Abstract

Iodine deficiency interferes with the prenatal and postnatal neurointellectual development of children through maternal, fetal and neonatal hypothyroxinemia. The purpose of this review is to provide information on clinical hypothyroidism in childhood and irreversible brain damage. We summarize the available clinical data on neurological, neuropathological and neuroimaging abnormalities due to various hypothyroid syndromes in children. This information will help us consider the possible consequences of iodine deficiency occurring during the critical period of brain development. In addition, recent advances in molecular and cell biology have led to an improved understanding of normal thyroid physiology and of the genes involved in thyroid gland development. This review will add new topics regarding the action of thyroid hormone on the early fetal stage of brain development.

Introduction

Children born in iodine-deficient areas are at risk of neurological deficits and mental retardation, because iodine is a constituent of thyroid hormones (THs) which are necessary for the growth and development of most organs, especially the brain. Iodine deficiency will impact on the neurointellectual development of infants and children if it occurs during fetal and early postnatal life. TH may be needed during the first trimester, since the first trimester surge of maternal free thyroxine (T4) is proposed as a biologically relevant event.

Some research indicates (Calvo et al., 2002; Morreale de Escobar et al., 1991, 2004) that human fetuses acquire the ability to synthesize THs at 10–12 weeks of gestation. In the second and third trimester, the fetus can potentially derive TH both from its own thyroid and the thyroid of the mother. Prior to 12 weeks gestation, the mother is the sole source of TH for the developing fetus. Current evidence indicates that there is substantial transfer of maternal TH across the placenta, and fetal TH exists in first trimester embryonic units (Contempre et al., 1993). The mother provides small amounts of T4 throughout the pregnancy. The main active TH, triiodothyronine (T3), is converted from T4 and the concentration is strictly regulated by a complex system. After birth, the neonate produces TH independently.

There are three types of TH deficiency known to impact fetal development, including (Figure 108.1) isolated fetal hypothyroidism (congenital hypothyroidism: CH), combined maternal and fetal hypothyroidism (endemic cretinism: EC), and isolated maternal hypothyroidism (primary maternal hypothyroidism). According to the review of CH (American Academy of Pediatrics, 2006), TH deficiency originates from birth and is mainly due to the failure of
the fetal thyroid gland. Normal or near-normal cognitive outcome is possible in even the most severely affected infants with CH, as long as maternal thyroid function is normal, and early and adequate postnatal therapy is available for the infant. In contrast, more severe damage is expected when both maternal and fetal hypothyroidism are combined throughout the pregnancy. Known as EC, this is typically caused by poor maternal iodine intake. Maternal hypothyroidism alone during early gestation can lead to mild but significant impairment of the fetus during the first trimester, although there are no cases of neonates identified with CH, because fetuses secrete THs on their own from the second trimester on, making any TH deficiency prior to that impossible to identify (Moreale de Escobar et al., 1991). This clinical research provides information about the effects of THs in the developing brain.

**Clinical Neurological Findings of Hypothyroidism in Children**

Table 108.1 shows a variety of neurological deficits in human thyroid diseases.

### Congenital hypothyroidism (CH)

CH is caused by decreased TH production. Approximately 1 in 3000–4000 newborns is born with CH in most regions of the world. Primary CH is caused by thyroid dysgenesis due to a missing (athyrotic), hypoplastic, or ectopic thyroid gland or by thyroid dysmorphogenesis (Rovet and Daneman, 2003). Recently, several of the genes involved in abnormal thyroid gland development and function have also been identified (Park and Chatterjee, 2005). Some novel syndromes combining thyroid and neurological abnormalities associated with mutations in these genes were reported, such as the monocarboxylate transporter 8 gene by Dumitrescu et al. (2004) and the thyroid transcription factor 1 gene by Devriendt et al. (1998). Central forms of CH at the level of the pituitary gland or hypothalamus are less common.

