doi: 10.4183/aeb.2016.1

HYPOTHYROXINAEMIA AND BRAIN DEVELOPMENT

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Abstract

The aim of this review is to indicate the current position on the role of thyroxine (T4) and fetal brain development with particular relevance to the human situation. Adequate maternal iodine nutrition and maternal circulating thyroxine (T4) concentrations are essential to ensure optimum T4 placental passage which in turn will ensure transport of T4 into fetal brain cells. These processes are discussed and the role of thyroid hormone transporters is considered. The emphasis on isolated maternal hypothyroxinaemia (IH) as an important factor affecting brain development is discussed from the animal experimental point of view as well as in the clinical setting. There is evidence of neurocognitive impairment as assessed by different modalities in children up to the age of 8 years and some suggestion of increased psychiatric disorder in older persons whose mothers had IH during gestation. Although international guidelines have not in general recommended thyroxine therapy for IH the recent demonstration of adverse obstetric outcomes in women with isolated maternal hypothyroxinaemia may warrant a revision of this strategy.

Key words: isolated hypothyroxinaemia, pregnancy, neurocognitive, animal, obstetric, guidelines.

INTRODUCTION

The aim of this review is to indicate the current position on the role of thyroxine (T4) and fetal brain development with particular relevance to the human situation. Thyroid hormones have long been known to be involved in brain development. For example there is a wealth of animal and experimental data summarised by Grave in 1977 (1) and further reviewed (2, 3).

The neurobiology of fetal brain development depends on many factors including the availability of thyroxine (T4) delivery to the fetal neurones (4) (Fig.1). While MCT8 facilitates thyroid hormone transport in to the neurone, OATP1C1 appears to be related to thyroid hormone transport into the astrocyte. At this stage it favours the transport of T4 more than T3 but as the deiodinase II is within the astrocyte this enables conversion to occur and then allows T3 to be transferred into the neurone. Other thyroid hormone transporters are probably regulating thyroid hormone transport in to the oligodendrocyte. These processes depend on maternal iodide supply, maternal T4 synthesis, maternal T4 placental transport and the conversion of T4 to T3 in the fetus by the Type II deiodinase. There is also an important role for the thyroid hormone transporters in one or more of these processes (5). Thyroid hormone receptor development in brain occurs very early in gestation, certainly before the fetal thyroid begins to function which is around sixteen to eighteen weeks (6). In early gestation thyroid hormone effects on genes related to neurodevelopment, for example, myelin, can be recorded. The immune system also changes during pregnancy with a shift from the TH1 to TH2 cytokine profile and influence of TH17 (7).

Circulating thyroid hormones are transferred across the placenta in the first trimester they traverse both the syncytio and in cyto-trophoblast (Fig. 2). In the third trimester, only the syncytio-trophoblast is involved (8). The details of the precise roles of the thyroid hormone transporters illustrated in Figure 2 are not clear at present.

The temporal nature of various brain structures in development is illustrated in Figure 3.

Note that T4 levels are derived solely from the mother until mid-gestation when there is an increasing contribution from fetal thyroid. However, the contribution of maternal thyroid hormone, although reducing, is still necessary right up to the end of gestation. Also shown are the activities of the D3 deiodinase and the D2 deiodinase during gestation and in the post-natal period. It is noted that neuron proliferation and the onset of neuron migration to difference brain structures occurs during the first trimester and is sensitive to thyroid hormone. In animal experiments it is seen that many genes are affected by thyroid hormone in early gestation. However, it is not clear at the present time as to why specific genes respond to thyroid hormone only

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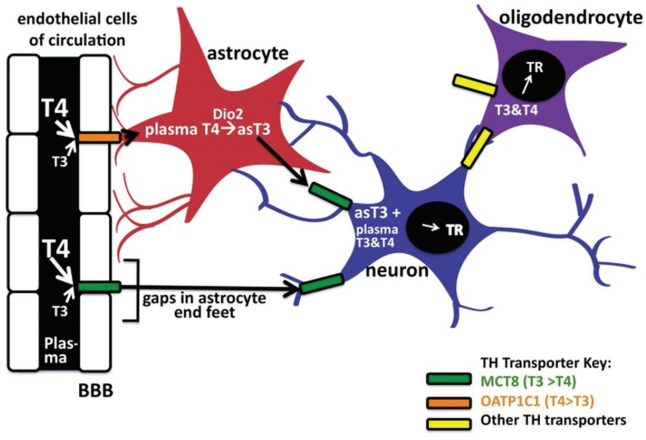

Figure 1. Transport of Thyroid Hormones into Neurones, Oligodendrocytes and Astrocytes. Shown is the transport of T4 and T3 from the endothelial cells of the circulation *via* specific thyroid hormone transporters to different cell types. Note that different transport mechanisms are suggested depending on the neuronal cell type. Intracellular conversion of T4 to T3 *via* deiodinase 2 (Dio2) is essential in the astrocyte. BBB = Blood brain barrier; TH = Thyroid hormones (4).

