Circulating 3,3′,5′-Triiodothyronine (Reverse T₃) in the Human Newborn

INDER J. CHOPRA, JOSEPH SACK, and DELBERT A. FISHER

From the Department of Medicine, University of California at Los Angeles Center for the Health Sciences, Los Angeles, California, and the Department of Pediatrics, University of California at Los Angeles-Harbor General Hospital, Torrance, California 90024

ABSTRACT Serum concentrations of 3,3′,5′-triiodothyronine (reverse T₃, rT₃), 3,3′,5-triiodothyronine (T₃), and thyroxine (T₄) were measured in cord blood and in venous blood samples obtained between 2 h and 30 days after birth in healthy full-term newborn infants. The mean serum rT₃ concentration of (mean±SE) 153±12 ng per 100 ml in 18 cord blood samples was significantly higher than the level (41±2 ng per 100 ml) in 27 normal adult sera; the corresponding mean serum T₃ of 12.7±0.8 μg per 100 ml in cord blood also was significantly higher than that (8.6±1.9 μg per 100 ml) in 108 normal adults. By contrast, the mean serum T₄ concentration in 15 cord blood samples, 24±3 ng per 100 ml, was significantly lower than the value of 126±3.2 ng per 100 ml measured in 108 normal adults. At 4 h of age the mean serum rT₃ concentration (165±13 ng per 100 ml) in six newborns was not significantly different from that in paired cord blood samples (194±25 ng per 100 ml); on the other hand, whenever studied, the mean serum T₃ and T₄ levels were significantly higher at 4 h than at birth. The failure of serum rT₃ concentrations to rise after delivery in response to the early neonatal thyrotropin (TSH) surge and at a time when serum T₃ and T₄ levels increased significantly prompted a study of the rT₃ response to 10 IU of intramuscular TSH in three healthy adult subjects. Just as in the newborns, serum rT₃ failed to rise appreciably in these subjects, even though serum T₃ and T₄ showed the expected increments.

Serum rT₃ concentrations in 1-4-day-old newborn infants did not differ significantly from values in the cord blood but were significantly lower in older neonates. The mean serum rT₃ level in 5-7-day-old infants was higher than that in normal adults, but in 9-11-day and 20-30-day-old infants, mean rT₃ values were statistically similar to the adult value. The mean serum T₃ concentrations in neonates between 1-30 days old were either higher than or comparable to the values of normal adults. The mean serum T₄ concentrations in neonates between birth and 30 days of age were significantly higher than the mean adult level. The mean serum rT₃ to T₄ ratios were elevated in 1-4-day-old neonates; the values in older neonates were similar to those in adults.

These results suggest that (a) factors other than TSH are important modulators of serum rT₃ in man; (b) high serum rT₃ concentration in the newborn becomes comparable to that in the normal adult by 9-11 days of neonatal life.

INTRODUCTION

Recent studies have shown that the concentration of 3,3′,5′-triiodothyronine (reverse T₃, rT₃) is much higher and that of 3,3′,5-triiodothyronine (T₃) is much lower in human cord blood serum than in the serum of adults (1). Several investigators have demonstrated that the low-cord serum T₃ concentrations increase to levels comparable to or even higher than adults within a few hours of birth (2, 3). There is currently no information regarding the changes in serum rT₃ concentration during the first few hours or days of life. The present studies were undertaken to obtain this information, and indicate that, unlike serum T₃, serum rT₃ levels gradually fall and become comparable to values in adults during the 2nd week of extrauterine life. Moreover, the circulating rT₃ concentrations show little or no change in association with the neonatal TSH.

1 Abbreviations used in this paper: rT₃, 3,3′,5′-triiodothyronine; T₃, 3,3′,5-triiodothyronine; rT₃/T₄, the serum rT₃ to T₄ ratios; T₄, thyroxine; TSH, thyrotropin.

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surge, whereas serum T₃ levels are known to increase considerably.

METHODS

Cord blood was obtained from 18 full-term newborn infants at the time of vaginal delivery; venous blood was obtained from six of these neonates between birth and 4 h of age. In addition, blood samples were collected from another 37 neonates between 1 and 30 days of age. Blood samples were also obtained from three healthy adult volunteer subjects 20-24 yr of age before and at periodic intervals after an i.m. injection of 10 IU of bovine thyrotropin (TSH, Thytropar®, Armour Pharmaceutical Co., Phoenix, Ariz.). Serum was separated from the samples after centrifugation. Serum concentrations of rT₃, T₃, and thyroxine (T₄) were measured by radioimmunoassay systems described previously (1, 4, 5). In most cases, all three iodothyronines were measured in the same sera. In a few instances, however, serum volume was too limited to measure T₃ accurately; only rT₃ and T₄ were measured in these cases. The values in various groups of study were compared by Student’s two-tailed t test for unpaired data.