At birth, symptoms of hypothyroidism are difficult to detect. Affected infants tend to have prolonged neonatal jaundice, and a large posterior fontanel; cool, dry, and

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**Table 108.1 Clinical summary of hypothyroid syndromes**

<table>
<thead>
<tr>
<th></th>
<th>Endemic cretinism (neurologic cretinism)</th>
<th>Congenital hypothyroidism&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Myxedema (adult hypothyroidism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth at birth</td>
<td>Not available</td>
<td>Almost normal&lt;sup&gt;a&lt;/sup&gt; &gt; 4 kg</td>
<td>Normal</td>
</tr>
<tr>
<td>Postnatal growth</td>
<td>Delay&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Delay</td>
<td>Normal</td>
</tr>
<tr>
<td>Suspected onset</td>
<td>Intrauterine</td>
<td>At birth—&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Any age</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>Characteristic inability</td>
<td>Hypotonia (+spasticity)</td>
<td>Unsteady gait (peripheral neuropathy/cerebellar ataxia)</td>
</tr>
<tr>
<td>Bone growth maturation</td>
<td>Delay</td>
<td>Delay</td>
<td>Normal</td>
</tr>
<tr>
<td>Pyramidal tract signs</td>
<td>Positive (89%)</td>
<td>30%</td>
<td>Negative</td>
</tr>
<tr>
<td>Distribution</td>
<td>Proximal and lower limbs</td>
<td>Not available</td>
<td>Negative</td>
</tr>
<tr>
<td>Deep tendon reflex</td>
<td>Delay in the reflexion phase</td>
<td>Delay in the reflexion phase</td>
<td>Delay in the reflexion phase</td>
</tr>
<tr>
<td>Cerebellar function</td>
<td>Normal</td>
<td>Cerebellar ataxia</td>
<td>Cerebellar ataxia</td>
</tr>
<tr>
<td>Intellectual impairment</td>
<td>Severe (mean IQ = 29.3)</td>
<td>Positive (various levels)</td>
<td>Drowsiness/dementia/poor concentration</td>
</tr>
<tr>
<td>Hearing impairment (%)</td>
<td>51</td>
<td>20</td>
<td>Hypothyroidism to euthyroidism</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypothyroidism to euthyroidism</td>
<td>Hypothyroidism to euthyroidism</td>
<td>Hypothyroidism to euthyroidism</td>
</tr>
</tbody>
</table>

<sup>a</sup>Growth of the athyroid fetus is normal body weight, length, and head circumference, but bone maturation is delayed in 30–50%.

<sup>b</sup>If untreated.

<sup>c</sup>Patients with severe form of congenital hypothyroidism are affected from prenatal period.
mottled skin; feeding problems; constipation; umbilical hernias; and decreased motor activity. Symptoms are more evident by the second month of life, and include decreased activity and hypotonia with diminished spontaneous movements. In subsequent months, if untreated, further neurological impairment becomes more evident and manifests signs similar to those of diffuse cerebral injury. Motor skills and intellectual development in these children are delayed. Bilateral dysfunction of corticospinal tracts is evidenced by the spasticity of the limbs, difficulty with fine volitional movements and extensor planter responses; deafness, major motor and atonic seizures, ataxia, strabismus, coarse tremor, and aphasia have also been noted in these children (Goldensohn and Appel, 1977; Menkes, 1995; Dussault, 1991).

If CH is left untreated, it results in severe and irreversible mental retardation; e.g., the mean intelligence quotient (IQ) of children with CH was 76 (Klein, 1980). Forty percent of children with CH require special education and display deficits in fine motor control, as well as learning disabilities (Song et al., 2001). Since the 1970s, most industrialized countries have established systematic screening of neonates. Previously it was believed that newborn screening and early postnatal treatment were successful in preventing mental retardation. Nevertheless, a number of prospective studies examining the intellectual outcomes in children with screened CH have revealed that their IQ levels average approximately six points below expectation, and that they have a greater risk of subtle neuropsychological and motor deficits (Derksen-Lubsen and Verkert, 1996). This wide variability appears to be linked to disease-related factors (such as the etiology and severity of the disease at diagnosis), and treatment-related factors (age at treatment initiation, dosage and length of time until TH levels normalize).