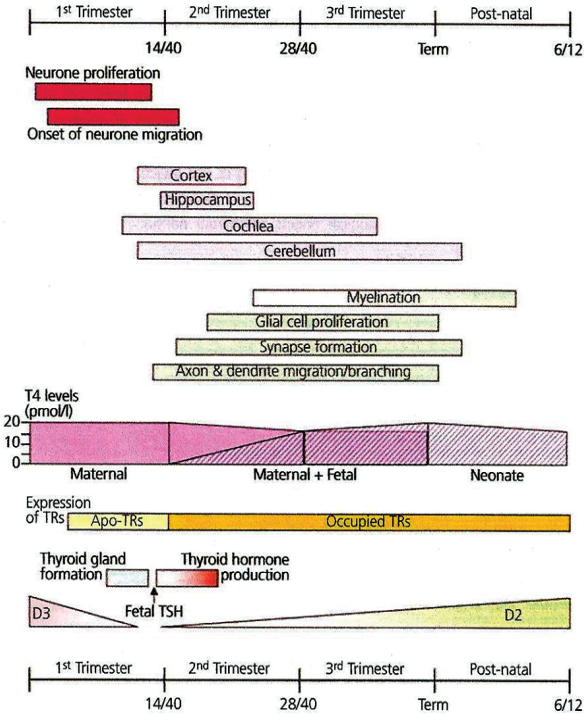

Figure 3. Relation of thyroid hormone supply from maternal and fetal sources to brain structure development ion the human. T4 = Thyroxine; TSH = Thyroid Stimulating Hormone; TR= Thyroid hormone receptor; Apo Trs= unbound thyroid hormone receptors (3).

in a temporally restricted manner. More information on the contribution of non-genomic actions of thyroid hormone is also required to better understand the developmental effect of the hormone on the brain.

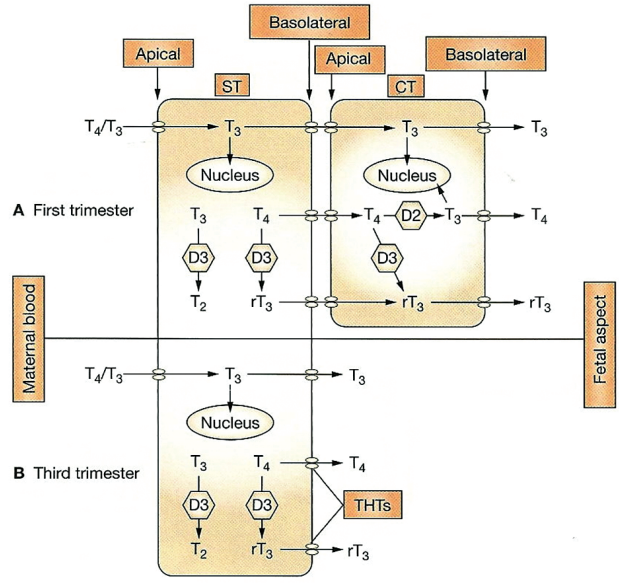

Figure 2. Illustration of Placental transport of thyroid hormones in the first and third trimesters of pregnancy. ST = Syncitiotrophoblast; CT = Cytotrophoblast; T4 = Thyroxine; T3 = Triiodothyronine; rT3 = Reverse triiodothyronine; D2 = Deiodinase 2; D3 = Deiodinase 3; THTs = Thyroid Hormone Transporters (8).

The aim of this review is to emphasise the role of thyroxine (as opposed to TSH) as an important factor for fetal brain development. In the clinical situation, isolated hypothyroxinaemia (IH) occurs between 2.5 to 10% depending on the definition of IH (9). This figure should be compared with the prevalence of thyroid antibodies (anti-thyroid peroxidase antibodies) at 10%. In contrast to the relatively high figures hyperthyroidism occurs in 0.2% and hypothyroidism (a high TSH) occurs in 2 to 2.5% with most of these being sub-clinical, i.e. a high TSH with a normal free thyroxine (10). There are variable definitions of IH but it is noted that total T4 and free T4 are normally distributed (unlike TSH). The first indication of the importance of IH was made by Man *et al.* (11) who noticed a low circulating level of T4 (based on butanol extractable iodine measurements) below the trimester specific reference range. IH should be diagnosed when the TSH is within the gestational reference range. Thyroid antibodies may be positive or negative. During the last 15 years there have been many studies which have included maternal hypothyroxinaemia defined as either the 10th , 5th or 2.5th lowest centile of FT_4 (eg 12-14). Causes of IH include iodine deficiency, modification of the thyroxine affinity for TBG, placental five prime deiodinase type III activity and placental angiogenic factors (15). Recently IH has also been associated with

iron deficiency (16); there is also the possibility of exposure to environmental contaminants or disruptors resulting in IH (17).