RESULTS

Serum rT₃, T₃, and T₄ in cord blood. The mean (±SEM) serum rT₃ concentration of 151±12 ng per 100 ml in cord blood samples of 18 newborns was significantly (P < 0.001) higher than the corresponding value of 40.5±2.0 ng per 100 ml in 27 normal adult subjects recently tested in our laboratory. The mean serum T₄ of 12.7±0.8 µg per 100 ml in the same cord sera was also significantly higher than that (8.6±1.9 µg per 100 ml) in 108 normal adult subjects. On the other hand, the mean serum T₃ level in cord blood of 24±3 ng per 100 ml in 15 cases was significantly lower than the mean value of 126±3.2 in the 108 normal subjects referred to above.

Changes in serum rT₃, T₃, and T₄ during the first 4 h of life. Fig. 1 shows the data on serum concentrations of rT₃, T₃, and/or T₄ during the first 4 h of life in six neonates so studied. Serum rT₃ concentrations did not show a consistent change; the value at 4 h was lower than the respective cord serum concentration in four cases and modestly higher than the corresponding cord serum value in the remaining two cases. The mean value of 165±13 ng per 100 ml at 4 h of life was not significantly different from the corresponding value of 194±25 ng per 100 ml in paired cord blood samples. On the other hand, whenever studied, serum T₃ and T₄ values were higher at 2 or 4 h after birth than the corresponding cord serum concentrations (Fig. 1).

Effect of TSH on serum rT₃, T₃, and T₄ in normal adult subjects. Inasmuch as there is a rapid increase in serum TSH soon after birth, which precedes the increases in serum T₃ and T₄ concentrations (2, 3, 6, Fig. 1), we were intrigued by the observation that there was little change in serum rT₃ during the first 4 h of life. To further examine the effect of an increase in serum TSH on serum rT₃ levels, we studied serum rT₃, T₃, and T₄ concentrations in three subjects given TSH (10 IU) i.m.; the data are shown in Table I. There was clearly an increase in both serum T₃ and T₄ concentrations maximal at 6 h and 24 h, respectively, after TSH
TABLE I
Effect of Intramuscular Injection of TSH (10 IU) on Serum rT3, T3, and T4 Concentration in Normal Adult Subjects

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>0 h</th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
<th>12 h</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24 M</td>
<td>rT3*</td>
<td>30</td>
<td>30</td>
<td>29</td>
<td>29</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3*</td>
<td>105</td>
<td>150</td>
<td>145</td>
<td>150</td>
<td>145</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4†</td>
<td>8.0</td>
<td>8.3</td>
<td>9.0</td>
<td>9.0</td>
<td>9.2</td>
<td>10.9</td>
</tr>
<tr>
<td>2</td>
<td>22 F</td>
<td>rT3</td>
<td>28</td>
<td>35</td>
<td>32</td>
<td>30</td>
<td>29</td>
<td>32</td>
</tr>
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<td></td>
<td></td>
<td>T3</td>
<td>112</td>
<td>150</td>
<td>185</td>
<td>185</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4</td>
<td>5.5</td>
<td>6.6</td>
<td>7.1</td>
<td>7.7</td>
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<td>27</td>
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<td>28</td>
<td>29</td>
</tr>
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<td></td>
<td></td>
<td>T3</td>
<td>75</td>
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<td>130</td>
<td>150</td>
<td>145</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4</td>
<td>6.8</td>
<td>7.0</td>
<td>7.4</td>
<td>9.0</td>
<td>9.7</td>
<td>9.7</td>
</tr>
</tbody>
</table>

* ng/100 ml.
† μg/100 ml.

administration; however, there was no consistent change in serum rT3 levels.

Serum rT3, T3, and T4 concentrations during the 1st mo of life. The results of measurements of serum iodothyronine concentrations in neonates between 1 day and 30 days of age are presented in Fig. 2. The mean and range of serum rT3 values in infants 1–4 days of age were comparable to those in cord sera (vide supra). However, the mean serum rT3 values in neonates 5 days of age and older were each significantly (P < 0.001) less than in cord sera. Several values in 5–7-day-old neonates were higher than normal adult values (Fig. 2), and the mean (±SE) rT3 values of 59±13, 63±20, and 54±7.9 ng per 100 ml in 5, 6, and 7-day-old neonates,

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**Figure 2** Serum concentrations of rT3, T3, and T4 during the first 30 days of neonatal life.