Subsequent studies found that children with more severe forms of the disease still have clinically significant intellectual impairment when compared with children in a control group or those with more moderate forms of the disease (Dubuis et al., 1996; Oerbeck et al., 2003). It was thought that these deficits reflected inadequate dosage because the children were initiated with relatively low doses of L-T4 (5–10 ?g/kg/day). After this observation, the American Academy of Pediatrics (1993) and the European Society for Pediatric Endocrinology (Grunerts et al., 1993) recommended higher initial doses of L-T4 (10–15 ?g/kg/day). A higher dose was deemed beneficial in closing the IQ gap between moderate and severe forms of CH (Simoneau-Roy et al., 2004). However, despite optimized treatment, some children with CH will still have subtle, persistent cognitive deficits (Rovet and Daneman, 2003). The safety of a higher starting dose level for children with mild forms of CH remains an issue because of the undesirable effects of hyperthyroxinemia on behavior and cognition (Gunn et al., 1996).

Alternatively, some signs of minimal brain damage in children with CH possibly reflect their TH insufficiency in utero. For example, although the mother provides a supplemental source of TH during the pregnancy, this does not seem to fulfill all fetal needs in the latter part of gestation. This may adversely affect brain development, as is the case in maternal hypothyroidism. Haddow et al. (1999) published a study of maternal hypothyroidism and the effects on the fetus. Haddow suggests that untreated mild maternal thyroid failure might reduce her child’s IQ score and affect intelligence, attitude and visual–motor skills. Subsequently, Rovet (2002) found that maternal hypothyroidism in early fetal development is correlated with later problems of visual attention and gross motor skills. TH deficiency later in pregnancy also increases the risk of fine motor deficits.

Children with CH often have school-related learning problems, particularly with arithmetic (Oerbeck et al., 2003; Song et al., 2001). Even in early-treated patients with CH, hearing problems were relatively common (Francois et al., 1994). Chou and Wang (2002) found that 25% of the children they studied had abnormal auditory brainstem potentials. In another study (Rovet and Daneman, 2003), children with CH-associated prenatal TH deficiency continued to experience effects during adolescence, particularly with their ability to process visuospatial relationships. These children also had specific neurocognitive impairment in selective memory, sensory motor skills and attention domains. Their particular deficits seem to implicate different neural structures and systems. Rovet suggests unique time windows of TH sensitivity by different brain systems.

Endemic cretinism (EC)

The most serious consequence of iodine deficiency on the brain and physical development is EC. Iodine deficiency is still widely preventable; in 1990, 1.6 billion people globally (28.9% of the world’s population) were at risk of iodine deficiency (Delange, 2001). Iodine deficiency impacts on thyroid function in pregnant women and neonates, and on the neurointellectual development of infants and children.

EC is characterized by mental deficiency, together with neurological syndromes described in detail by Delange (1991). Iodine deficiency results in defects of hearing and speech, characteristic disorders of standing and gait of varying degree, and hypothyroidism and stunted growth. There are two types of EC; one is marked by dominant neurological disorders (neurological cretinism), and the other by symptoms of severe thyroid insufficiency (myxedematous cretinism). Neurological cretinism shows neurological defects such as: (1) mental impairment; (2) deaf-mutism; (3) impaired voluntary movement activity involving paresis or paralysis of pyramidal origin, chiefly in the lower limbs, with hypertonia, clonus, and plantar cutaneous reflexes in
Other Causes of Hypothyroidism

Other Causes of Hypothyroidism

extension, along with occasional extrapyramidal signs; (4) spastic or ataxic gait and, in the most severe cases, extreme difficulty walking or standing; and finally (5) strabismus.