With respect to iodine, the WHO recommendation for iodine intake during pregnancy is 250 mcg per day (18). In Europe there is a high prevalence of mild iodine deficiency (19), especially in pregnancy (20) where it has deleterious effects on the neurocognitive performance of children (21). For example, a study in England has reported that there is a reduction in verbal IQ, total IQ and reading comprehension in children eight years old whose mothers were noted to have low urinary iodine in pregnancy (22). The general iodine situation in Europe has shown discrepancies between school children and pregnant women; a re-emerging of iodine deficiency in industrialised countries. While the iodine status in some countries is satisfactory many have an inadequate iodine status in pregnancy. It is estimated that about 400 million people from twenty countries in Europe still have limited access to iodised salt (19). Although it is conceded that there is a necessity to lower salt consumption for cardiovascular reasons, this should not negate the strategy of introducing iodised salt as the concentration of iodine in the salt can be adjusted accordingly (23). When iodised salt is introduced there is a gratifying response in median urinary iodine and this was shown in Romania over ten years ago (24). However, in that country pregnant women are considered to be iodine deficient. The European Union has recognised this problem by the award of a grant (EUThyroid) from 2015 to 2018. The main aims of this study are to develop a European map of iodine status, to build the capacity of national iodine studies, to perform harmonised studies about iodine status and establish thyroglobulin as a biomarker for individual iodine status. In addition, it is hoped to provide evidence for the effectiveness of IDD prevention and monitoring programmes in Europe.

As indicated above, first documentation of the adverse effect of maternal IH on the psychoneurological performance of progeny was shown by Man *et al.* (11) who demonstrated developmental deficits as early as eight months, but at the ages of four and seven, noted lower psychological scores compared to non-hypothyroxinaemic progeny. In six sibling sets the outcome was better when thyroxine therapy was given during pregnancy (25). However, scant attention was paid to this study because of the possibility of socio-economic confounding factors as well as the relative inaccuracy of assessment of thyroid function at that time. The subject was re-awakened by the demonstration that psychomotor development in infancy appeared to be correlated with the maternal free thyroxine at twelve weeks gestation (12). Since then, examples of maternal IH and decrement in cognitive function have been obtained. For example, expressive language delay (26), poorer cognitive performance at five and a half years (27), lower mental scores in two year old infants of women with FT_4 less than 5^{th} centile (28), children aged five to six showing a poor performance in simple reaction time test (29) and children aged eight who scored 4.3 points lower in an IQ test compared to children from normal thyroxinaemic mothers (30). In addition there has been some evidence of maternal hypothyroxinaemia being associated with abnormal neuropsychiatric function. In six year old children there was a four times incidence of autistic symptoms (31). A Finnish nested control study showed an odds ratio of 1.75 (CI 1.22 to 2.5 $p = 0.002$) in relation to the development of schizophrenia (32). In eight year old children, symptoms of attention deficit hyperactivity disorder were more prevalent (33). This has been noted previously (34). In contrast there are some studies where maternal IH was not associated with any neurocognitive defect. There is no association between IH (free T4 at the fifth centile) and neurodevelopmental delay at nineteen months (35). However, this comprised a relatively small sample number (forty-three children). There was no association between mid-gestational free thyroxine and neurocognitive development at two years (36). However, as indicated above the influence of fetal thyroid production is already evident at mid-gestation. In a large number of children, recently reported, there was no association between maternal gestational free T4 and subsequent intellectual development at one year in four hundred and fifty-five children and at six to eight years in two hundred and eight-nine children (37).

EVIDENCE OF ADVERSE EFFECTS ON THE BRAIN OF IH IN ANIMAL MODELS

Studies in mice and rats have shown changes in neuronal migration, changes in cytoarchitecture of the cortex and hippocampus, and reduction of cerebellar granular precursors (38, 39). In addition, there is an alteration in the neurogenesis of axon and dendrite formation as well as myelination synaptogenesis and neurotransmission. A recent study (40) has shown that gestational hypothyroxinaemia can affect the distribution of the glutaminergic synaptic proteins and neuronal plasticity through an astrocyte dependent

mechanism. This study involved co-culture model of astrocyte and hippocampal neurons to identify the sub-unit of the NMDA glutamate receptor (GLUN1) and the synaptic adaptor protein CD3 squiggle. It emphasised the importance of neuron astrocyte cross-talk and deleterious effects of gestational hypothyroxinaemia. Changes in gene expression in the fetal cortex using an acute thyroid hormone injection model have been recently documented (41). In the mouse model identification of transcription factors mediating actions of thyroid hormones were documented. In addition, novel tier thyroid hormone response elements were identified in these genes in addition to specific micro RNAs affected by thyroid hormone treatment. It appears that a short period of low maternal thyroxine alters transcriptional response of the fetal cerebral cortex to exogenous T4 treatment. These data, if applicable to humans, may have important implications for the administration of thyroxine to pregnant women.

