Transient Hypothyroxinemia in Preterm Infants

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Introduction

Transient hypothyroxinemia in preterm infants is common, with low levels of plasma thyroxine (T4) and triiodothyronine (T3), but normal levels of thyroid stimulating hormone. Thyroid hormone is essential for normal human brain development. The levels of receptor-active thyroid hormone, T3, are controlled by numerous factors, and disruption of any of these at critical phases of brain development can lead to severe and persistent motor and cognitive defects. Low plasma T4 in preterm infants is linked with later neurodevelopmental deficits in motor and cognitive function¹. In infants <30 weeks gestation, supplementation with T4 for up to 6 weeks, increased total T4 and free T4, but not T3, and did not improve neurodevelopmental outcome².

Methods

Analysis of iodothyronine sulfotransferase and deiodinase enzyme activities used radiolabelled iodothyronines as substrates³. Serum iodothyronine levels were determined by radioimmunoassay methods.

Results and Discussion

• In preterm infants total T4 levels are low in cord serum and at 7, 14 and 28 postnatal days compared to maternal values, but FT4 values at birth, and postnatally, are similar to maternal values. T3 levels in cord blood are significantly lower than maternal values, and although increasing postnatally, some infants at one month of
age still have values lower than maternal. T4 sulfate (T4S) and T3 sulfate (T3S) are elevated in preterm cord serum compared to mother (5 to 20 folds) and this persists over the first month. These amounts of sulfated iodothyronines are substantial, and levels of T3S are of the same order of magnitude as T3. Sulfated iodothyronines do not interact with thyroid hormone receptors, but sulfatase enzymes can desulfate T3S, and hence T3S represents a potentially significant source of bioactive T3.

- T4 is the predominant secretory product of the thyroid, and is peripherally converted to T3 by outer ring deiodination (ORD) or to inactive reverse T3 (rT3) by inner ring deiodination (IRD). Hepatic type I iodothyronine deiodinase (D1) catalyses ORD and/or IRD of iodothyronines, and is responsible for most of the T3 in serum, through monodeiodination of T4. D1 activities in mid-trimester human fetal liver are high and remain so through gestation, post-natal life and into adulthood. Type III iodothyronine deiodinase (D3) catalyses IRD of iodothyronines and is expressed in early human fetal liver decreasing with gestation. The apparent failure of preterm infants to convert T4 to T3 is therefore not due to developmental inadequacy of D1.

- Sulfation of T4 has a dramatic effect on deiodination. IRD of T4S and T3S by D1 is approximately 200 and 40 times faster, respectively, than the IRD of the non-sulfated compounds, whereas the ORD of T4S is completely blocked. Sulfation is therefore a primary and critical step in the metabolism of thyroid hormones, when D1 activity is normal. We have shown that iodothyronine sulfation is localised predominantly to the choroid plexus in human fetal brain.

- The majority of brain T3 is derived locally from ORD of T4 by the type II iodothyronine deiodinase (D2). Brain also expresses D3, and the balance of these activities has a major role in determining brain T3 levels. In animals there are spatial and temporal changes in expression of D2 and D3 with brain development. We have shown D3 is localised to the cerebellum in human fetal brain, in contrast to adult cerebellum where this enzyme is not expressed.
Conclusion
The metabolism of iodothyronines in the human fetus and preterm infant is substantially different from that of adults and animal models. Our long-term aim is to fully understand the metabolism and interconversion of iodothyronines during human development to allow identification of the critical steps in the hypothyroxinemia of prematurity, which are amenable to therapeutic intervention. A multi-disciplinary approach is necessary to accelerate the achievement of this objective.

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References


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