Neurological cretinism has a characteristic standing posture characterized by flexion of the neck and flexed hips and knees with abductor tightness (Hollowell and Hannon, 1997). In this situation, the trunk tilts forward, the feet are flat and everted, and the gait is broad-based and knock-kneed. The arms are often held in a curious posture with shoulders abducted and the elbows and wrists flexed. Most individuals have characteristic gait disturbances ranging from an abnormal posture and rhythm to an inability to walk.

The damage increases with the degree of iodine deficiency. Only if correction takes place before or during early gestation can the occurrence of neurological cretinism be prevented (Pharoah et al., 1971). In Ecuador, an attempt to study the effects of preventing iodine deficiency in early fetal life revealed that there had been no new cases of EC in the treated village, while six cases appeared in the control group (Ramirez et al., 1972).

Juvenile hypothyroidism

During the early months of an infant’s postnatal life, TH deficiency may cause organ-related dysfunction and growth failure. Hypothyroidism of this period is caused by congenital problems (late appearance), autoimmune diseases and decreased TH production due to lack of iodine or drug effects.

The effects of decreased TH production are similar in children and adults, but TH deficiency results in growth and development abnormalities unique to younger childhood, especially when it occurs during infancy. Hypothyroidism that occurs after age three is not associated with mental retardation, but rather results in physical growth retardation (Fisher, 1991).

We summarized the clinical data of infancy onset of hypothyroidism from some reports (Foley et al., 1994; Arii et al., 2002; Zegher et al., 1992) in order to ascertain the neurological prognosis when TH deficiency is present in the early months of life (Table 108.2). Out of seven infants aged less than one year at the onset of hypothyroidism caused by chronic autoimmune thyroiditis, dyshormonogenesis, or of unknown origin, five had permanent mental retardation and one had hearing problems. Moreover, out of eight infants who had longer intervals between the onset of symptoms and the initiation of T4 therapy, five had permanent mental retardation. Foley warned that if infants with hypothyroidism are not treated early, their intelligence and neuropsychological function may be permanently impaired. The patients in our study (Arii et al., 2002) showed deceleration in linear growth, spasticity in the lower limbs with deformities, and intellectual impairment (Figure 108.2). The neurological symptoms were not progressive, but were irreversible despite T4 treatment.

Early-childhood onset of hypothyroidism with later T4 treatment is characterized by intellectual impairment, motor disturbances and hearing problems. The spectrum of neurological deficits of TH deficiency in early childhood is similar to that of CH and EC.

Zoeller and Rovet (2004) summarized the models of maternal hypothyroidism, hypothyroxinemia and CH. If TH deficiency occurs early in pregnancy, the children