RECENT CLINICAL STUDIES

In an effort to evaluate the strategy of screening for thyroid function in early gestation with levothyroxine (T4) intervention therapy a prospective randomised controlled trial of T4 treatment *versus* no treatment in mothers with thyroid dysfunction was undertaken with the primary outcome being the assessment of IQ of the children tested between three and three and a half years (41). In this randomised trial, antenatal screening at a median gestation age of twelve weeks and treatment for hypothyroidism did not result in improved cognitive function in children at three years of age. Possible reasons for this negative outcome include the relatively late age of screening during gestation, as well as the non-specificity of the psychological tests. The results of a further randomised trial being undertaken in the USA are awaited with interest. Neuroimaging studies have shown some reduction in high hippocampal volume in children from mothers with inadequately treated hypothyroidism in pregnancy (42). Of more relevance to the current discussion is the demonstration (43) of an inverse association between FT_4 and offspring IQ in a large data set. This was accompanied by the indication that total grey matter volume was also associated with mean child IQ at the age of six to eight as was cortex volume. Of interest is the fact that TSH was not as obviously associated with mean IQ as FT_4. Furthermore, the data relating to free T4 indicates a potential deleterious effect of high normal or excess maternal FT_4 in pregnancy on child IQ. Another factor which may influence the IQ is the activity of the deiodinase II which converts T4 to T3. There are data relating the deiodinase II gene polymorphism THR92ALAD2 (44). In the adult hypothyroid population receiving thyroxine there is some evidence that this polymorphism is associated with continuing symptomatology of hypothyroidism despite normal thyroid hormone levels, leading to a preference for combination therapy in the treatment of hypothyroidism (45). Recent data from 3,043 children from the Avon Longitudinal Study of Parents and Children and 221 children from the CATS II study indicated that children homozygous for Thr92Ala and exposed to lower FT_4 levels had increased odds of an IQ <85 (46). Meta-analysis of these cohorts revealed increased odds of an IQ <85 OR=2.69 (95%CI 1.46, 4.89) p=0.002 for FT_4 in the lowest quartile and homozygous for Thr92Ala and OR=7.19(95%CI 2.36, 22.0) p=0.0005 for FT_4 in the lowest 2.5% and homozygous for Thr92Ala (in preparation).

DOES IH AFFECT OBSTETRIC OUTCOMES?

Early studies showed not apparent adverse outcomes, but Pop had noticed an increase in breach and caesarean section associated with FT_4 less than 10^{th} centile (47). An increase in pre-term labour and macrosomia has also been noted (48) in addition to another study indicating more fetal distress, small for gestational age and muscular skeletal malformations (35). An increase in premature delivery and larger fetal and infant head size has also been shown (49). Recently analysis of Welsh participants in the Controlled Antenatal Thyroid Study has indicated that a high TSH was associated with miscarriage or stillbirth after twelve weeks in the untreated women (OR = 5.46, 95% CI 1.66 – 17.9 p = 0.004) with no miscarriages occurring in treated women, In women with IH offspring of untreated women had lower birthweight, earlier delivery and were more likely to have an early Caesarean section than those who received levothyroxine (50). These data suggest correction of IH might improve obstetric outcomes although replication particularly in iodine sufficient areas are required.

The consensus on whether to treat isolated hypothyroxinaemia is not clear. There is the opinion that the available evidence does not support treatment of the condition (52) Guidelines from the American Thyroid Association (53) and the United States Endocrine Society (53) broadly suggest that it probably should not be treated, although partial replacement

may be initiated at the discretion of the care giver. The European Thyroid Association Guidelines (54) suggested no benefit in terms of obstetric outcome but recommended considering treatment in the first trimester because of the neuropsychological reasons. It was not recommended for trimesters two and three. In view of the adverse obstetric outcomes of IH already discussed it may be suggested to treat IH when discovered at any time during gestation.

In conclusion, maternal hypothyroxinaemia is associated with impaired neuropsychological impairment of the offspring. Animal data show adverse effects on brain structure and function. There are some associations with IH and adverse obstetric outcomes. There are no randomised controlled clinical trials which show the benefit of treatment and there are no studies of outcome or treatment of IH and thyroid antibodies together. It is suggested now that careful evaluation of trimester specific free thyroxine range should be always undertaken. In the first trimester IH less than a 2.5th together with thyroid antibody positivity should be treated. IH less than 2.5th possibly should be treated at the discretion of the care giver.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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