Circulating 3,3′,5′-Triiodothyronine (Reverse T_3) in the Human Newborn

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ABSTRACT Serum concentrations of 3,3′,5′-triiodothyronine (reverse T_3, rT_3), 3,3′,5-triiodothyronine (T_3), and thyroxine (T_4) were measured in cord blood and in venous blood samples obtained between 2 h and 30 days of postnatal life from healthy full-term newborn infants. The mean serum rT_3 concentration of (mean±SE) 151±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 T_4 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 T_3 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 rT_3 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 T_3 and T_4 levels were significantly higher at 4 h than at birth. The failure of serum rT_3 concentrations to rise after delivery in response to the early neonatal thyrotropin (TSH) surge and at a time when serum T_3 and T_4 levels increase significantly prompted a study of the rT_3 response to 10 IU of intramuscular TSH in three healthy adult subjects. Just as in the newborns, serum rT_3 failed to rise appreciably in these subjects, even though serum T_3 and T_4 showed the expected increments.

Serum rT_3 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 rT_3 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 rT_3 values were statistically similar to the adult value. The mean serum T_3 concentrations in neonates between 1–30 days old were either higher than or comparable to the values of normal adults. The mean serum T_4 concentrations in neonates between birth and 30 days of age were significantly higher than the mean adult level. The mean serum rT_3 to T_4 ratios (rT_3/T_4) 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 rT_3 in man; (b) high serum rT_3 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 T_3, rT_3)[1] is much higher and that of 3,3′,5-triiodothyronine (T_3) is much lower in human cord blood serum than in the serum of adults (1). Several investigators have demonstrated that the low-cord serum T_3 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 rT_3 concentration during the first few hours or days of life. The present studies were undertaken to obtain this information, and indicate that, unlike serum T_3, serum rT_3 levels gradually fall and become comparable to values in adults during the 2nd week of extrauterine life. Moreover, the circulating rT_3 concentrations show little or no change in association with the neonatal TSH

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[1] *Abbreviations used in this paper:* rT_3, 3,3′,5′-triiodothronine; T_3, 3,3′,5-triiodothyronine; rT_3/T_4, the serum rT_3 to T_4 ratios; T_4, thyroxine; TSH, thyrotropin.

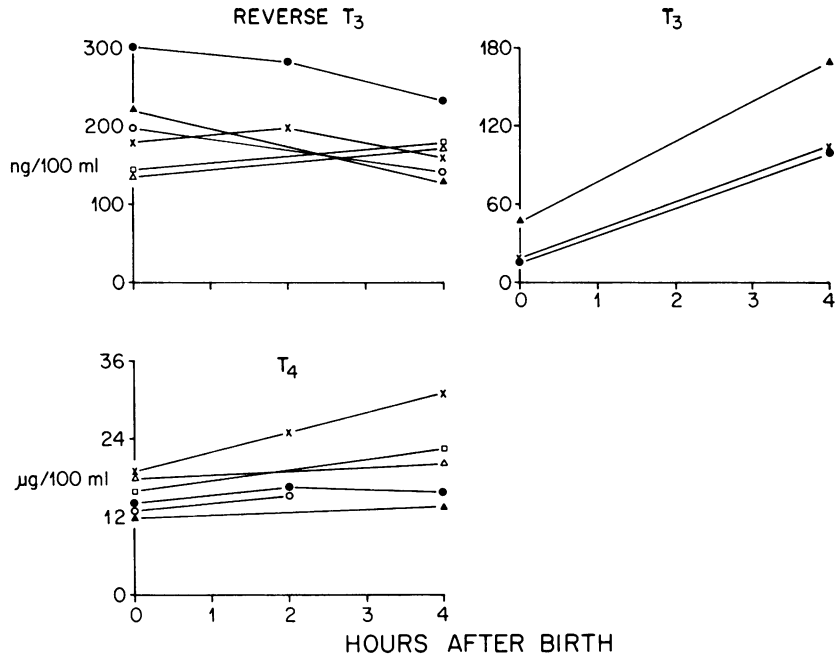

FIGURE 1 Serum concentrations of rT_3, T_3, and T_4 during the first 4 h of neonatal life.