Table 108.2 Neurological symptoms of acquired infant-onset hypothyroidism

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at onset (m)</th>
<th>Age at diagnosis (m)</th>
<th>Treatment</th>
<th>Neurological finding</th>
<th>Etiology</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6–12</td>
<td>1.1 y</td>
<td>Soon after</td>
<td>Normal</td>
<td>Autoimmune thyroiditis</td>
<td>Foley et al., (1994)</td>
</tr>
<tr>
<td>2</td>
<td>6–12</td>
<td>2 y</td>
<td>Several months</td>
<td>Neurosensory hearing loss, speech delay</td>
<td>Autoimmune thyroiditis</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6–9</td>
<td>1.2 y</td>
<td>Several months</td>
<td>Mild motor delay, speech delay</td>
<td>Autoimmune thyroiditis</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6–9</td>
<td>9 m</td>
<td>Soon after</td>
<td>Mild mental delay</td>
<td>Autoimmune thyroiditis</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6–9</td>
<td>5 y</td>
<td>Several years</td>
<td>Moderate mental delay (DQ46), spasticity in lower limbs with severe contractures</td>
<td>Autoimmune thyroiditis</td>
<td>Arii et al., (2002)</td>
</tr>
<tr>
<td>6</td>
<td>12–18</td>
<td>15 y</td>
<td>Several years</td>
<td>Mild mental delay (DQ58), spasticity in lower limbs with severe contractures</td>
<td>Autoimmune thyroiditis</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6–12</td>
<td>2 y</td>
<td>Several months</td>
<td>Mild mental delay (DQ65), spasticity in lower limbs</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>~3</td>
<td>3 m</td>
<td>Soon after</td>
<td>Normal</td>
<td>Dyshormonogenesis</td>
<td>Zegher et al., (1992)</td>
</tr>
<tr>
<td>9</td>
<td>12–18</td>
<td>3 y</td>
<td>Several years</td>
<td>Normal</td>
<td>Dyshormonogenesis</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>12–18</td>
<td>5 y</td>
<td>Several years</td>
<td>Normal</td>
<td>Dyshormonogenesis</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>12–18</td>
<td>4 y</td>
<td>Several years</td>
<td>Normal</td>
<td>Dyshormonogenesis</td>
<td></td>
</tr>
</tbody>
</table>
display problems in visual attention, visual processing and gross motor skills. If it occurs later in pregnancy, children are at additional risk of subnormal visual and visuospatial skills, as well as slower response times and fine motor deficits. If it occurs after birth, it predominantly affects children’s language and memory skills.

Neuropathological Findings in Hypothyroidism

Stein et al. (1991) reviewed the neuropathological findings observed in human autopsies of people with CH and EC. These findings include normal brain architecture, minimal cerebral atrophy, a reduced number of pyramidal and Betz neurons in each layer V, and abnormal axonal and dendritic development of the pyramidal neurons in the cerebral cortex and brainstem. Retarded myelination (Duckett, 1994) and diminished size of pyramidal tracts may also be observed (Eayrs, 1960).

Bernal (2005) reviewed the morphological aspects in the brain of the hypothyroid rat and found: (1) altered cell migration, particularly in the cerebellum and cerebral cortex; (2) increments in cell density, caused by a reduction in the neuropil; (3) markedly reduced dendritic arborization in the Purkinje cells of the cerebellum, and decreased and altered distribution of the pyramidal dendritic spines in the cortex layer V; and finally (4) delayed myelination and poor myelin deposit in the white matter and fewer myelinated axons. This study further showed that hypothyroidism produces changes in the colossal projecting neurons, which may be due to the maintenance of juvenile patterns of projections. In addition, a recent report (Lavado-Autric et al., 2003) indicates that focusing on maternal hypothyroidism can produce migration defects in the fetal cortex, when the neurons migrate out to an inappropriate site instead of forming layers at the appropriate site.

Abnormalities in specific regions of the cerebral cortex and its corticospinal projections, associative cortex and myelination are likely to contribute to neurological impairments in both rats and humans afflicted with hypothyroid disorders. However, although these findings provided us with information about the role of TH in brain development, they do not provide insight into the developmental timing of TH action on specific brain areas that may underlie the aforementioned observations in children.

In humans and rodents (Stein et al., 1991), neurodevelopmental events occur in a defined sequence: neurogenesis; migration; axonal and dendritic outgrowth; elongation and branching; synaptogenesis; and finally myelination. These neuroanatomical events of normal brain development are ongoing from early gestation to postnatal life. A variety of different agents, including TH, may alter these events. The manifestations of hypothyroidism relate to the type, timing, severity and duration of TH deficiency, and the different events that occur in different brain regions and cell populations. Abnormal events due to TH deficiency can disrupt the normal sequence of neuroanatomical processes. Therefore, earlier, more severe and longer deficiencies lead to more severe neuroanatomical disruption and subsequent behavioral and neurological impairment. Because of the severity of the condition and the timing of development (brainstem, cerebral cortex and cerebellum develop sequentially), there may be interference with both brainstem and cerebral cortex development in EC, while the cerebral cortex may primarily be affected in CH.

