal iodine turnover rate $R_3$ was maximal at 10–20 days. After weaning, the thyroxine deiodination rate $r_{13}$ significantly decreased. It was about 90 % of $R_3$ in newborn and 10 days old rats and only 40 % in adult females.

Disposal rate constants of extrathyroidal $^{125}$I ($K_{125}$) and $^{131}$I ($K_{131}$) were much smaller than the turnover rate constants $\lambda_1$ and $\lambda_3$ respectively ($P < 0.05$) in pre-weaning rats and not significantly different in 1 month old and adult rats. In young animals, this result is explained by a significant peripheral accumulation of radioiodide during the experiment time. Thus retention of
was maximal at birth and on day 10 because thyroxine was strongly deiodinated and \([^{131}I]I\)odide derived from \([^{131}I]L-T_4\) was considered to behave like \([^{125}I]I\)odide.

In order to test the acceptability of the kinetic method used, some observations were made. Not less than 94–95\% of plasma \([^{131}I]I\)thyroxine present at the end of the experiment was a part of injected radiothyroxine, indicating that the thyroidal recycling of iodide was negligible (Table 4). The theoretical thyroid accumulation curves of \([^{131}I]I\)odide were calculated by the formula (9) and always agreed with the experimental data (Fig. 1). In adult female rats, calculated \(k_{13}\) was 2.4 ± 0.6\%/h (Table 3) when the thyroid \(^{131}I/^{125}I\) ratios were included in the formula (8) and 3.0 ± 0.4\%/h when the \(^{131}I/^{125}I\) ratios in the urine were used instead of thyroid ratios (non-significant difference). Collection of urine in young rats was not made because mothers ingested the excreta of their puppies.

**DISCUSSION**

In suckling rats, the thyroid is probably the main source of circulating thyroxine; the maternal milk is another possible source. However, according to Hoskins et al. (1958) “the mammary gland does not secrete thyroxine in a physiologically active form”. Thyroxine level in sera of suckling rats is little modified when the hormone is suppressed in the milk by thyroidectomy of the mother (Strbak et al. 1974). The thyroid of young rats synthesizes hormones

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>Thyroid (1^{31}I/1^{25}I) ratio (a)</th>
<th>Plasma BE(1^{25}I) (% (1^{25}I) dose/ml) (b)</th>
<th>Plasma ([^{131}I]T_4) (% ([^{131}I])T_4 dose/ml) (c)</th>
<th>Plasma ([^{131}I]T_4) from recycling (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (10)</td>
<td>0.56 ± 0.06</td>
<td>0.60 ± 0.20</td>
<td>6.1 ± 1.4</td>
<td>5.5 ± 2.3</td>
</tr>
<tr>
<td>10 (10)</td>
<td>0.45 ± 0.05</td>
<td>0.17 ± 0.03</td>
<td>6.0 ± 0.9</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>20 (11)</td>
<td>0.39 ± 0.06</td>
<td>0.19 ± 0.08</td>
<td>3.2 ± 0.4</td>
<td>2.2 ± 1.1</td>
</tr>
<tr>
<td>30 (10)</td>
<td>0.41 ± 0.04</td>
<td>0.12 ± 0.07</td>
<td>2.0 ± 0.1</td>
<td>2.5 ± 1.7</td>
</tr>
<tr>
<td>Ad. (♀) (4)</td>
<td>0.32 ± 0.03</td>
<td>0.05 ± 0.03</td>
<td>0.5 ± 0.1</td>
<td>3.2 ± 2.3</td>
</tr>
</tbody>
</table>

* Maximal per cent of plasma \([^{131}I]I\)thyroxine released by thyroid recycling of \([^{131}I]I\)odide derived from peripheral thyroxine deiodination. It was calculated as: \(100 \times (a) \times (b)/(c)\). Number of rats in brackets.

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(Florsheim et al. 1966; Vigouroux 1972a) and releases thyroxine in the blood as does the adult thyroid (Vigouroux 1974). These observations allow us to compare extrathyroid thyroxine turnover rate (Rₜ) and thyroxine secretion rate (TSH) by the thyroid, in pre-weaning animals.

The present results indicate that, in the rat, thyroxine secretion is more intense before than after weaning, as it was also observed in young animals equilibrated with ¹²³I (Vigouroux 1972a). Confirmation of this is given by the fact that, in hypothyroid young rats, the minimal daily dose of exogenous thyroxine capable of preventing the enlargement of the thyroid and of correcting the difficulties in maturation of the cerebellum, corresponds to the TSR as determined here (Clos et al. 1974). In adult females, the thyroxine secretion rate is comparable with values given by other investigators (Gregerman & Crowder 1963; Simon 1964).

Up to the present, peripheral thyroxine deiodination rate has not been measured in vivo in newborn and young rats. The very marked deiodinating activity observed here, during the 2 first post-natal weeks, confirms the in vitro data of Burman et al. (1973): thyroid hormone is more deiodinated by liver and kidney of newborn than of adult animals. In adult females, less than half the peripheral thyroxine is deiodinated. This agrees with results obtained in rats by methods different from ours. The thyroxine deiodinative clearance is lower than its faecal clearance (Galton 1972; Cullen et al. 1973). Peripheral thyroxine deiodination is considered a good index of the utilization of the hormone by tissues (Escobar del Rey & Morreale de Escobar 1964). Hence the neonatal rat tissues seem to use a great deal of thyroxine, just at the time when the hormone is necessary for numerous maturation processes, particularly in the nervous system (Legrand 1967) and in the skeletal system (Scow & Simpson 1945). Moreover, such a thyroxine utilization also explains the high α-glycerophosphate oxidase activity observed in the rat liver from birth up to weaning (Hénon 1967).

The size of the iodide compartment in fast equilibrium with the plasma iodide is 5–10 times greater before weaning than in the adult. Stolc et al. (1973) also found a much higher iodine concentrations in the peripheral tissues of young than of adult rats. In young rats, the amount of total extrathyroidal iodine exceeds the amount of iodine in the compartment 1 (Vigouroux 1974). This suggests that before weaning, there is an iodide compartment in slow equilibrium with plasma iodide.

ACKNOWLEDGMENTS

This work has been supported by the D. G. R. S. T. (France), (contrat n° 72.7.0102). We wish to thank Professors A. Jost and J. Legrand for their interest in this project and Miss M. C. Visbeck for her skilled technical assistance.
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Received on November 5th, 1975.