surge, whereas serum T_3 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 rT_3, T_3, and thyroxine (T_4) 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 T_3 accurately; only rT_3 and T_4 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 rT_3, T_3, and T_4 in cord blood. The mean (±SEM) serum rT_3 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 T_4 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 T_3 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 rT_3, T_3, and T_4 during the first 4 h of life. Fig. 1 shows the data on serum concentrations of rT_3, T_3, and/or T_4 during the first 4 h of life in six neonates so studied. Serum rT_3 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 T_3 and T_4 values were higher at 2 or 4 h after birth than the corresponding cord serum concentrations (Fig. 1).

Effect of TSH on serum rT_3, T_3, and T_4 in normal adult subjects. Inasmuch as there is a rapid increase in serum TSH soon after birth, which precedes the increases in serum T_3 and T_4 concentrations (2, 3, 6, Fig. 1), we were intrigued by the observation that there was little change in serum rT_3 during the first 4 h of life. To further examine the effect of an increase in serum TSH on serum rT_3 levels, we studied serum rT_3, T_3, and T_4 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 T_3 and T_4 concentrations maximal at 6 h and 24 h, respectively, after TSH

TABLE I

Effect of Intramuscular Injection of TSH (10 IU) on Serum rT_3, T_3, and T_4 Concentration in Normal Adult Subjects

Case	Age/sex		Time of bleeding post-TSH						
			0 h	2 h	4 h	6 h	12 h	24 h	48 h
	yr								
1	24 M	rT_3*	30	30	29	29	38	38	37
		T_3*	105	150	145	150	145	135	85
		T_4‡	8.0	8.3	9.0	9.0	9.2	10.9	9.5
2	22 F	rT_3	28	35	32	30	29	32	35
		T_3	112	150	185	185	175	175	125
		T_4	5.5	6.6	7.1	7.7	7.4	9.2	7.6
3	24 M	rT_3	27	28	28	27	28	29	—
		T_3	75	100	130	150	145	135	—
		T_4	6.8	7.0	7.4	9.0	9.7	9.7	—

* ng/100 ml.
‡ μg/100 ml.

administration; however, there was no consistent change in serum rT_3 levels.

Serum rT_3, T_3, and T_4 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 rT_3 values in infants 1–4 days of age were comparable to those in cord sera (*vide supra*). However, the mean serum rT_3 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) rT_3 values of 59±13, 63±20, and 54±7.9 ng per 100 ml in 5, 6, and 7-day-old neonates,