Zoeller and Rovet (2004) proposed that one of the best examples of temporal changes in the sensitivity to TH during brain development is that of the cerebellum, because the rodent cerebellum grows rapidly during the first two postnatal weeks (Figure 108.3). Studies of the cerebella of hypothyroid rats demonstrate that TH plays a role in cell proliferation in the external granule layer, migration of these cells to the internal granule layer, and apoptosis in their destination during the developmental period from birth to weaning. In addition, although myelin basic protein is directly regulated by TH, its expression is not sensitive to TH in the late gestational fetus. Schwartz et al. (1997) found that the critical period of TH responsiveness is temporally shifted accordingly, because the process does not occur simultaneously in all brain areas.

Neuroimaging in Hypothyroidism

Cerebral computed tomography (CT) scanning in patients with EC was reported to show basal ganglia calcification in 30% (15 of 50 cases) and mild cerebral atrophy in 8% (4 of 50 cases) (Halpern et al., 1991). All three children in our study of infant-onset hypothyroidism who exhibited
Other Causes of Hypothyroidism

Other Causes of Hypothyroidism

Other Causes of Hypothyroidism

motor and mental deficits (Figure 108.2, Pt 5–7 in Table 108.2, Arii et al., 2002) had multiple calcifications in the bilateral basal ganglia and subcortical areas in a brain CT (Figure 108.4). This distribution was common to all patients. Magnetic resonance (MR) images in these patients showed only mild atrophy (not shown).

Some causes of intracranial calcifications can be speculated, such as latent hypoxic damage, vasculitis and direct brain injury due to energy insufficiency because of hypothyroidism. In previous studies, the correlation between basal ganglia calcifications and spasticity or other neurological symptoms in EC was controversial (Halpern et al., 1991; DeLong et al., 1985) although they are found in asymptomatic or nonspecific symptoms, such as dementia, in adult-onset myxedema (Burke et al., 1988). However, the frequency of hypothyroidism-associated intracranial calcification is 30% in patients with EC (Halpern et al., 1991).
Four of six adult patients in another study showed hypothyroidism (Burke et al., 1988). Therefore, the intracranial calcifications may result from metabolic derangement as a result of hypothyroidism. MR images have demonstrated hyperintensity on T1-weighted images and hypointensity on T2-weighted images in the basal ganglia of patients with EC (Ma et al., 1993), and a neuropathological study of CH has demonstrated that cerebral blood vessels are thickened with calcium and iron deposits (Dekaban, 1970). Recently, TH was found to lead to an upregulation of matrix Gla protein in arterial smooth muscle cells. The TH facilitates the matrix Gla protein gene expression in smooth muscle through TH nuclear receptors, leading to prevention of vascular calcification in vivo (Sato et al., 2005). Therefore, hypothyroidism may directly cause vascular calcifications.

Brain MR spectroscopy showed that intratertiary hypothyroid neonates from mothers with iodine deficiency had significantly decreased N-acetylaspate levels, an index of neuronal development, in parietal white matter and the thalamus. This can be normalized with early T4 treatment (Akinci et al., 2006). The findings may suggest the efficacy of early postnatal therapy, which might be able to reverse hypothyroid brain damage. In addition, functional MR images revealed that working memory is impaired in adult patients with subclinical hypothyroidism, mainly due to disorders of the frontoparietal network (Zhu et al., 2006). Again these deficits were improved with T4 treatment. Hence, advances in neuroimaging may provide more information on the temporal effects and functional reversibility in the human brain.

**Molecular Biology**

Brain development proceeds through precisely coordinated neuroanatomical events in time and space. These events are determined by genetic and epigenetic factors, such as TH. TH deficiency during critical periods of development leads to profound and potentially irreversible defects of brain maturation. There is renewed interest in the action of THs on brain development and function. Over the last 10 years, genes regulated by THs have been identified in the rodent brain, facilitating an understanding of the role of TH nuclear receptors (TR) through the analysis of phenotypes of mutant mice for the different isoform receptors.