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subjects. The mean serum rT3 value of 40±13 ng per 100 ml in 9-11-day-old neonates and that of 36±8.4 ng per 100 ml in 20-30-day-old neonates was comparable to the corresponding value in normal adults. As against rT3, the values of serum T3 concentrations between 1 and 30 days of life did not follow a consistent pattern; the mean values were either higher than or comparable to the mean value in adult subjects. The mean serum T4 values were significantly higher at all times of study than the corresponding value in normal adults. There was no significant relationship between rT3 and T4; this was the case in 1-4-day-old neonates whose rT3 was clearly high as well as in older neonates whose rT3 was normal or nearly normal.

The ratio of serum concentrations of rT3 and T4 was examined in all cases presented in Fig. 2; the data were expressed as (rT3/T4 X 100). The mean value in cord sera was 0.88±0.13. The values at 1, 2, 3, 4, 5, 6, 7, 9-11, and 20-30 days of age were 0.81±0.10, 0.94±0.23, 1.38±0.35, 0.99, 0.32±0.08, 0.54±0.17, 0.38±0.07, 0.31±0.13, and 0.40±0.13, respectively. The mean ratio at 1-4 days of age did not differ significantly from that in cord sera. However, the mean values in 5-day old or older infants were significantly (P < 0.001) lower than that in cord sera. The mean rT3/T4 values in infants between 1 and 4 days of age were significantly higher (P < 0.001) than the mean value, 0.46±0.03, in 26 normal adult subjects; the mean values in older infants were, however, similar to that in normal adults.

**DISCUSSION**

The present data on changes in serum T3 and T4 during the neonatal period are similar to results reported previously (2, 3). The increase in serum T4 during this period can be attributed to the dramatic rise in serum TSH occurring immediately after delivery; in one previous study, serum TSH was noted to rise to a mean peak value of 86 μU per ml 30 min after delivery, and elevated serum levels had persisted when studied up to 48 h of postnatal life (6). The increase in serum T3 also is, at least in part, attributable to the TSH surge. However, the finding of no change in serum rT3 levels during the first 4 h of life is intriguing. It could be explained if there were little or no rT3 in the neonatal thyroid. There is at present no available information regarding the rT3 content of the thyroid in the newborn human infant. However, even though rT3 has been demonstrated in the thyroglobulin of adult subjects (1), there is little or no effect of exogenous TSH on serum rT3 concentrations of normal adult subjects (Table I). The reason(s) for this is not clear. It could be explained if the thyroidal contribution to circulating rT3 were minimal, if the metabolic clearance rate of rT3 were much faster than that of T3 or T4, or if both factors were involved. The rate of disappearance of rT3 from circulation of adult man has been reported to be much faster than that of T3 or T4 (7). Additionally, studies currently in progress in our laboratories suggest that less than 5% of the circulating concentration of rT3 is derived from thyroidal secretion in either the fetal or adult sheep; 95% or more apparently originates from peripheral monodeiodination of T4 to rT3 (Chopra, Sack, and Fisher; unpublished data).

The mechanism(s) responsible for the high serum rT3 concentrations in the newborn is not clear. Serum rT3 concentrations in the first 4 days of life are similar to those in cord blood, suggesting that the elevated rT3 levels in newborn cord serum (1, *vide supra*) are not due simply to the stressful process of delivery, but probably result from some alteration(s) in iodothyronine metabolism in the fetus and newborn. The elevated serum rT3 values decrease after the 4th day (Fig. 2) and become comparable to adult levels by 9-11 days. These data suggest that the alterations in iodothyronine metabolism change in direction toward those in normal adults during this time. Recent studies from our laboratories indicate that serum rT3 levels are similarly elevated in fetal and newborn sheep and that the production rate of rT3 is markedly increased in fetal sheep relative to the adult sheep (8).

It is interesting to note that the period of normalization of serum rT3 in the newborn approximates rather closely the period of physiological jaundice at this time of life. The proximity of these events together with the information that liver is of considerable importance in metabolism of T4 (9, 10) lead one to consider that maturation of hepatic function may participate significantly in the normalization of high serum rT3 in the newborn. However, further study is needed to examine the influence of liver on serum rT3 compared to that of other organs.

The physiological significance of markedly high rT3 in the fetus and newborn remains unclear. Reverse T3 has little calorigenic activity (11, 12). However, iodothyronines have several metabolic effects other than increasing oxygen consumption (13-16). Studies examining the effects of rT3 in these various metabolic events may help in the evaluation of the biological purpose to rT3.

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