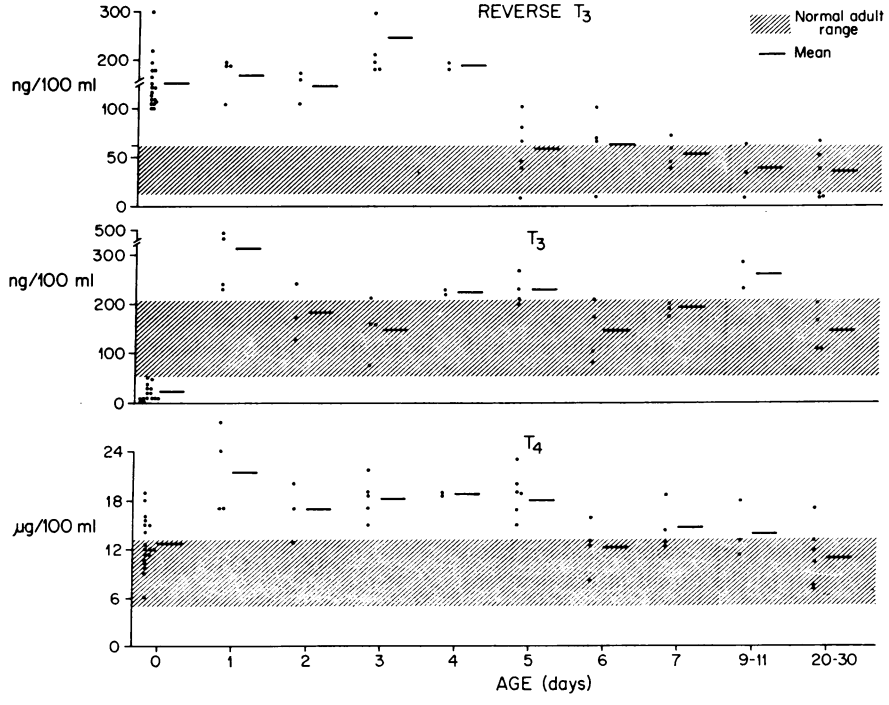

FIGURE 2 Serum concentrations of rT_3, T_3, and T_4 during the first 30 days of neonatal life.

respectively, were significantly ($P < 0.025$), albeit only modestly, higher than the corresponding value 40.5 ±2.0 in normal adult subjects. The mean serum rT_3 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 were comparable to the corresponding value in normal adults. As against rT_3, the values of serum T_3 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 T_4 values were significantly higher at all times of study than the corresponding value (*vide supra*) in normal adult subjects. There was no significant relationship between rT_3 and T_4; this was the case in 1–4-day-old neonates whose rT_3 was clearly high as well as in older neonates whose rT_3 was normal or nearly normal.

The ratio of serum concentrations of rT_3 and T_4 was examined in all cases presented in Fig. 2; the data were expressed as ($rT_3/T_4 \times 100$). 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 rT_3/T_4 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 T_3 and T_4 during the neonatal period are similar to results reported previously (2, 3). The increase in serum T_4 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 T_3 also is, at least in part, attributable to the TSH surge. However, the finding of no change in serum rT_3 levels during the first 4 h of life is intriguing. It could be explained if there were little or no rT_3 in the neonatal thyroid. There is at present no available information regarding the rT_3 content of the throid in the newborn human infant. However, even though rT_3 has been demonstrated in the thyroglobulin of adult subjects (1), there is little or no effect of exogenous TSH on serum rT_3 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 rT_3 were minimal, if the metabolic clearance rate of rT_3 were much faster than that of T_3 or T_4, or if both factors were involved. The rate of disappearance of rT_3 from circulation of adult man has been reported to be much faster than that of T_3 or T_4 (7). Additionally, studies currently in progress in our laboratories suggest that less than 5% of the circulating concentration of rT_3 is derived from thyroidal secretion in either the fetal or adult sheep; 95% or more apparently originates from peripheral monodeiodination of T_4 to rT_3 (Chopra, Sack, and Fisher; unpublished data).

The mechanism(s) responsible for the high serum rT_3 concentrations in the newborn is not clear. Serum rT_3 concentrations in the first 4 days of life are similar to those in cord blood, suggesting that the elevated rT_3 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 rT_3 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 rT_3 levels are similarly elevated in fetal and newborn sheep and that the production rate of rT_3 is markedly increased in fetal sheep relative to the adult sheep (8).

It is interesting to note that the period of normalization of serum rT_3 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 T_4 (9, 10) lead one to consider that maturation of hepatic function may participate significantly in the normalization of high serum rT_3 in the newborn. However, further study is needed to examine the influence of liver on serum rT_3 compared to that of other organs.

The physiological significance of markedly high rT_3 in the fetus and newborn remains unclear. Reverse T_3 has little calorigenic activity (11, 12). However, iodothyronines have several metabolic effects other than increasing oxygen consumption (13–16). Studies examining the effects of rT_3 in these various metabolic events may help in the evaluation of the biological purpose to rT_3.

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