The concentrations of T3 are controlled by deiodinases type 1 (D1), 2 (D2), and 3 (D3). D2 transforms T4 into T3, whereas D3 transforms T4 and T3 into inactive products, reverse T3 and 3′-diodothyronine, respectively (Bernal et al., 2003). Development regulates the expression and local activity of D2 and D3 in the brain (Kaplan and Yaskoski, 1981). In addition, despite the restricted access of molecules from the blood to the brain parenchyma due to the blood–brain barrier, small amounts of T4 and T3 may enter the brain in the fetus through specific transporters (Sugiyama et al., 2003). T3 is formed by deiodination of T4 and delivered to neural cells, then reaching the TRs. T3, acting in the target cells by binding to TRs, controls the expression of genes involved in myelination, cell differentiation, migration and signaling. Many effects of TH on developmental processes in the brain can be correlated with the controlled expression of specific molecules. Bernal (2003) described the role of TH and TR, as presented in Table 108.3.

Bernal et al. (2003) and Bernal (2005) reviewed TH action on brain development. In mammals, T3 receptors are the products of two genes known as TRα and TRβ that encode nine protein products, which arise by alternative splicing and different use of the promoter. It is known that there are two types of receptors and four different receptor isoforms, but the physiological role of nonreceptor proteins is still unclear. Different receptor isoforms are unlikely to serve different physiological functions by selectively regulating specific genes. The most prevalent view is that the receptor isoforms are mostly equivalent in their biological activity in vivo, and that their physiological role is due to their different patterns of temporal and regional expressions. In addition to transducing the T3 signal, the TRs are also active in the unliganded state, mainly as repressors of transcription.

The role of TH is the coordination of seemingly unrelated maturation processes. TH can influence these processes only temporarily during overlapping windows of development with regional specificity. Studies of clinical thyroid disorders and experimental models show that the timing of TH deficiency produces different effects, as illustrated in Figure 108.3 (Zoeller and Rovet, 2004). Furthermore, it is important to confirm the precise time when the TH’s critical point of activity in brain development occurs, such as the rate of cell division or cell death at specific times in the development of the cerebellum, in order to prevent the irreversible neurological deficits of hypothyroidism in childhood.

**Summary Points**

- Iodine is a constituent of THs; therefore, iodine deficiency impacts on thyroid function in pregnant women, their fetuses and neonates.
- TH is required for normal brain development beginning in the first trimester, before the onset of fetal TH secretion. Even during the early months of postnatal life, TH is necessary for brain development; however, it is unclear when this critical period is completed.
- The effects of TH are restricted to a subset of neuroanatomical events occurring at that time in different areas of the brain. The impairment of specific neuropsychological functions depends on the timing of TH deficiency.
- Generally, combined maternal and fetal hypothyroidism causes severe fetal hypothyroxinemia in early gestation (EC).
- Postnatal early T4 treatment is successful in preventing mental retardation in most cases (CH).
Other Causes of Hypothyroidism

- Infant-onset hypothyroidism can also cause irreversible neurological deficits similar to CH and EC.
- Patients with severe cases of EC, CH, or juvenile hypothyroidism can demonstrate irreversible motor, intellectual impairments and hearing problems.
- Neuropathology and neuroimaging cannot be distinguished among children with hypothyroid diseases. Specific distributions of intracranial calcifications are common in hypothyroid diseases.
- More sensitive neuropsychological tools and prospective long-term follow-up studies reveal that even mild TH deficiency in fetal and postnatal life can produce deficits in specific neuropsychological functions.
- Genetic models illustrating TH deficiency and TH receptor deletion and mutation help us to understand how these conditions affect brain development.

References


